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The evaluation of psychotropic drugs

You became involved somewhere around 1955/56, on the back of all the funding that came from Congress, which was put into the psychopharmacology service centre.

Back up a bit. I got into psychiatry because my mother had a manic-depressive illness and maybe into research because I read *Arrowsmith* by Sinclair Lewis at an impressionable age, but anyway I went to a medical school where one of the clinical pharmacologists was doing double-blind studies with placebo fairly prominently.

Now that was early. Who was doing double-blind studies at that point?

Yes, 1945–47. Harry Gold was his name. It was Cornell University Medical College. But this wasn't in a psychiatric disorder. He was doing double-blind studies showing that placebo was relatively effective in pain – in angina. Actually I think a psychologist, called Hollingsworth, who did a double-blind study of caffeine for the Coca Cola company back in 1920 or something like that, was the first. I have never actually seen the reference but I believe this to be true.

Anyway, I got drafted into the Army with the doctors' draft, after doing a residency in psychiatry at Payne-Whitney, part of New York Hospital. When I came out of the Army, the National Academy of Sciences needed a doctor to be executive secretary of five committees that they had. They sent a notice to all the doctors getting out of the military that summer. I responded to it and got hired.

What was the National Academy of Sciences

It was created, I think, in the time of Lincoln, to advise the Federal Government but not be part of it. It's the National Academy of Sciences – National Research Council and it's at 2101 Constitutional Avenue Washington, in a beautiful marble building. It's a sort of a quasi-federal agency and it prides itself in not doing any one activity for a prolonged period. They were doing all the reviewing of grants for the American Cancer Assocation, when I was there, but stopped that after a few years,

and they used to run the Committee on Problems of Drug Dependance for several years. They had a small pot of money from the Rockefeller Foundation to distribute for sex research. Kinsey had originally got this money from this Committee and then the Rockefeller Foundation gave it directly to Kinsey.

While I was there Congress got upset at Kinsey for his study on the sexual behaviour for the human female or something or other and decided that the Rockefeller Foundation might lose its tax free status over the sale of the book and their relation with Kinsey. The Foundation ordered the Committee, that I was executive secretary of, not to give grants to Kinsey. Kinsey put in for a grant anyway and the Committee looked at it and said 'oh Shit'. He'd asked for money to import erotic Peruvian pottery! He may have done it to keep the Committee either amused or out of trouble. If he'd put in for a grant on abortion or homosexuality, I think we would awarded him the money and who knows what would have happened after that.

There was a small amount of money from the Licenced Beverage Industry to support alcohol research. I had the fantasy that this money was given mainly so all of the companies that made a lot of whiskey and the like could say 'go see them – don't ask us – ask the National Academy of Sciences'. The Academy's total amount was like £350,000 a year, so we woud say we've spent all our money. I think it was something of a run around. Some people got some money.

Then there were two Committees – one on sex and one on psychiatry – who were supposed to advise the Army. When the new drugs came out, the Psychiatry Committee was having real trouble finding a focus. The reason I got hired was that I'd interned at the Brigham, where the head of medicine was a guy named George Thorn, who was an expert on stress and the adrenal gland. He was Chairman of the Committee on Stress and I think I got hired because I was an old intern of his and I knew something about psychiatry.

Anyway, reserpine and chlorpromazine began to be mentioned. There had been a few meetings and I went to a couple of them. The Committee was having trouble advising the Army because the Army wouldn't tell them what they wanted to be advised on – in fact, I inferred that they didn't want to be advised on anything. And so the Committee really didn't have a role. But I went out to NIMH to find out what they were doing and found that they were about to give a grant to an eminent psychopharmacologist named Ralph Gerard on how to evaluate drug treatments in psychiatry. I turned up just in time because they gave the grant to the National Academy of Sciences and I was the staff member employed on the grant to do all the leg work.

At that stage had anyone any idea how to evaluate the drugs?

Well, I think it was pretty clear that you ought to do double-blind

placebo-controlled trials and in fact the Veterans' Administration was getting organized to do such a study and they did one comparing reserpine, chlorpromazine and placebo. At this time, the VA had already done some multi-hospital studies – whether you'd call them trials or not. They had done some work on lobotomy across a number of facilities and they had done multi-hospital trials in tuberculosis. So they had the model already working well before that.

That's interesting because if you look at the UK for instance psychopharmacology didn't begin in the main classical centres – Oxford, Cambridge or the Maudsley . . .

Exactly the same here. The people involved – Heinz Lehmann – at what is now the Verdun, it's the Protestant State Hospital in Quebec. Henry Brill, who was coordinating things for a number of researchers in different New York State Hospitals. Nate Kline, as a crusader in his own right, I think funded by Mary Lasker, with the help of a reporter named Mike Gorman, who was completely funded by Mary Lasker were going around making noises about how everybody must do such and such. At that point Frank Ayd was a private practitioner with what could be called a dubious reputation in the Baltimore. He was viewed by people at Johns Hopkins as possibly unethical. Whenever a new drug came out he would have treated 120 patients with it and come out with a paper within a month after the drug came out. To his credit, his observations were usually quite correct. The bottom lines were all fine. And he provided free treatment to every religious grouping of any spectrum you want, in Baltimore. I just never quite understood how he could see so many patients without much of a hospital base. There was a guy named Bill Winkleman who ran an outpatient clinic for some Unions in Philadelphia and he was the first person to try Thorazine in outpatient anxiety.

They were mainly State Hospital types. Al Kurland, who was probably the eighth person in the United States to try chlorpromazine, was research director at Springfield State Hospital in Maryland and he tried it on six or eight patients and said 'gee, this stuff does something I've never seen done before'. He put a second mortgage on his house and bought stock in SmithKline and French and made a fair amount of money out of it, as a matter of fact. In these days, when you get patients who have been admitted for the 17th time and are still failing on the drugs that we've got you can begin to think the drugs don't work but I think the Kurland story gives you a better idea of the impact of the drugs on a naive patient population.

How much influence did the clinical trials that were happening in the UK have, because there is a little bit of controversy . . .

My vague memory is that Charmian and Joel Elkes had done a small double-blind trial on thorazine and that came out positive. Other than there were the Delay and Deniker papers from St Anne's in Paris and

and there was somebody in Lyon who had done an earlier study of chlorpromazine.

There was also a trial done by Linford Rees in people who are anxious and . . .

Yes, I think I read about that at the time. The principle was clear from tuberculosis and other things and I had, at least, had experience with Henry Gold. We had actually done a study of one of the early anti-hypertensive drugs in anxiety, a double-blind trial, while I was doing my psychiatric residency. That was probably around 1950/51. So that wasn't unheard of, when we got around to organizing the conference with taskforce committees on how to study drugs in animals, etc. and what about their effects on psychological functioning and how do you do clinical trials. The meeting was held in September of 1956 and by that time Congress had already appropriated $2 million for psychopharmacology.

Why did they come up with such a huge amount of money?

Well, Nate Kline and Mike Gorman testified to Congress. Nate actually proposed a $2 million study – his idea was that there would be 10/12 State Hospitals, each of which would have a research team derived from some not too far away medical school and the whole thing would cost $2 million. He had the whole design printed in the Congresional Register. Bob Felix, who was Head of the National Institute of Mental Health, and was recently recovering from psychoanalysis, was opposed to ear-marked funds and felt the funds weren't needed because NIMH was doing some things anyway. But they got the money shoved down their throats whether they wanted it or not. I think they offered the job to Joel Elkes, who came over to run a branch of the NIMH, at St Elizabeth's Hospital – the other side of Washington from Bethesda, and probably they offered it to other people, I don't know. I was the only live body, aged 31, who knew something about research, something about running committees and grant review – and the money was to be used for grants.

Part of my job in the first year was to defend the NIMH portfolio in grants in psychopharmacology, which was pretty lousy. I was doing things like claiming money given to somebody who was studying carbon dioxide effects on cells and vessels and what not – you could argue that in humans carbon dioxide was a form of biological treatment in psychiatry, so that got called a psychopharmacology study. The person doing it had absolutely no interest in psychiatry that I know of. There was a grant to a guy named Carl Pfeiffer, which included one paragraph in which he said he might give some drugs to some schizophrenics to see if they made them worse and thereby learn something about the disease. There was a study of aftercare in schizophrenia that happened to mention that some of them might be on thorazine – there were essentially very few studies that would come close to what one might think a clinical psychopharmacology progamme should be supporting.

There was a feeling from the literature, that I've read, that it wasn't possible to evaluate the drugs in the sense that these new-fangled scales couldn't capture the complexity and richness of clinical reality and to pretend that they could might be a serious mistake.

I didn't have that feeling and nobody was telling me that you couldn't do it. But yes, there is a constant flow of review articles, written by psychologists, saying, that with the antidepressant drugs in particular, but it will apply to any of them, that you can break the double-blind by the side effects and therefore the study is invalid and therefore you cannot prove that the drug is better than placebo. I don't know what you'd do with that one because by the time you have a placebo that has the same side effects as the drugs, you may have a drug that may very well work in the illness. I think this is one of the limitations of the world. I'm prepared to say that if there are nice sizable differences between drug and placebo and people are getting better: the fact that you are likely to guess a drug that made people better well that's one of the things that you are tending to have happen. This isn't a reason for breaking the double blind.

No, I think the real problems to be sorted out were that I don't think any of us thought that Nate Kline's plan was workable in any sense. Relations between State Hospitals and University Medical Centres were on the order of non-existent and most of the University psychiatric facilities had psychoanalysts as Chairmen and no experience in doing new drug evaluation. There really wasn't a cadre there – there wasn't really anything other than the VA that was set up that could do double blind studies at all easily. I had the good luck to pick up at a meeting a consultant named Sherman Ross, who was a Professor of Psychology from Maryland, who was on sabbatical at the time. He worked with me for the first year and taught me a lot about research and psychology and recruited for me two or three psychologists, including one guy who was very good at computers, and so by the second year, we were beginning to get into shape to actually think about the logistics of how we would do the study. Gerry Klerman had come on board for two years to do his doctors' draft requirement.

How did he come on board?

There was something called the Berry Plan. It was required for a number of years that if you had gone to medical school and weren't physically unfit in some sense or the other, you had to do two years in some branch of the Armed services. A number of people had figured out that the public health service was a branch of the armed services and that, if you were a bright young resident from a good programme, that could get the National Institute of Health to pick you up and you could do your two years of required military service doing research in Washington, which struck some people as good for their careers. There was some risk that

you might end up on an Indian reservation or at a prison but most of them ended up in Washington.

Gerry Klerman had trained in Massachusetts at the Mass Mental Health Center and came and worked with me. I had hired a social psychologist named Sol Golberg by that time and he and Gerry combined to go out to get the study on chlorpromazine up and started. This reported in 1964. It was a nine-hospitals study of three antipsychotic drugs and placebo. We just went to an APA meeting and figured out places we thought we knew somebody who we thought could do the study. We didn't put it out on competitive bid the way you'd have to these days and we didn't get approval from anybody. We just asked 10 places to put in grants, with a common protocol and a couple of paragraphs describing what their patient flow was like. One of the 10 places got disapproved because we didn't think they could get enough patients to meet the study needs in the time required.

So we ended up with nine hospitals, mainly public. The Institute of Living at Hartford and the Payne-Whitney Clinic at New York Hospital were I think the two private hospitals in the group – a couple of city hospitals in DC and St Louis, and State Hospitals in places as diverse as Danville, Kentucky and Sykesville, Maryland and Rochester, New York, and Manhattan. Anyway we got up and running reasonably well and, in fact, we came out with the kind of results you would want – anything that could come out significant did. It was clear the drugs worked – even with the dropouts you could discriminate placebo from the active drug. There were no significant differences between any of the drugs, Thorazine, Mellaril and fluphenazine, on any of the outcome measures. There were clearly differences on side effects – we had recorded them but we didn't know how the hell to score them. We could describe percentages but we didn't have, and nobody still has, a really good apples and oranges comparison system for describing whether the side effects of drug A are worse than the side effects of drug B when they have different side effects. But other than the side effect area, the drugs seem to be really remarkably similar.

Did this come as a surprise that the three drugs were so similar?

It didn't seem to be at the time. The people, who had studied the drugs in open clinical trials, didn't have any strong views. Doug Goldman, in Cincinatti, felt that perphenazine was, in fact, the best of the available antipsychotic drugs in terms of the balance of side effects and clinical effects. We hadn't included it so we couldn't prove that. I still think it's a good drug. He may well have been right, but I don't think it's a big enough difference to pick up without a very large study.

Because the French have always had this idea that this group of drugs aren't all just one group of drugs: there are activating neuroleptics, sedating neuroleptics . . .

We were either blessedly or ignorantly free of that preconception, other than sort of thinking 'gee we ought to study several drugs because they might be different'. We studied three drugs mainly because we wanted to generalize and we were looking to see if there were differences but nobody had any clear hypotheses that there would be. We did work out some predictors of which kind of patients did well on which drug. We tried to replicate some of the differences in a second study without placebo and they didn't replicate, so we gave that one up as a bad job. And, in fact, until clozapine came along, I don't think anybody had found a reliable, in the sense of repeatable, significant difference between drugs, other than on side effects. The French may well be right but I don't think they can prove it.

We couldn't even find a difference between depot and oral fluphenazine. We ran a study of that and failed to find a difference, I think because we had such good research nurses, making sure everyone took their pills. Everybody got placebo shots and active pills or vice versa and there were nurses dropping by once a week and calling up once a week saying 'are you taking your pills?' Under that system everybody took their pills and the relapse rate was identical between the injections and the pills. You wouldn't have expected it to be if we had done it under battlefield conditions in outpatient clinics, with nobody bothering whether people took their pills.

The other big thing that came of the 1964 trial was the idea that the drugs weren't just tranquillizers, they seemed to be actually therapeutic for some aspects of the illnesses . . .

Well, they certainly worked on almost anything that was wrong with schizophrenics. In fact, if my memory serves right, among other things if you looked at symptoms, that weren't present at hospitalization and turned up afterwards, the drugs were better than placebo on that. The placebo patients developed more new symptoms, after admission to the hospital, than the people on drugs. And it didn't look like they only worked on patients with hallucinations and excitement. They worked fairly broadly across the field.

We weren't studying a population of back ward hebephrenics – we did do that a year or two later. Eventually, we did a high dose/low dose placebo study in chronic schizophrenia, plus a doctors'choice group, and you could interpret the results any way that you like. At the time, we said that in the less elderly, chronic schizophrenics, the high dose did a bit better than the standard dose. Viewed another way you could say that the high dose caused a lot more side effects and hardly anybody got discharged and it wasn't all worth all the trouble, which I think is probably the correct inference.

The only other interesting thing to come out of it was that whatever class of drug activating versus sedative, that the patient had been on at the

State Hospital, before they even started the study, there was a bigger difference between high and low dose in those patients on that class of drugs than there was in patients who had been on the other class. So whatever the State Hospital doctors were doing they were guessing right or something or other. People who had been on stelazine before were more likely to do better on high dose stelazine and people who had been Thorazine or Mellaril before were likely to do better on high dose Thorazine. But there may be other explanations for that.

Did Nate Kline and Mike Gorman get in beneath the analytic radar as it were?

Oh yes, they got directly under it. I don't think the analysts were capable of organizing to prevent anything happening even if they had so wanted to, which I'm not sure they did. I think their position was more of armchair doubt or disbelief or something or other. Within two or three years, I had a very small private practice, I was getting calls from analysts saying 'can you please prescribe drugs for Mrs Jones'.

Why wouldn't they actually prescribe them themselves?

Well, there was a period of time and a group of analysts who felt it was unclean. There were also odd beliefs that you shouldn't mix administration with therapy in some form or other and a number of hospitals were run on a therapy/adminstrator split with one doctor being in charge of ground privileges and so on and somebody else purely talking to the patient and examining their psyche. But really it wasn't like a political contest. The analysts tended to be aloof, and not awfully talkative, and they certainly didn't picket Congress saying 'don't give money for these drugs'. I don't think most of them cared much what happened at the State Hospitals.

Was that, do you think, because they didn't see the ultimate threat to their livelihood as it were?

No, I don't think they did. About three years after that, let's say 1960, I went to a meeting of the Association for Research in Nervous and Mental Disease on psychopharmacology, and I sat next to a very talkative biological psychiatrist named Ted Robie. He was not a research figure but he knew all the analysts in New York and he would keep leaning over to me and say 'there's another one – they're running scared, they're running scared'. I think that's more of the flavour of the thing. They were quietly going to meetings about psychopharmacology to find out what was going on and wondering a little bit about whether the drugs were okay. I think it gradually became clearer to almost everybody, after the VA study first and our study second, that Delay and Deniker were actually correct and that the double-blind trials are the only useful way of proving it – even though one could argue that very little new has been found since Delay and Deniker reported and what they observed in an open study turned out to be pretty much correct.

What role did John Overall and Leo Hollister play in all this – they ran the VA study and helped to actually devise the rating instruments and all.

There were really two or three people doing rating instruments at that point. John Overall developed the Brief Psychiatric Rating Scale, which proved to be the handiest and the longest lived of the rating instruments for schizophrenia and it was widely used in the VA. Jim Klett was the psychologist statistician in the VA who actually analysed the data from the collaborative studies – he was a friend of Overall, but Overall was in Texas and Klett was at Perry Point, Maryland, North of Baltimore.

Leo had his own research operation in Palo Alto and he used Overall as a consultant. Leo was an internist not a psychiatrist, so he may have had less impact than he would have had as a psychiatrist. These things tended to be run out of a central office with advice from other people rather than run from individual hospital stations, as they were called. Leo with John Overall certainly did a lot of interesting studies on a variety of drugs in that period of time. The first evidence that Librium and Valium caused physical dependance came from Hollister, in fact.

This was extremely early wasn't it? He picked it up about 1961/62.

Yes well he gave a lot of it to chronic schizophrenics and stopped abruptly and by God some of them had seizures. I've never talked to him about what he thought would happen, when he did it – these were the days before you had to get informed consent, which probably made life a good deal easier.

Viewed another way our study and probably the VA study, probably included an unknown proportion of people who would now be considered to be bipolar disorder or amphetamine psychosis or something or other. All of these conditions responded to anti-psychotic drugs, which makes the study less precisely relevant to schizophrenia. John Kane said recently that our improvement rates for schizophrenia have been dropping over time. We got better improvement rates back then than they are getting now. Part of it may just be that if you've got a chronic schizophrenic and he stops talking his pills and he ends up back in hospital, and therefore eligible for study no. 17 in 1993, it's a lot harder to get the worms back in the can. Somebody, who was doing fine on 200 mg of Thorazine before he stopped taking his pills and then relapsed, may require 1200 mg and 8 weeks before things begin to finally settle down. One of the problems with managed care is that they expect psychotics to get better in three days and you barely have time to establish a relationship and set up some kind of an aftercare programme in that period, you don't really get them better – you may get them sleeping better at night but you aren't going to really knock much of the psychosis down.

Phillip May also came out with a trial around 1964 which is, who was one of the first to report using chlorpromazine without any therapy input.

I think probably in most of the studies with chlorpromazine nobody would consider using therapy input because the State Hospitals didn't much have staff to do that anyway. But Phil May is an interesting story. He got support originally from NIMH to compare psychotherapy, supervised by trained analysts, with drug therapy versus psychoanalysts alone or drug alone, ECT alone or milieu therapy – meaning none of the above. He got the study done but he got turned down for more money for the analysis. The State of California's Research Department wouldn't give him money because they believed that he was biased in favour of psychoanalysis because his wife was an analyst. I managed to figure a way of getting him a contract out of NIMH, without going through the grant procedure, to give him enough money to finish the damn thing and write the book.

It turned out psychoanalysis was really quite ineffective in this study. So much for the biases he may or may not have had because of his wife; I think he was interested in finding out the truth. His was the first study to tackle the psychotherapy question relatively head on. Various people complained, probably correctly, that the therapy was done mainly by advanced residents and junior staff and that they weren't really psychoanalysts – that was because there wasn't enough money in the world to hire enough analysts to get out in the State Hospitals to do the therapy.

Jack Ewalt had the same idea. What he did was, he took a bunch of chronic schizophrenics in Boston State Hospital and transferred them to Mass Mental Health Centre, which was then called the Boston Psychopathic Hospital, and he gave them an intensive treatment with daily psychotherapy and rehabilitation and group therapy – you name it. His idea was you can give them a lot of everything and then when you've proved that that's good, you dissect it out and try to get at which part is more essential than which other. In fact, what he provided was a toxic dose of interpersonal contact. Patients off drugs got a lot worse at the Mass Mental Health Centre; they blew apart at the seams under all this. John Wing, at your end of the world, had a theory which I think is quite correct, that if you overstimulate schizophrenics they go actively mad, and if you lock them up in an attic they go catatonic. The ones at Mass Mental got overstimulated and got substantially worse if they weren't on anything. You wouldn't do the study quite that way these days but it fairly clearly showed that you didn't get people a lot better by giving them a lot of psychosocial therapies all at once.

Let's hop back a bit. Because gearing up to the NIMH study, you'd begun to run the early clinical drug evaluation, the ECDEU programme.

That was sort of a parallel event. It seemed to me as I wandered round talking to people that drug companies were perfectly good at giving money but they didn't give it in a consistent fashion. The people who were doing what I saw was a good job of evaluating new drugs for the

drug companies, could certainly use some kind of continuing sort of baseline support. You know, a secretary, a nurse and a half-time doctor and it would be good to have a programme, whereby the better people are doing this kind of stuff, got five-year grants to do studies, and would meet together and tell the psychopharmacology programme, namely me, and each other what they found out. I managed to sell that to the National Institute of Health because we had enough money going around and, I think at one point, we had 15, 16 or 17 program grants of this sort going. The grants gradually died, mainly because review committees don't like that kind of support. They like hypothesis-orientated research and most of the people weren't doing that. Maybe they didn't deserve it any way, I can't judge.

However, the early clinical drug evaluation programme had then developed a life of its own and now meets yearly as the New Clinical Drug Evaluation Programme. It's sort of parallel with ACNP, only you don't have to meet criteria to be a member. It meets in Florida in early June. It was under 20 investigators when it started. The meeting is attended by over 300 people now. There was an argument about whether drug company representatives should sit in or not and after a while we let them sit in and its now evolved into something rather parallel to the Committee on Problems of Drug Dependence which I had already been exposed to. I had gotten the model from them. There really is a value in having a meeting where clinical investigators and basic scientists present research and the company representatives come and find out what's going on and do a certain amount of bartering over who's going to do studies and the Federal Bureaucrats with an interest in the area also are present. If everybody is at the same meeting, they can hash out things that they might not do otherwise.

In the Committee on Problems of Drug Dependance, they used to and I think still do, pass the hat to the drug companies and get some unrestricted funds out of the companies. They supported a programme where a guy named Nathan Eddy would review new chemicals that might be used for analgesia and do simple stuff in mice and then he'd send them on to Michigan to be tried out in monkeys, dependent on morphine, to see if the new drugs would substitute. And then they would go the Addiction Research Centre of the NIMH to be tried out in man and other people would see if they were effective analgesics. Anyway, this programme is a little bit like that. It's a nice four days in the sun in Florida. We have training sessions on how to use some new instruments and a general review for people from outlying places, who don't get to get to that kind of meeting very often.

It seems to me that you have been a person who has tried to bring people together. Now not everyone else in the field at the time would have been in the business of doing that. Yale or Harvard wouldn't have been in the business of bringing people

from the public hospitals in. The NIMH as such, if left to Bob Felix, wouldn't have been particularly in the business of . . .

Probably not. He had a special programmes branch. The NIMH idea was one study of industrial mental health and one study of child development and another study on adoption and one for each thing some staff member had a special interest in – it risked being a bypass route for flaky projects – that may be a little harsh.

I wasn't conscious of it at the time, it just seemed to happen but I turned out to get along well with people. My other role was to hire people to do the research and the analysis, whiile I answered all the nasty letters from Congress and wrote all the annual reports. I happen to write easily. So I did a lot of the basic crap you have to do to keep a programme alive – defend it and go to meetings and write documents. I actively enjoyed the review committee process and had a good enough relationship with the review committee members that I could speak up and say if I felt they were going off the deep end on something or other. I could occasionally change the course of the grant's review by saying something.

It all seemed to work out very well and I enjoyed going to State Hospitals. In fact, I enjoyed it so much that when I got frustrated with some things happening in the NIMH, and I got offered the job of superintendant at the State Hospital in Boston I took it because I thought it might be fun. It was fun for about five years until I began to feel I was burning out and thought I better go and do something else.

Who did you see as being the key people in the field, sa,y between 1955 and 1965?

Oh goodness, I guess at the advisory level people like Danny Friedman, who actually didn't do any of this research but was really excellent person to have on a committee and to talk to about both political and other problems. He was probably the person I felt closest to as a general person to rap with in the late hours of the evening as to how things were going. Louis Lasagna was another. He wasn't a psychiatrist but he knew a lot about the FDA and about clinical pharmacology and he was a very useful review committee member. Heinz Lehmann I used a fair amount and Henry Brill and Phil May and Gerry Klerman.

Seymour Kety?

Yeh, he was sort of so senior that I wasn't quite sure how to use him. But again he wasn't a psychiatrist. He and I were both at McLean for 10 years and I think I saw him about 4 times. He had a big centre grant in schizohprenia and they never included me in it. I don't know whether I'd have contributed anything. I never could tell whether they were paranoid or whether they just didn't think about it.

There was a guy named Neil Waldrup who was over at St Elizabeth's

who I knew fairly well – actually the reason I left NIMH, at least on paper, was the people at St Elizabeth's wanted me to take over a research ward over there and it seemed like a great idea to have a pilot plant. The money was probably going to dry up anyway, so maybe it was just as well the move didn't happen. But having a ward where my staff could try out instruments and we could do some pilot testing of study designs seemed like a great idea and I said fine. Two years later, it became clear that they hadn't cleared it with anybody higher up in the hierarchy and when it got up to the then Stan Yolles level, the Director of NIMH, he said 'no, he's over-committed already'. I was moderately pissed at that.

About the same time, drug abuse was beginning to get hot and a guy named Roger Meyer, who had come down on this two-year plan to work with me and handle the drug abuse end of it, got split off from me and ended up in what eventually became the National Institute of Drug Abuse, which was run outside of the psychopharmacology programme. It probably made sense but if it had been inside my programme, I probably would have been too busy to think about going anywhere else. With those two things having been not given or taken away, I got offered this job in Boston. My parents lived in Boston and I was raised there and it seemed like a good time to go try being superintendant at the State Hospital.

With the ECDEU unit actually running by 1960, why was there a need for ACNP?

Well the ECDEU was really a pretty restricted format; it wouldn't have included people like Julius Axelrod, wouldn't have included Phil May, wouldn't have included Danny Friedman and a variety of people, because it was really designed only for studying investigational drugs and the people who do that tend not to be the leaders of science. A few people were exceptions, like Leo Hollister. But I think people, also, thought that we needed a broader organization and model. I think the CINP came first and I think we were sort of modelling it after the CINP. There was a meeting at the Barbizon Plaza. Nate Kline and I and Paul Hoch took the leadership in this – Paul Hoch died two or three years later. He was sort of the autocratic Prussian type and tended to run things.

Ted Rothman was very heavily involved wasn't he?

Yes, he ended up being the guy who did a lot of the work. Ted offered himself. I think he was a private practitioner in LA and he had the time and the interest and was getting older. Anyway, he took over and did a lot of the organizing and was a good example of a practising clinician who decided this was a good way to spend his time, which I didn't have and Paul Hoch didn't have. He ended up carrying the organization on his shoulders for the first three or four years. His main area of research

had been giving intravenous speed to people to help them talk in psychotherapy.

Quite a few of the people in the group were interested in giving drugs to people to abreact them.

Yes, there was a wave of LSD interest going on and we supported some research in that. There were some Josiah Masey conferences, for instance, on LSD that were really pretty wild that I went to. It was certainly an interesting area. I suspect it works in some people, some of the time, but it's damm hard to prove. Drugs that do fabulously in 15% of some unknown number of people pose a terrible problem. I think everybody knows patients who do remarkably well on something or other. You hate to take them off of it but it's hard to convince a drug company to keep something on the market on the basis of it. Short of taking people who you already know are responders on and off a drug, it's hard to think of a design that will pick them up.

ACNP has been run by your secretaries. Oakley Ray has been there for a lifetime really and he almost is ACNP . . .

Dick Wittenborn was there for six years before that and Ted Rothman before him. I think we figured that having an enduring secretary makes a lot of sense so I think we set it up with three-year terms and tended to re-elect people if they wanted to be re-elected and things were going along all right. We've had a backup in case somebody dropped dead or broke a leg or something. But it's worked reasonably well as an administrative device. Presidents come and go each year and one year spans a time when, unless you did something remarkably notable like make the organization go broke or pass a law, or get the Nobel prize or something or other, it tends not to be remembered.

How much of an impact did the antidepressants have on the Psychopharmacology Service Centre? You were geared up to look at chlorpromazine, then the antidepressants began to . . .

Yes, and we did some studies of Librium and Valium without anybody telling us to and when the antidepressants came along we set up a multihospital study of antidepressants which got published. It turned out to be very hard to prove that imipramine did anything. We did imipramine, placebo and chlorpromazine and then we did phenelzine, diazepam and placebo – in hospitalized depressions, mainly but not exclusively private hospitals. A guy named Al Raskin, who was a psychologist, did most of the work. We ended up having too many instruments and we ended up factor-analysing factors and we either died of data poisoning or by that time the patients you got in inpatient wards were a mix of people with bad personality disorders or people who had failed on the drugs on the outside. Our dosing scheme was, I think, irrational in retrospect. We ran

up to a peak dose on the third and fourth week and then started coming down again and we probably should have run for 12 weeks and kept everybody at the top dose.

So we were able to show that imipramine was better than placebo and that non-retarded depressions did better on chlorpromazine than retarded depression and that was nice. But it was less clearly positive compared with the antipsychotic study.

What about phenelzine, diazepam and placebo?

That didn't show much of anything either but we didn't keep them on a high enough dose and we didn't keep them on it for long enough. Some time thereafter, we supported Don Robinson, who showed that you've got to give at least a mg per kg and probably keep it up for 6–8 weeks or something like that to get a decent response out of phenelzine. But we didn't know that much at the time. We knew about the cheese reaction, because I remember a patient overdosed on cheese and related edibles and in fact got a hypertensive crisis because she turned out to be on phenelzine. Anyway, it was not a great success and we didn't try again after that. About that time money was beginning to get tighter and I think I left while the study was still ongoing or about to be published.

Jerry Levine who had been my deputy took over and he was interested in the NCDEU business and went through a phase of inviting data from a variety of investigators who weren't necessarily funded by us. Jerry got interested in using the dataset and he actually was responsible for setting up the blips system. Jerry was much more organized than I was.

When did the need for operational criteria begin to become apparent?

We felt it from the beginning but we didn't really do a lot of work on it. Criteria like a score of 18 on the Hamilton scale were fairly easy to come by. I guess it was Bob Spitzer, 20 years ago now, who began to really get into diagnostic interviewing. In fact, the Present State Exam I think was in advance of anything sensible over here. There was the Diagnostic Interview Schedule, which turned out to be rather inadequate instrument, at least when administered by ordinary people, without any clinical training. But that was the first standardized interview that I can remember and then Bob Spitzer and various other people in Columbia went on to develop better instruments.

I guess these probably grew not so much out of my programme as out of the US/UK diagnostic study, which was run, in the US, out of Columbia. Spitzer was involved to some extent. That showed that us crazy Americans were over-diagnosing schizophrenia to a large extent. Up to that point, we were allowing for clinical judgement and the training of the people doing ratings and hoping for the best. Certainly, when we were doing anxiety studies, which is another area – the whole idea of

panic disorder grew out of Don Klein's work and I think he was actually grant-supported by us.

He and Max Finx at Hillside had done this wild study, which was a wonderful commentary on the analytic view of the world. Hillside was primarily an analytic hospital and Max Finx and Don Klein were doing all the shock treatment. When the drugs came along, the head of the hospital said 'well if somebody isn't better after a month of analytic therapy, they can get sent to Fink and Klein and they can put them on drugs'. They were the only people allowed to do drug therapy in the hospital, so they randomized almost everybody to Tofranil, Thorazine and placebo independant of what symptoms they presented with.

Yes, and actually got some interesting results . . .

I don't think they reported it but the nicest study was that Don had made research diagnoses on a large number of patients at Hillside. They weren't doing formal diagnoses quite the way they are done now, but they had criteria and they were making criteria-based diagnosis. So they had a group of patients that his staff thought were not schizophrenic and the Hillside regular staff thought were schizophrenic, and another group where they both agreed they were schizophrenic, and he made the prediction, that if a patient ran out of money and was transferred to Creedmore State Hospital, which was not uncommon, that the real schizophrenics would stay at Creedmore for a long time and the non-schizophrenics would get discharged rather rapidly. He checked it out and the results were significant at the 0.001 level. The people his research staff did not think were schizophrenic, I think had a mean stay of like three weeks and the real schizophrenics had a mean stay of nine months. There was a whopping difference and that was the first story I remember of the power of diagnosis in actually demonstrating something tangible. That and the prediction about drug response.

We deserve a little credit for introducing lithium to this country because we gave a big grant to Ralph Gerard to run a study of chronically hospitalized patients in the Ypsilanti State Hospital, near the University of Michigan, Ann Arbor. They had research wards there and used every test known to man. One of the people on the grant was Sam Gershon, who had come over from Australia for a couple of years, and brought lithium with him and the first papers on the use of lithium in American patients was done by Sam at Ypsilanti under that grant.

And it worked?

Oh yes. At the time, you'd go buy the pure chemicals, lithium carbonate, by the kilo from a chemical supply store and then you'd get a drug store pharmacist to put it into capsules for you. And then Rowell Labs, a company in Minnesota, got interested in it and began making it for some investigators and then, eventually, SmithKline and French and Pfizer got

interested. The FDA was giving out INDs to all kinds of people who wanted to use lithium. Almost anybody who said they wanted to treat patients with lithium, they'd get an IND number. When I was superintendant at Boston State it wasn't on the market and yet I had about 15 patients on it.

What was Boston State Hospital like when you went there? The drugs had been out over 10 years . . .

Milt Greenblatt had been running it for 5 years before and Walter Barton was the notable superintendant for 10 years before that, so the population had dropped from a maximum of 3000 down to about 1600 by the time I had got there. The nursing supervisors were throwing beds out of windows to dramatize the fact that the patients will never come back. The catchment area idea of breaking the city down into geographic areas, each of which would be responsible for its own patients, had started, and they were beginning to work out how to divide the hospital up into defined catchment areas to meet the needs of the new plan.

Where the catchment area idea come from?

Jack Ewalt. There was a commission on mental health and illness that was funded by Congress and Ewalt was chairman of it and it came out with a report strongly recommending community mental health centres. There was some underlying idea that even elevator operators can give therapy and you don't need high priced professionals all the time and you've got to treat everybody and there should be federal grants to support staff and improve liaison between the state hospitals and the community. And it sort of worked – you can argue it both ways. Boston State Hospital went out of existence about four years after I left. We peeled off into mental health centres. The state built buildings for some of the mental health centres and we moved patients to pre-existing buildings in their catchment areas for others.

Whether it was a good idea in the long run, I tend to think not in retrospect. I think the State hospital had a place and now a major problem in Massachusetts from my viewpoint is that we've got very few places where we can serve the kind of patient who takes a long time to get better and where real rehabilitation is done. We tend to have more people who are home and crazy than we should have and nobody's going to pay for their treatment. We've closed most of the State Hospitals although not all of them. But the procedure to break up into community mental health centres had already started and when I took over as superintendant we continued along that. We had a grant to improve community services for the catchment areas that the hospital was supposed to be getting and we did a number of things but most of the innovative things we did were done before we broke up into catchment areas rather than afterwards.

For instance, we worked a deal with the Department of Welfare

whereby we could put five chronic patients in one apartment, in a three-decker. Boston is littered with buildings with three apartments, one above another, and the landlord would usually live in one of the apartments and he got paid a little extra to keep an eye on the patients. The Welfare Department provided the funds to pay the rent, so we didn't have to deal with it. The landlord showed the patients where to buy groceries and our staff went out to fill up the chinks and provide some education. We had a home treatment service, which was sort of crisis call-out in the home. The psychiatric resident and the nurse would go out to the house, if they heard there was somebody crazy out there. They would drive out to the house, park the car in front of the driveway so the patient couldn't escape on wheels, go in, often backed up by the police, and offer to give the guy a shot of depot prolixin, if he didn't want to go to the hospital with that nice man in blue standing right behind.

We started day hospitals and we did cognitive training of pre-school black kids who lived in the surrounding area. I even did a study of dexedrine in over-active kids in the schools adjacent to the hospital. I published it in *Psychopharmacology*. I knew it would work fine. I needed some money for helping fill out the cracks in the grant for the Outreach Programme and I got $10,000 from SmithKline French for doing that study and used that to help pay travel and buy stuff for community centres we were trying to set up for the community.

Where did you do your clinical training?

I was trained by Oscar Diethelm, who was interested in psychiatric history. He was Adolph Meyer trained, so he believed in distributive analysis which was talking about your mother today and arriving at some kind of conclusion as to how that influenced your life and you talk about daddy the next day and your brother and sister the third day. Distributive analysis was a somewhat more superficial therapy, with life charts – Meyer was interested to relate somatic and social and intrapsychic things and trying to see how things interacted with each other during parts of the life span of a patient.

How strong was the Meyerian strand in US psychiatry?

I wasn't conscious of it as a strand. The place was eclectic. You'd got patients whose average length of stay was three months and you saw them three times a week and tried to do what you could with them. We did shock treatment and insulin sub-coma. If you asked me, was I Meyerian? I would have said no. But it struck me as sensible. You met with Diethelm once a week to go over all your patients. He would come round and visit each of your patients with you, once a week, and Tom Rennie, who was the other guru on the staff, did the same thing. We had two supervisors for each patient, which is a little odd in present day psychiatry but it certainly felt like your patient was being attended to. Diethelm would

take notes on those little 3 × 5 cards and I'd get a few patients who had been in the clinic before and he would pull a little 3 × 5 card and tell you all kinds of things about these patients.

So it was a nice comfortable place. All the patients were locked up so they couldn't fail to come back for their interviews. There was almost no outpatient experience. It was probably good training for my future because you had to write a five-page single spaced case summary, which you'd get typed, on each patient. If it was too long or too short you'd get yelled at and then you had to present it or if you weren't presenting you had to comment on the patient and he would start with the most junior resident and work his way around the room and everybody had to say something about the patient. So you got used to talking in public. You probably got more experience in writing under pressure than people do in this day and age, where they tend to write illegible 11/2 page admission notes and the occasional progress note but nothing else.

On the history issue, in Josephine Swazey's 1974 book on chlorpromazine, and she cites you a lot, do you think she had the picture right?

Yes, she talked to me at some length. As I remember the book, I thought she had it right. There's also a book on the history of psychopharmacology by Anne Caldwell, who was in the National Library of Medicine, which was too full of Laborit worship. I think Laborit had a real role but she thought he walked on water. My comment after was the reason nobody ever got a Nobel prize for this was that one it was a company drug, and who the hell did you give a prize to, and second that the principal person in getting the drug into man was the equivalent of a Head of Anaesthesia at the Naval Hospital in Virginia. He was not a prime mover in French academic medicine and he had an oddball theory of stress which may, in fact, be right but I'm in no position to judge one way or the other.

After Boston State Hospital, you did what?

I got offered a Chairmanship of Psychiatry at Temple University in Philadelphia and my then wife, who has since died, said to try it for a year and if you like it we'll move. At the end of a year, we were losing beds and psychiatry had been kicked out of the planned new teaching building. I figured the medical school was going broke and I didn't like Philadelphia much anyway, so I went back to Boston. I ended up at McLean because they seemed glad to have me and I ended up running a psychopharmacology consultation service. I've been doing that more or less ever since.

We set up an affective disorders clinic with Alan Schatzberg, who's now Chairman at Stanford. The hospital is now quietly going down the tube. We've managed to lose money, even when all beds are filled, and we've got things all re-organized, practically like the way I had in Boston State, with triage, etc. – keep them out of hospital at all costs, provide

some place to sleep for the night if they really need it, a day programme, give some of them a therapist and a case manager. Trouble is nobody wants to pay for that in this country. There's no way of funding it, whereas at Boston State I had 1800 employees and if I freed up some employees by closing or emptying a chronic ward, I could then use some of them to be case managers in the community so it worked. It was a lot easier to do then than now. So I'm not sure it's going to survive.

I know you worked with Joe Schildkraut. How much of an impact do you think his amine hypothesis had? It seems to me that things like that helped to bring psychopharmacology into the public domain. People could understand the idea of low chemicals and that treatment was aimed to restore that . . .

'I have a chemical abnormality'. Yes. I think some of it's pseudo science and some of it's real. For 15 years or so, Schatzberg and I got most of the patients that Schildkraut studied. We could get drug-free patients from McLean, collect urines and do ratings and send the stuff to Joe to run all the chemical analyses and so forth. Most of his work for the last 15 years has been based on McLean patients. It was a generally interesting collaboration and there clearly is something about MHPG – people with high MHPG are different from those with low MHPG. I'm not sure whether we're measuring the right thing of course. If you compare Prozac and Tofranil, you get pretty much the same predictors of improvement. Low MHPG people do better on Prozac, they also do better on Tofranil. You'd think there would be something different about them, given the different mechanisms of action. I don't quite know what to make of it.

Talking about fluoxetine and its impact in the US – how do you account for that?

One pill a day for ever. It's very easy for internists. I think primary care docs really never learned how to manipulate tricyclics well – the side effects, waiting, etc. Fluoxetine at one pill a day for ever is the ideal primary care physician's drug. I think part of it was that there is something like 5–10% of patients on fluoxetine, who get remarkably better. Like the 'Listening to Prozac man', at McLean I treated 100 or so patients before it came on the market and a handful of them really were astoundingly better. They had been sick for 10/15 years and were clearly better than they had ever been before in their lives and there were just enough of them to make a difference. You certainly got a small handful of people who said 'wow am I better'! and went on television and said they were better. At the other end, you see people who have been on Prozac for two years and are still waiting for it to work. So it doesn't do that to everybody but it does it to just enough to hit the talk shows and get a lot of sales going.

What about a group of patients who may get worse on it?

Yes. I'm one of the authors of the suicide paper . . . I didn't realize

it would be quite that famous. I don't know whether Teicher or I would have published it, if we'd known, although I guess we would have done. Yes, I have seen people, at least a handful, that clearly got more agitated and got weird thoughts and suicidal drive. Tony Rothschild, who has taken over my depression programme in McLean, found three people who had jumped off something while on fluoxetine, who didn't kill themselves, and agreed to take it again. He re-created the same desperate driven quality with fluoxetine.

Is it a form of akathisia?

I think it probably is but whether you get the neuromuscular form or whether it's purely psychic I don't know. One patient I followed through it was so distressed by thoughts telling her to kill herself over and over again, that I never got around to asking her whether her muscles felt funny. The psychic end is so predominant that you forget to ask about the muscle end. I told her to take some Ativan and go to sleep and she did and within 36 hours it had passed. At the end of it she said 'gee, I've been depressed for 21 years, and suicidal a lot but that was ridiculous'. She thought it was clearly different than anything she had ever experienced before which is why I put her case and my name on the paper. Lilly doesn't believe it.

Sy Fisher, who is now at the University of Texas in Galveston, does prescription surveys and he did a study in which a big chain of drug stores in the South and South West participated, where if you filled a Prozac prescription you got a thing saying that 'if anything unusual good or bad happens to you on this drug, please call this 800 number'. They did the same thing for everybody who filled out trazodone prescriptions. I would have preferred another drug because who knows how many people get trazodone for insomnia. What they got were all the usual side effects of both drugs, in about the expected proportions. Plus about 1–2% of the people on prozac, and none of the people on trazodone, called up and said I've got suicidal ideas that I haven't had before and another 1–2% phoned up and said I've got crazy ideas that I hadn't had before.

So I think it does happen but I think it's rare. I think now most people have heard about it. Propranolol reverses it quite nicely. Two of three patients that Rothschild re-created it in, he added propranolol and they left the hospital still on fluoxetine, happy as clams. I think it is now known enough that the FDA didn't need to put a warning on it. So I think it's rare and the drug has certainly prevented more suicides than it's caused. I don't think it's a bad drug, I just think it does funny things every once in a while.

We've got much fewer drugs going through now because they say the costs are so big and the industry stands to lose so much if the drug goes wrong. How much has the climate changed in which drugs are brought out?

Yes the risk:benefit ratio for the drug company has changed. I haven't heard of a new antidepressant in the last nine months and I don't know whether it's because there are so many antidepressants out there now that how can you hope to gain any decent proportion of market share no matter how good your drug was or whether it's because the cost is so much. When I've been asked, I've told people I wouldn't mess with an antidepressant unless it was clearly faster acting than existing drugs. If you've got a three-day response, at least half the time, and the side effects are no worse, I'd try it, but I'd throw it out if it took an average of three weeks to handle depression. I think you need some kind of compelling and striking difference. I think you need something more than 'gee, this works through receptor no. 17'.

That's neither here nor there.

Yeh, it's interesting, it may even be relevant but it certainly doesn't make or break a drug. I wouldn't go to market just because it worked on one receptor and not on another. I would love somebody to get one of the rapid reversal MAO inhibitors on the market but I gather they're all being killed by the companies. They may be right. Doctors are peculiar beings. You say the word MAO inhibitor and they think hypertensive crisis and don't prescribe the drug, I think.

That had a huge impact didn't it? Mythologies develop, don't they?

I got so pissed about Lilly saying 'don't you agree that all the doctors know that fluoxetine doesn't cause suicide' that I did a survey of everybody in the Mass Psychiatric Society, who'd answer the telephone about whether they had ever had or thought they'd had a patient who had been made suicidal by fluoxetine, or whether they had heard of anybody, and if they had, did they think they were prescribing less now than they were before. You could make a case that if they had some personal experience with fluoxetine in a patient who they thought got suicidal, they were more likely to warn patients and be a little more gun shy. Not a lot but a little bit.

But I threw in priaprism and Trazodone and seizures and buproprion, at the same time. Now, particularly with buproprion, they might never have heard of anybody ever having a seizure on buproprion, except for the package insert, but they wouldn't touch it with a 10-foot pole. It was really the kiss of death for buproprion. I don't know whether I think seizures are all that bad. I'm not in favour of them but compared to whatever else! It's like the MAO issue, which is the only reason I am raising it. I think that buproprion is a good deal better drug than its use suggests – I've been paid as a consultant by the company so obviously I should state that somewhere. But the idea that it might cause seizures, has caused doctors to avoid it like the plague. It's the same with the MAOIs.

I think we should call this perversity of prescribers the Cole Effect. It's curious how these things happen. Sometimes, ideas just get into popular consciousness and other times they don't. You would have thought that suicidal ideation would have killed off fluoxetine but it hasn't.

But the company probably did exactly the right thing which was to stone wall and the FDA didn't do anything. The company was publishing meta-analyses of everything in the world–8000 patients in 6-week trials with no increase in suicidal ideation . . .

But you could argue that Upjohn did the same with Halcion but it hasn't been as successful. It's . . .

One of the things is that diazepam and then alprazolam were the bad drugs in this country. I gather lorazepam is the bad drug in England and Serax is the bad drug in Australia. Whichever benzodiazepine is the most widely used is the one that causes the problems – probably because whatever is used most widely stands the largest chance of being taken by murderers, rapists or whatever. I don't know whether that's a reason or not but I don't think the drugs are significantly different from each other.

We haven't really got a handle on all this on just why these things play the way they do in public. Talking of which, Listening to Prozac seems to me to mark a point where American psychiatry went biological at street level, would you agree?

I guess that's probably true. Peter Kramer can be somewhat foggy but he makes valid points and he certainly popularized the whole idea. He did an editorial for a throwaway newspaper called *Throw Psychotherapy from the Train*. He said that the rates that were being paid to do psychotherapy by third party payers were just ridiculous and we've got to refuse to accept them. Let's just do psychotherapy like they did in the old days, namely if people can pay for it fine, and if they can't, fine. We won't take $27 per hour for doing something which we think is worth more than that and if people go without, it's just too bad.

The other wave I detect is that cognitive – behaviour therapy is rising in competition to drugs with somewhat more force. There's now been the three hospitals' trial comparing cognitive therapy, interpersonal therapy, tofranil and placebo. Tofranil is better but I keep wondering whether they didn't do something wrong, somewhere. They tried to train social workers to do these therapies and I think there is a problem in skills transfers and because of this I think the non-drug therapies didn't do as well as they might have if they had been done by people who had been trained to do them, who thought it was their favourite therapy. Imipramine worked a little less well than I would have thought and there was a funny business about the psychotherapies doing no better than placebo and then in the last two weeks everybody got better – like they had to

please their therapists. I don't know quite what to make out of that one. There have been enough other studies of cognitive therapies that I'm prepared to believe it works, whatever the NIMH study shows. I think, having watched patients, it doesn't work in the very agitated depression, the kind you are seriously thinking about ECT with. You've got to be able to understand what you're there for and do homework to be able to do these therapies and the kind of hand wringing, oh-my-god-doctor-help-me-I'm-dying type of patients, simply can't do the work necessary.

The other thing that I heard from the analysis of the results, which seems to me to be both unfortunate but probably correct, is that with interpersonal therapy, the better your interpersonal relations were at entry to the study, the better you did on interpersonal therapy and with cognitive therapy, the less bad your cognitions were at the beginning of the study, the better you did on cognitive therapy. So each treatment worked better in a way like the Meninger psychotherapy study, which, as Don Klein said, the only finding was that the less sick you were to start with, the better you were at the end. It probably is true that you could learn how to improve your interpersonal skills if you're fairly good at it to begin with and it's easier to correct your cognitions if they're not so screwed up that you can hardly hear the therapist to know what they are talking about.

Are the drug therapies in a permanent advantage vis à vis psychotherapy because they've got a company behind them to market them?

Probably yes. The real question which is not well answered is whether the psychotherapies, which are supposed to teach you something, are any better at preventing you from getting sick again. We are trying to keep people on antidepressants for rather long periods of time and the relapse rate goes up if you stop too soon so you wonder whether . . . There's an old article on imipramine in the *Canadian Journal of Psychiatry*, around the time of the first conference with imipramine in Montreal, saying imipramine is an addictive drug because if you stop it you get depressed again, therefore you are addicted to it. The same model would say that diabetics are addicted to insulin. But there is some truth to it and the question is even more acute with Xanac and panic disorder so I don't know how it's going to work out in the long run.

If the behavioural therapies were able to be shown to give people increased, inner strength to deal with life in the future, I would be impressed and be inclined to refer patients more often than I am now. On the other hand, behaviour therapies are not cheap and not always readily accessible. They end up being more expensive than pills. Pills are not cheap but they tend more often to be paid for by insurances.

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