Clinical Psychopharmacology
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Where and when did you train?
Well I studied Biochemistry in Glasgow and then I was directed to "work of national importance" - that always sounds much better than it was. I went to work with Distillers, who, I think, made 33 Scotches and 2 antibiotics. I was lucky or unlucky enough to get the antibiotics. I worked in Liverpool for a couple of years and then went to Medical School in Liverpool. The Dean was Scottish and, when I went to apply, he let me know that I would be all right. That was important because I had a very poor record as a student in Glasgow. I would have to say that either he saw something that nobody else had or he was just being nationalistic. So, I did medicine in Liverpool and I interned there for a year and that was when I decided that I was going to go into Psychiatry. It is interesting how people decide a bit earlier, particularly in the States, you have to declare what you are going to do before you graduate, but I was still interested in paediatrics until my final year. When I decided on Psychiatry it was a question of going to London because Liverpool was not very good.

Was Frank Fish there then?
No, Frank Fish hadn't arrived. We had Barton Hall, who was a very pleasant man, but a bit stiff. He was a Reader so there wasn't even a department. I always remember we got lectures in psychotherapy but I never had any clues what he meant by psychotherapy. I wouldn't have said he was a good lecturer either. London seemed more attractive. Then I think I was sitting at tea-time, while everybody else was looking at a Test Match, reading the Lancet, when I saw an ad from McGill about training there. I wrote a hand written letter and I'm not sure whether I got a cable back or an air mail letter accepting me - from Ewan Cameron.

Which year was that?
That would have been 1956. When I went to McGill, my notion really was that I would spend a year in McGill and maybe a year or two in the States, end up in Mexico and come back to London with the notion of going to the Maudsley.

What did you make of Cameron?
Well, he was very unusual. He was a super-administrator. If he had gone into General Motors, the Japanese would never have penetrated the American market. His Institute was his body image. If there was a crack in the stairs you always felt that more people would get ECT that day than if the Institute had been whole. He had a lot of bright, stimulating ideas, except he was a terrible researcher. If he had seen himself as an administrator, I think he would have been top of the line. He did have a Day Hospital, which apart from the Marlborough Day Centre and centres in the Soviet Union, was the first of its kind. He was very innovative and energetic but he just had wild ideas - naive and simplistic. You probably know about some of the wild things he did. Before I got there, I think he gave intra-thecal hyaluronidase on the notion that depression might involve some abnormality in the blood brain barrier and this would allow the flow back and forth of whatever it was to resume. You can imagine what his neurological colleagues thought of somebody just shoving hyaluronidase into CSF.

Do you know what the outcome of that was?

Well, I would guess it was positive, but there were never any controls and that was the worst part of it. For instance, another thing that he was giving intravenously was ribonucleic acid. I had a patient with Alzheimer's who had been in the hospital for three months and I don't know if she ever found her way back to her room. However, there was a psychologist who worked with Cameron who showed that her memory had significantly improved. Now some of these people had quite clear rigors probably from pyrogens in the RNA - I don't know where they got them from. There were wild leaps in the dark, I would have called them, that he did without much concern.

Of course, he was more famous for his psychic driving which one or two people have written about. That was financed at least in part by the CIA, although whether Cameron knew about that or not history may or may not tell us. I was once approached by a foundation to let me know that they were interested in something I was doing. Now if I had pursued that I would never have investigated them to see from where they got their money. I would have taken the money and I think most people would. So, if the CIA were laundering money, it's conceivable that Cameron didn't know. But the research itself was just awful. It was uncontrolled. Some of it was bizarre. I remember a woman who should have worn a helmet with a radio receiver in the ear, transmitting "I like people, people like me". When I came in to see her one day, she was sitting on the bed, soaked in urine with her foot in the helmet which was still going on making the pronouncements, literally in her case, "I like people, people like me". It was a male voice and she was responding "well of course he does and that is what has been the problem in our marriage". So, part of this woman's problem was her husband who was successful in more ways than one and she felt the voice coming from the helmet was his voice repeating this about himself. There were other things like that. It was difficult because everybody felt it was strange but nobody did anything about it.

I was in my first year in psychiatry at the time and I would argue that the Allan was the most stimulating place in the English-speaking world at the moment even though the rest of the city spoke French. They were just a marvellous group of people around. You had Sloane who became the Chair at Temple and then USC. Charlie Shagass did all his sedation threshold work there which was well in advance of his time and probably is still more robust than a DST, but he did it at the wrong time. Cleghorn was there. The department of psychiatry had Murray Saffron, a steroid chemist, who actually had a doctoral candidate working within the department of psychiatry who I believe got a Nobel Prize later on. Ted Sourkes was there working on catecholamines.

Malmo was doing work on galvanic skin responses, which was interesting. We had to interview patients who were hooked up to this and so were we. I used to tell people in the United States that it was a great way to learn about transference. You would be asking some delicate question of the patient and you could see her GSR rising and you would look over and yours was rising in parallel. Kral was there. He wrote a very good paper on the amnestic syndrome at that time. Robin Hunter, Tom Boag and Jim Tyhurst who all became Chairs. Clifford Scott, who was president of the International Psychoanalytic Association was there and Miguel Prado, a pupil of Cajal's who came over to work with Penfield and got seduced by psychoanalysis. Eric Witkower and a whole bunch of other people were there - all of them in one

department. It was a small building and everybody met, socialized and had tea together. You could talk about football or anything with them which was very different from being a young doctor in England.

In the Maudsley

Well I have never been to the Maudsley but even in Liverpool things were pretty formal. When I left England, I still had to meet the Consultant on the steps even though it was pouring with rain. So it was a much more informal and stimulating atmosphere. You saw a lot of patients, worked very hard, and you did a lot of things. For instance, everybody gave amytal interviews; everybody gave amphetamine interviews; everybody gave LSD. All of these things were on the go at that time, so you had a lot of experience. When I came to the States, it was astonishing how little people knew about psychiatry. It was hard to believe. You almost felt grandiose. There was a trainee that I met taking a course that I went to for the Boards and at that time he had never heard of Bleuler. He felt that any book that had not been translated into English for all these years couldn't be up to much - he ended up working in a teaching hospital.

Tell me about Charlie Shagass and his work because like you I think he has been under-estimated.

Well Cameron, by administrative fiat, said that everybody who came into the hospital had to have a sleep EEG. You, as the resident, had to go and give the sodium amytal. That produced the data for Charlie's work. It turned out the sedation threshold was a good predictor of response to ECT. He continued working in electro-physiology until he died last year in his 80's. He left there and he went to Iowa. When Sloane, who had been at the Maudsley, took the Chair at Temple, he discussed with me at dinner in New York who he should bring in. He brought Charlie and he brought Joe Wolpe - I advised him against Joe because of the psychoanalytic sensitivity but to his great credit he ignored me and the two best known people at Temple later were Joe Wolpe and Charlie Shagass. Charlie didn't go back to sedation threshold though he did study drug effects. He had a grant that ran for about 30 years and did a lot of interesting work and was the president of the World Biological Psychiatry meeting when we put on the 4th World Congress in Philadelphia.

Why did you come to the States?

Well I made one or two goofs in evaluating things. I really would have liked to have gone to spend some time in France. I thought Montreal might combine the best of Britain and the best of France, but I think it probably combines the lesser part of both. But, at any rate, when I went there I got paid $85 a month and my rent was $80, so I ate in the hospital 7 days a week. I think I also had a bit of nostalgia, which would be called culture shock in the States, but it's not nearly as good a word, and I was a bit fed up with some of the things. Cameron came and offered me a Fellowship to stay on, which I felt he should have offered me beforehand. Though, retrospectively, it was up to me to have asked rather than him to have offered. So, one weekend, I just applied to every training programme in the United States that was approved for three years that took foreign medical graduates and paid $300 a month. I posted all the letters on the Monday and on the Friday Cleghorn came and told me that I had been naughty. I asked him what he meant and he said that he had just had a call from Nate Kline in New York.

On the Sunday morning I was wakened early - I remember being cheesed off - and there was Nate Kline on the phone, this very breezy person, talking to me about a Fellowship in research, because in my one page hand-written CV, I said I was interested in research. I went down to visit a couple of times and he just kept phoning so I didn't go anywhere else to be interviewed. I just went to Rockland. Not a well thought out plan - it was just easier.

What was Rockland like at the time?
Well it was out in the country, pleasant grounds, a lot of space, horrible buildings. They were huge buildings; it was probably one of the last of the big hospitals where they felt that bigger was better. The wards were unbelievably crowded and in this place was a small group of people doing research.

You hear that the research labs were in their own building, which Nate had actually drawn the plans up for - there are all sorts of stories about him having marked out the floor-space ?
No, what happened was this. Per Vestergard had come over to work with us from Denmark, where he had been very influenced by Gjessing of periodic catatonia fame. He was collecting and analysing steroids in urine. He seemed to think if he only had enough urine he could answer all the questions. So every time he got money he bought a new freezer and had a whole basement filled with frozen urine. Then came the great New York electrical "brown out" and it all thawed. I don't know how Nate had finagled him into coming, but I think he expected he was going to have these marvellous labs and what he got was the toilets - it was a big room with 10 toilets with no seats and not even a curtain separating them. There was a picture of that in a Vestergard grant application, a picture of Per sitting on one of the toilets like "The Thinker", then a picture of him with a hammer and then a picture of a smashed toilet. So Per built his labs in what would colloquially have been called the "section" in New York. The actual ward was just a routine hospital ward the only difference was that there were much less patients.

Later that ward was re-designed so that there would be much more observation. Somebody who was interested in space and territoriality came to work on that ward after me. They chalked up the ward into spaces so that they could have somebody continuously recording who was sitting in whose chair. They showed that people had their own territory and their own space. I had known that just by watching my grandfather - nobody ever sat in his chair.

The research building was a hospital building and they would break down parts of what had been wards and make labs out of them or a Day Room. Before that, some of the wards in the hospital had just beds and the beds were much closer. There were wards where you could not have walked on the floor since the beds were so close together. There was one ward in that hospital that should probably have held 30 odd beds in a way that would have passed today's standards but there were 100. I actually read The Snake Pit when I was there and experienced deja vu and then I found out that yes, indeed, The Snake Pit was written in and about Rockland.

Tell me about the discovery of Reserpine by the hospital glazier

Right, this is something I really should have tried to document but I am inclined to believe it. Reserpine came from Jack Saunders who was working with Ciba at that time. There had been other people who had done some work with it in the States, but I don't think they announced it as dramatically, or with as much flourish. Anyway we had the research ward where patients never got any drugs because they were being followed "endocrinologically" and they were sort of almost untouchable. But on another of the very busy wards they had given patients Reserpine. Now, no one noticed very much - they were not impressed. Then the glazier in the hospital told somebody, "I don't know what they are doing on that ward but there has been less broken glass than in all the time I have been working here". That was the rating scale that showed it.

It says something about how far we have or haven't advanced. At the time, I wrote a grant on the notion that thyroid status would be a predictor of outcome, particularly with drugs. So, we did a study where patients were actually given either Reserpine or Perphenazine or Phenelzine to look at outcome and this involved a lot of rating. Many of the patients got better and I probably discharged half of that ward. I didn't like the waiting for Godot approach - just following patients and not giving any interventions even though these patients had never been on drugs. But I also had another ward elsewhere because of another NIMH grant I was brought in to bolster up a bit. The psychiatrist who had been doing studies had a pocket diary and on one page of that diary was all of the material for each patient for the whole study - the patients' age, all the demographics and the outcome and none of these pages were full. I thought that was awful. But before that, there was no documentation at all, so this psychiatrist had made a giant leap forward in terms of documentation of what had happened to patients. In practice, drugs were given to patients and then somebody said the patient had improved or hadn't improved and that was all the data.

Moreover, at least in some of the studies, patients were getting other drugs. Joe Barsa, who did some of the work with Nate Kline, ran a building with some 500 patients with another doctor. Now if you are responsible for 250 patients and have to give an annual physical and whatever else is required because you are responsible for the physical care of these people - there is no way you could do research. So, in point of fact, there were drugs that I know people got almost as a baseline treatment and then other drugs were added. That was the state of how things were at that time. It was only later that more sophisticated things were done. The studies that I did were predominantly open studies on patients whom one knew well and to whom you gave a new medication after they had been off medication for a month. Later we did some controlled studies as well. But all we were doing was saying a drug was active or was not active.

Can I ask you about Nate - who was he?
Well he was from Atlantic City originally. His family was made up of business people and he said that they were disappointed that he did not go into the business but went to Medical School instead. I'm not sure if I really believe that. He did a Masters in Psychology before he went to Medical School. Then, he went into the Navy and when he came out of that, he decided he was going to go into research. He applied for a job in research in Worcester where they gave him the job of Director of

Research - so he started at the top. He was there for a short while and then, somehow or other, he got this job at Rockland.

Actually, I'll tell you an interesting story that says something about Nate. I met George Nicklin at a cocktail party at the UN last night. George had been at NYU and he had a bee in his bonnet that there was a toxin that caused schizophrenia - a lot of people thought along these lines after LSD. His question was what would happen if you got a hallucinating schizophrenic and transfused his blood into a normal subject and vice versa. George was a Quaker and he recruited another young Quaker who had volunteered for some public duties and he volunteered for the cross-transfusion study. So we did a controlled study in which tubes were coming in and out of the patient and the volunteer and they did indeed exchange half of their blood. I reported somewhere that the patient got slightly worse and the control got married but nothing else really happened. Now he had tried to do that study at NYU and was told that it couldn't be done. Eventually they told him that if you go to Nate Kline, he could probably do it. So that is why he came and did it at Rockland and that was Nate - he was open for that.

He was an enthusiast in many ways. Ewan Cameron didn't like him. I think Cameron felt he was too flamboyant and also made extravagant claims. I think Cameron was a more knowledgable and a better clinician than Nate. Before reserpine, Nate had given a paper on "normalcy", trying to define what was normal. I think Dick Wittenborn came and helped him with some rating scales at that time. This was in the early 50s. Then Reserpine came along and that catapulted him into the limelight. Now this has to be seen historically against a background where everything in America was psychoanalysis. When these drugs were discovered it was not easy to convince people that they worked. Clearly Nate did a good job of this.

Then, somehow or other the Laskers became interested in mental health, with Mike Gorman, and they endowed money and gave the Lasker award. They were very instrumental with one or two other people in pushing Washington to get money for mental health. So suddenly there was more money for research than anyone knew what to do with. Jonathan Cole was really running around looking for people to give money to. Nate had been involved in an early study of reserpine for which he got the Lasker award and there was a lot of hullabaloo, so it was natural research monies would go his way. He had a good relationship with the Director of the hospital so I think he could also get monies and positions from there and from the State and from other outside funding.

The grant that I wrote could very well have been the first NIMH grant that Rockland had. Jonathan Cole, when he came to site visit, told me that it was a good idea for us to expand and ask for more money, but that I was too junior to be the principal investigator - which was true. The only problem was that Nate became the principal investigator and he really saw it as a book. Some of the other very eccentric people who were working around the place just saw the grant as a way to advance their own work and so they did the work in passing rather than with any commitment. Eventually, that grant which must have added up to over a million dollars - a lot of money in those days - produced little or nothing at all.

You would have come there just after the Iproniazid story had started rolling and presumably before Jack Saunders and Nate began to argue over who had really made the discovery. Did you get any impression over what had really happened? What was Jack like?

Well, Jack was a tall solemn gentleman who was apt to get bad tempered. I always found it was easier to deal with him face to face. He got more bad tempered on the phone than he did face to face. But, he was a bright guy and he had a lab and he did studies. Now Jack wasn't a psychiatrist, so in effect when I started doing the clinical work I took that away from Jack - even though I'm not quite sure how it came about that he was doing it in the first place. Thereafter, Nate was the senior and Jack the junior entrepreneur and the other people did the work. By the time I got a second grant, I was on my own and Nate never really interfered with what I did. Nate, at this time, was very busy going around the world, to Haiti and Tibet, giving lectures and he had a very busy private practice. Nate got into the limelight and Jack sort of stayed in the shadows.

Nate had a lot of the characteristics that would make him attractive company whereas Jack would have been a much more dull person socially. When iproniazid first came out, I remember Cameron talking about it. Nate had gone to some meeting where he was supposed to talk on one subject, but instead he made some pronouncement about Iproniazid. Jack somewhere along the line got upset - I think it was when Nate got his second Lasker award. Somebody should check whether Nate was on the selection committee at that time. There always was a rumour that he had nominated himself. Jack gave a presentation at the New York Academy of Science where he said it the way he felt it happened and that was that until Nate wrote an article for JAMA when he got the Lasker about how Iproniazid had happened. That is where I think Saunders took exception.

Clearly also Harry Loomer had been the person who actually gave the patients the pills. These were in-patients, so some of them would have suffered from affective disorders and goodness knows what. I have no idea what the population was, but it was an open study on a busy admission ward. Nate had also used some of it on his private patients as well. Looking back at it, it was remarkable that they ever discovered anything. They nearly missed Reserpine and, if you think about it, getting a new antidepressant when you have a busy ward or you have a busy private practice and you are give a drug openly could be very difficult.

So that was when Saunders got irate and in the JAMA article there were certainly things that, for me, were very dubious. In the article, Nate said that the next thing that happened was when Coppen in England and we here independently worked with Tryptophan and 5-hydroxy-tryptophan found it improved the rate of onset of recovery. Well, I had been in Bill Sack's office when he received a re-print from the Lancet by Alec Coppen about giving Tryptophan to patients on Monoamine-oxidase inhibitors, showing that it had an added effect. Sack's suggested using 5HT because he was doing biochemical studies with it. Nate started a study of 5HT after the Lancet article was published, gave it to quite a few patients very quickly and had his "24 hour cure for depression" published the same year as the Coppen study - but the idea was clearly Coppen's.

But he was quite happy to sell this as something he had come to independently ?
Yes. It was cleverly written - independently; it certainly was not a collaborative study. I never particularly believed the finding. In a very naive way, I had gone in to cover Nate's private practice when he went to Europe for six weeks in the summer - he needed somebody in the office. The FDA had decided, that if you treated patients, they needed a case history to give them some information. Nate had done a study for which he had no case histories. He might have had a page of longhand writing and that would be the admission history of a patient.

So the idea that you read in the obituaries that they got a very detailed work up by him first ...
No. That came along later. At that time essentially, I came in to reconstruct case histories. So we phoned and patients came in. I would ask them when they came here and that we were interested in getting information - which we were - and we asked them how they were feeling at that time and as best we could, we would get that information. And that was in many ways how I got involved. We did a study with desipramine.....

Well I was about to ask you about that. That was you, Nate and Brodie. What did you make of Brodie and how did the two of them get on together?
I liked him. I only saw them together once in Paris. Brodie had shown that imipramine was demethylated to desipramine. He was a well known scientist. Nate and I gave this drug openly to some 20 odd patients. I was a rather junior person who saw the patients and wrote it up but Nate added the conclusion which was that desipramine worked faster than imipramine and I was too junior and naive to argue about it.

This is the finding Brodie would have wanted.
Of course, but retrospectively, once one had got to know a bit more about depression it was silly. That is Brodie's only clinical paper I think which is quite amusing.

I went on working with Nate but I stopped after we did a controlled study in depression which I thought was foolproof. We had an independent diagnostician who saw the patient, did the initial interview and decided whether the patient would enter the study. Nate did the prescribing and then I saw them independently, and rated them. When I went to analyse the data, there were 39 patients and I think only 19 had no other drugs added to their regimens. I never wrote it up. That was when I decided that it was unlikely that we would ever do something controlled.

What was incredible also was the patients who came. I suspect that early on in his career, Nate had treated somebody in the Sephardim and so we had a lot of Sephardic Jews. Then we had patients referred by Albert Ellis and other, you could say almost fringe people, who were smart enough to know that a patient was not doing well and if there was an alternative treatment maybe that would be a good idea. Moreover, I think there were probably some other non-physician referrers. In all events we saw a lot of patients who did indeed make very dramatic responses. When you think of Listening to Prozac, you know we were Talking with Tofranil a bit earlier. We saw many patients because there weren't very many people doing that

sort of work in the city. In that area, I'm sure that Nate had a very positive influence both in terms of treating patients and pushing pharmacotherapy against academic inertia as well as resentment by people who were not about to believe this.

He kept, at least through to about the mid-60s, referring to the MAOIs as psychic energisers rather than antidepressants. Was this for legal reasons because of the Lasker court case or was it because a lot of people actually think that they were not the same kind of agent as the tricyclics.
Well, no. There was the paper from Mortimor Ostow and I think that concept probably was Ostow's. I would speculate that, to Ostow, the idea of a psychic energizer fitted in with a dynamic theory of depression. I don't see any legal angle in that.

But he had to use the concept later in court to sustain the case that he was the actual discoverer - he appealed to the paper that he had written with Ostow in 56 so that he could point to the fact that even before he found the drug he had proposed that there could be this kind of a drug. Did you ever feel that he was trying to play that kind of game?
No I did not. In the 58 paper, the presentation at the CINP in Rome, he talks about people resisting getting well and, to me, the concepts are very psychodynamic and very dubious. I think that there are indeed people who don't want to get well but they are not usually people with major depressions. No I think that he was a person of his time. Did you know that Nate was psychoanalysed by Paul Schilder? I remember him saying that it never took. I think people didn't know how to describe these drugs at that time. Don't forget that in some of the original tuberculosis studies these drugs were called euphoriants and they were called stimulants and so on. It was some time before anything was called an antidepressant.

But oddly enough Max Lurie as early as the 53 paper was talking about Isoniazid as an antidepressant. He had been giving it to non-personality disordered people and to people who were out-patient depressives and not to people on the backwards.
Well this is fascinating because, if you read these early papers, neither Kline, Crane or anyone else mentions that paper. Now I tried to follow-up on this after I last spoke to you because the Lurie paper references Bill Turner. I spoke to Bill at the December meeting. He is high up in his 80s but he was there with a poster. He took down the details and promised to get in touch me but I haven't heard from him and I don't know his address. But anyway, Bill had used Isoniazid as well and it is interesting that Lurie in Ohio knew of Turner's work and Turner was in Long Island and that is where Crane was working in the Tuberculosis Sanatorium when he picked this up. So it is strange that nobody mentioned these other papers.

Indeed and the Isoniazid story is quite believable because in Paris Jean Delay had used it as early as 52 and had said it was an antidepressant. How do you explain the fact that Max Lurie is unheard of?
Well, I think there are two things. People don't read the French literature and vice versa. And Lurie published his work in a Mid-Western Journal and not a national journal. Current contents or any of these things hadn't been invented. But you would have thought somehow or other that it must have caused some ground swell somewhere because there weren't all that many things that people were saying. The

other thing that I liked about the Lurie paper is that he said that his patients seemed to take about 2 or 3 weeks to get better which is much more impressive than these instant responses. But neither it Delay mentioned and clearly that was in the literature and should have been available. It is fascinating to think about it given the fact that Isoniazid is not a Monoamine-oxidase inhibitor. Wouldn't it be interesting if it had a totally different mechanism of action?

I worry about the fact that nobody knows very much about the kinetics of the MAOIs. There's very little work on that at all. Its conceivable that 85% MAO inhibition is going to be achieved by a dose of phenelzine that will give you enough phenelzine to do something elsewhere. With tranylcypromine you can get a tremendous amount of inhibition. In a study that I was a volunteer in I got over 80% inhibition after 10mgs, just 1 tablet. So that if we are really talking about getting 80% inhibition, 1 tablet a day would do most people and some people could do with 1 tablet once a week. This suggests to me that raising Monoamine-oxidase levels with tranylcypromine is not the mechanism of action and you have people like Jay Amsterdam who is treating treatment resistant depression with 90, 120, 140mgs of tranylcypromine and certainly I feel that I have seen people who did not respond to 30 but did to 60. So I don't know what is going on there. Its an interesting area for somebody to look at.

Can I take you to one of the other things that began happening in Rockland which was computers and Gene Laska. Can you fill me in on that development.

Well essentially we had the RED grant, which was for the Research in Endocrinology and Drugs, which was the one I mentioned before - Nate abbreviated it to the Red Grant. Somebody, I think Ted Cranswick, said that you'll have to watch that Nate because you will have people investigating you. Ultimately, I had somebody from the FBI come to see me about one of my nurses. She had belonged to a poetry reading society out in the Bush in Australia and there had been some leftish person there, and then she came to London when the "ban the bomb" marches were on. Anyway, she came to work with me and the FBI came and asked what was the work that I couldn't have had an American nurse do. I told them that she was working on what we called the RED project.

As it turned out, Sobell, who had been a spy, was in the same building. He was the guy who took off to Israel and was extradited from there to the US and then just before his plane landed in London he took an overdose of Nembutal and died in a London hospital. He was dying of Leukaemia anyway. He had worked in the other half of the building and had an adjoining door - the phone was on our side. Sobell was a psychiatrist, who, when he had left Lithuania, had been pressured about his family. He had done some things donkeys years before and because of that the phone was tapped and I guess they checked up on everybody who came to work there, which is where the nurse story came in.

At any rate we were collecting masses of data because in effect patients had their thyroid status measured all the time. Their steroids and behavioural ratings were also done and by the time we had a year or so's worth of data, somebody said "well what are we going to do with it". We didn't have a statistician. Then Gene Laska came from IBM to talk to us about the idea of having some computing skills there and eventually he came and joined us.

Why?
I think that it probably looked interesting. Of course very soon he had a huge grant for the multi-state information system - it was a 5 million dollar grant. They began computerising the hospital records and drug prescribing and all of that. Indeed, sometime in the early 70s, I ran a hospital service, in-patient and out-patient, where everything was computerised so that nobody wrote anything. You just filled in a mental status or an anamnesis and your secretary put these forms into the computer. On the way home and in the morning you got a typed report with a differential diagnosis. I think Nate probably saw that computers would become important. But essentially Gene Laska's first task was to manage the RED data. Afterwards he built up this other thing on his own with Nate's support.

We published a computerised mental state in the 70s which had a Hamilton and a Wing scale buried in it and then you had a narrative output - that was Scribe. It was a clever gimmick. I remember at a meeting in Madrid there was a NOSIE scale where you could get a narrative like a nurse's report from filling in this and you could get it in six different languages. You could fill it in in English and get the report in Russia or Spanish.

But there wasn't a big follow through with it. The doctors didn't like the computerised records. When I left, that all disappeared. I think they felt that you were missing the human touch. Certainly there was no way that you could have done a Sherlock Holmes - if somebody did have a short leg or a cross eye you're not going to get that. But, they were all legible and they were there forever and it wasn't a bad idea. During it all through the WHO connection, places like Indonesia went from having no medical records to having them computerised. The bureaucrats loved it because their inventory control of drugs became efficient for the first time in history. When everything was done by hand how did you decide how much you would get in the way of drugs for your building's monthly order? If there were suggestions of rationing, people ordered more than they needed and stored, but in the first year when the computers were used thousands of dollars were saved just because nobody could order more than they needed, just in case. The computer told them here's what you did last month and here's what you will need if your prescriptions are correct and that was that. So Gene came around that time and stayed. He has moved out of computers and into trial design and he has done a lot of work on carryover effects in analgesia etc.

When did you get involved with ACNP?
I got involved in the 60s because of Nate who said that this is a good organization and I should join. In the days when I applied, nobody had to write gargantuan letters of recommendation and all of these things. They were always from the very beginning unique meetings. Unique because of the site in the first place - they were always in the Winter in Puerto Rico in the week before high season. This was because it was cheaper and ACNP was essentially an East Coast outfit.

Why has psychopharmacology been an East Coast thing in the States ?
I don't know. From the start, you had Heinz Lehman in Montreal, Fritz Freyhan in Delaware, Kinross-Wright in Texas and the others in the State Hospitals, Nate, Denber and Tony Sainz up in Syracuse. The drug companies also were here so it

was easier to go to your own backdoor than go elsewhere. But, the early people were all hospital based which has always fascinated me. Psychopharmacology began in the State Hospitals and the VA and had to almost hammer the doors of academia down. Everywhere else in the world, knowledge begins in academia and spreads outwards.

It isn't only in this country but its throughout Europe.
Yes. It was because these were the people who were on the front line who had to do something and you are more likely to get the desperation treatments. I think people in the State Hospitals had this approach so that when drugs came into the State Hospitals they spread like wildfire. In order to control people at the time, you were using atropine, hyoscine and sodium amytal, as well as wet packs and ECT. When I came to Rockland, I couldn't believe that they gave ECT without anything. And, not only that, but the man who gave it wasn't very smart. When I talked to him about using muscle relaxants and so on he thought that was a bit silly. They simply had tongs and they went around just buzzing people. So there was a huge need for something to happen.

There had been a social revolution in Britain and other countries after the war, which drove mental health change. I think change in America came a bit later in mental health and it was driven here by psychopharmacology. It's hard to talk about British psychiatry without talking about the Maudsley, which certainly doesn't have the most therapeutic reputation. But you have to compare that with here, where in academic circles, nobody was doing anything. The other thing, that we do in psychiatry, which is strange is that we send away the most difficult patients to the State Hospitals. So, on the one hand, we look down on the State Hospital doctors and think they're not very good but we send them the most difficult patients. This is a strange phenomenon. Usually you send the most difficult people to the Chair of the department.

Another thing that was good about the ACNP was the way it was kept small. In the beginning, it was small and then they realised that they had accidentally stumbled on a good idea. They had these siestas on the beach or at the pool and you could get anybody and have a long conversation with them. When you go to other meetings if you want a long conversation with somebody you end up having dinner with them. There are many people, however, that I would like to have a long conversation with that I might not want to have dinner with and you can only have dinner once a day but there you could have had this three hour thing and you could get two or three people together and get the information you wanted. And then there was a real interchange of information at the workshops and other sessions.

So, they deliberately kept the size down as it evolved. That has always been one of the tensions in the organization because, on the one hand, it gets the name of being elitist and there are people out there who you know are clearly superior people that should be in any organization but they are not in the ACNP. But I think it has worked out quite well.

You were the President of ACNP at much the same time as the American Society for Clinical Psychopharmacology was being formed?

I was President in 92 and ASCP was formed I believe the year afterwards. The ASCP was really Gerry Klerman, Don Klein and Paul Wender who talked about it and invited some people to a meeting in Washington. I went along to hear what they had to say. It seemed to me that it was a good idea. The ACNP has an educational wing but it is a small organisation and by its very definition it has top-notch pharmacologists and psychiatrists, psychologists, statisticians, everything, but that's not a big deal for practitioners. So there was the question of the big gap between what we know and what is happening out there and who is going to try and narrow the gap. The idea was that the only way to do it was to have an organization where people who are in the front line would have some say.

It was clear to me that there would be some tension as it would overlap with the ACNP. But they are two different constituencies. ACNP is a small organisation that is heterogeneous and they are never going to be able to do the educational job that it needed. It is conceivable that this organisation will be helpful because already they have twice as many members as ACNP. While most of the people who are on the board are people who have reasonably distinguished research and academic credentials, there is a hope that as the organisation progresses it will be less involved with name recognition and with democratic organisation, teaching and other problems as well as research. I think there is enormous room for doing this kind of thing because you have got dozens of people who have seen a lot of patients who could provide information if they agreed to do something jointly by electronic bulletin board or whatever. The organisation is still a fledgling organisation but I think it is pretty stable. Its not a breakaway from ACNP, but something in parallel.

Its probably many people's dream in medicine to go "eponymous". You've done this. How did the Simpson-Angus scale come about?
We first started measuring extrapyramidal symptoms in the early 60s and already by 1964 had published a paper on this, which included a rudimentary rating scale. I finalized the scale thereafter and we used it from 1965 onwards but it was not until we combined a series of papers in 1970 that the scale was ever published. The reason for the delay was simply that we were a very busy unit. Scott Angus joined me at this time and he was a very pleasant fun person to work with. We did the writing up which then appeared as a monograph in Acta Scandinvica.

The reason for developing the scale was simple. In the early 60s, little was known about the relative potency of antipsychotics. Given that they appeared safe, people were apt to give them until they saw some side effects. To an extent everyone believed that if there were no EPS you did not have an active agent. We evaluated new drugs continuously and it seemed to us, therefore, that if we could quantify extrapyramidal symptoms, this would be a better way to measure relative potency than the effect on psychotic symptoms.

I modified the scale further in the 80s for two reasons. One was that originally all the work had been on inpatients and, therefore, we had items that required an examining table on which the patient could sit with their legs "hanging down, swinging free" but I took this leg rigidity item out as it did not contribute very much. I also took out head dropping and substituted head rotation. The other major change was to include akathisia.

That leads nicely onto Clozapine. As I understand it there was a point when shortly after Clozapine was first banned in this country there were only about 4 people who were using it - you, Nate, Herb Meltzer and one or two others. What do you make of the Clozapine phenomenon ? I sense you are not as enchanted with it as some other.
Well it clearly is a unique drug. The first time we gave it to patients, everybody in the ward knew very quickly that it was something different because we saw people getting better and we never saw any extra-pyramidal symptoms (EPS). So I think it is more active than any drug that we possess. I think it is a drug of choice for people with akathisia or any tardive condition particularly dystonias but also dyskinesias.

But can you criticise study 30 on the basis that half the patients were being poisoned with huge doses of comparators and lo and behold the other half who weren't been poisoned did slightly better.
That was certainly a critique here. You could make an argument, and I don't know that I absolutely believe it, but I think it is still up to somebody to disprove that the beneficial effects of Clozapine are totally EPS-related. We have data from the 60s where we just happened to have somebody rating EPS and somebody else rating Psychopathology and we found that emotional withdrawal and EPS parallel each other beautifully. Other people have shown that too. But I'm not sure that anybody is clever enough to separate negative symptoms from the akinesia and Parkinsonism. The question of how much more efficacious than other drugs it is is, I think, still up for grabs. We are getting figures in some places that a substantial number of people are going back to work. I haven't seen that. The dramatic cases I have seen have been affective disorders.

Oh now that is interesting. Because it is a tricyclic of sorts...
The people who took up the bed and walked have been clearly people with affective disorders or who were very sensitive to EPS from typical neuroleptics. I have a tape of a young woman who was very hebephrenic and would come in dishevelled and disorganized, talking gobbledegook. If you gave her any drug, she would turn into a beautiful neat tidy young girl but she couldn't stand any of them because of akathisia, so she was always coming back in. When we gave her Clozapine she had no problem. We have done a study, which is unpublished still, a controlled double blind cross over of 100, 300 or 600mg of clozapine, where patients get 16 weeks of each dose, the idea being to find out which worked the best. The bottom line was that we got something like a 24% response - 12% of them during that study and the other 12% when we raised the dosage to 900 mg. Unfortunately the 900mg was an open tail but I believe that after 48 weeks in a research ward you are not going to get much placebo response. We have blood level data and some of the people at 600mgs did not have adequate levels. This was an older and more chronic group of patients. I guess my bottom line would be yes it is better than anything else we have got but perhaps not as good as some people are saying. In terms of Clozapine and Risperdal, John Davies in his metanalysis came up with about 30% extra benefit for Clozapine and about 15% for Risperdal.

Given that we are advancing on many fronts, I think that if you took a treatment resistant population and did the original study over again you might get a lesser response because you have creamed off some of the patients and you are left with even more-treatment resistant patients. But this idea that they go on improving

forever I think is just social learning - their symptoms are gone and they are beginning to do other things.

What about the question of akathisia and dysphoria with other neuroleptics
Yes. Haloperidol produces a lot of akathisia, perhaps more than any other drug, though one would need to study this to say it more clearly. In our Clozapine study we had 44% akathisia in a lead in period with 10mgs of Haloperidol and almost 0% with clozapine. One of the nice things about the new atypicals coming along is that they will finally teach us what the dose of Haloperidol is. In the Sertindole studies, for instance, it is quite clear that 4mgs of Haloperidol is active, not quite as good as 8mg but the EPS at 8mg are very substantial. We did a study comparing three doses of Fluphenazine - 10, 20 and 30mgs - and we did not see any difference in outcome between the three dosages. When we looked at predictors apart from chronicity of illness the most important predictor of poor outcome was akathisia.

By akathisia you mean something other than just the actual movement of the feet you mean something closer to dysphoria?
Well perhaps. When you read the Barnes scale, you think that a lot of people have subjective distress. A lot of people do, but I think as you get more chronic patients, they don't complain at all. So our definition of akathisia was the one that was recorded by the staff, not by a scale.

Very often your average prescriber fails to appreciate the effects of this - having seen grown men cry on 4mgs of Haloperidol, I'm sure that if you have that experience even if you know there is an antidote for it it is going to put you off taking the drug.
Oh yes. Well on the question of why do patients not take their medication, Ted Van Putten, who did not do controlled studies of these things, was I think absolutely right when he wrote that this was a big cause of people not taking medication. The young girl that I talked about would be a good example. People have difficulty describing it - we say people feel like jumping out of their skin. My explanation of akathisia to residents is that you feel like you have a constant infusion of adrenaline - just slightly more than you can tolerate. It is extremely dysphoric and indeed we wrote about that same little girl in one of our papers a long time ago when we discussed psychotic exacerbations caused by neuroleptics - iatrogenic psychosis you might call it. There she was crawling around on the floor until her knees bled and was importunate with the nurses. Illness or akathisia or both? Parkinsonism is easy to recognise compared to this. One of the problems with akathisia is you can get it on a 1mg of Haloperidol - at a sub-therapeutic range. Phil May in terms of patient dysphoria and George Awad have done some nice things about this. But it may all go out of the window - it wouldn't happen with Clozapine.

Let me take you back to your roots and ask you to comment as a Scot on either the Prozac or the Listening to Prozac phenomena and the whole ADDH thing. We don't have ADDH over in the UK. Perhaps we do but culturally at the moment we don't. Who is right.
You don't have Borderline Personalities either. I think the guy who wrote Listening to Prozac could have been Talking to Tofranil 20 years earlier if he had not been preoccupied with psychodynamics. There was no question that in the 60s we were referred patients by good psychotherapists who knew they were stuck in treatment.

The cases were mild endogenous depressions and you prescribed drugs and you got marvellous responses. Over my career, what I see is that what I once believed was not treatable, and then later might have said was personality merging into the tail-end of an illness, has come into the treatment range. Incidentally there was a poster yesterday claiming that fluoxetine was beneficial for some normals. Richard Belon was a co-author.

If people had asked me 20 odd years ago what sort of people responded to Monoamine-oxidase inhibitors, I might have glibly said people that you think would do well on psychotherapy and who don't. I think Peter Kramer had a big investment in psychodynamics and that over time fluoxetine gave him a rationale to escape - it was something different so his old teacher wouldn't have been right and he wrong and so he used fluoxetine. The other thing about fluoxetine is that it didn't have the side-effects or dosing problems of tricyclics - one size fitted everyone. Now who are these people who respond - I think they are in the group I have just referred to.

I think of the Columbia people, Jean Endicott and Wilma Harrison, and the PMS studies. There was a certain sub-group of PMS people who were really chronic dysthymics, who really only become very symptomatic pre-menstrually leading to their inclusion in PMS. Now these are the people you can treat with anti-depressants. Clearly if you treat females with tricyclics, whatever else they get, they are going to gain weight, as with the the MAOIs, so I think that Prozac got all of that market immediately. In the US non-psychiatrists were targetted by Lilly and the one dose strategy carried the day with these people.

At all events physicians, including psyciatrists, who not have prescribed tricyclics began to prescribe fluoxetine. For some psychiatrists there had been a little bit of religiosity, a belief in the sanctity of the self which you invade that when you give drugs, so that you have this notion that the real treatment is the talking. I think these people began to give drugs with fluoxetine. A good example recently was a case that a resident presented to me of a woman hospitalised for her diabetes. The intern, who had been a doctor for less than six months, realised she was depressed and gave her fluoxetine. She didn't respond. When the resident presented the history to me it was clear that she had been hospitalised a year or so before in our ward, had been treated with nortriptyline and did very well. So I said well you must promise me that you will phone that intern and say that we in psychiatry don't mind you treating depression but you must take a history. I doubt if that intern would even have treated a patient with a tricyclic.

When I was working in Philadelphia, I got referrals from some very good therapists. They would have somebody who did not meet all the criteria for major depression but had some of them. Now, if I had been seeing the patient for the first time, I probably would have waited a bit before I did anything. As they had done the wating, I would just give them an antidepressant often with surprising and rapid results. So that is the area that people are getting into as part of the Prozac phenomenon. I'm also sure there are a lot of people who are getting Prozac for the wrong reasons.

ADHD is a different phenomenon. It has become a very respectable middle class illness. It offers the possibility that I didn't fail at school because of being stupid or I didn't fail this, that or the other because of my aptitude but because of course I had

an attention deficit disorder and that makes it all respectable. I am being cynical but there is a lot of it going around with people self-diagnosing themselves but on the other hand it exists.

Yes I would agree with you that it actually exists and it has always been there and should be recognised and there is the adult form too but when did it begin to roll. How has it come to be such a huge thing now.
I don't know how much Paul Wender has to do with that. Paul Wender is a psychiatrist who was involved in the adoption studies in Denmark. He lives in Utah and came out with the Utah scale for attention deficit disorder and has done a lot of studies.

The areas that I would see that everybody should be aware of include having a history when they are young. And you do see cases who have difficult concentrating and focussing who when you give them a stimulant do much better. I can think of one case I saw who I gave a stimulant to - the first thing he noticed was that he felt more relaxed. The second thing was that he could concentrate better. The third thing was that he could sleep better and fourth thing was that he got a shift in his appetite so that he ate more. Everything it would have done to me, it did the reverse to him - it relaxed him, made him sleep more, had a contradictory effect on his appetite etc. He was a good case but it must be there when they were young, which it was in his case.

Clearly the diagnosis has been overlooked but going back to the Prozac thing, how far do you guys here go over the top with these things. Enthusiasm seems to be a US thing. There is a ground swell from the critics of psychiatry that this is just one more instance of the pharmaceutical industry raping our children.
Well I have heard people saying that but clearly you get lots of mothers who testify the other way round. When they showed that methylphenidate had an effect on growth, it was a big boost to the critics but then Rachel Klein showed that growth caught up over time. But clearly you would like not to use drugs if you can get away with it. When you ask Rachel Klein why don't the Germans or Swedes use these drugs, she would say they have more discipline in school. Now I would rather have kids getting discipline in school than getting amphetamines. But that is the choice and it is clear that the American people want it both ways.

It is just beginning to hit the UK now; the stories are beginning to appear in the media and the BAP are beginning to think that we should convene a Round Table to look at the question of paediatric psychopharmacology.
Well you should do that anyway because there is a fair amount of research going on. Tom Cooper has been measuring Methylphenidate levels and metabolites in these kids for some time. It would be good to draw attention to this and to conduct disorder which is also a big problem and again, to me, something with huge environmental influences. A colleague of mine drew up entry criteria for a study of conduct disorder in terms of the aggressive acts and verbalizations but he had to reduce the entry criteria because few were meeting it and of those who did on admission, 50% didn't meet it after they were in the hospital for a week. Now in the new Managed Care setting they are all going to get drugs coming in the door and they are going to do very well because 50% at least would do very well anyway. The

same is true of adolescent depressions. Willy-nilly you get the 50% response rate by changing the environment. But then, these kids with conduct disorder are sent back to the ghetto and behave the same way. What is the influence of drugs in all of these things?

What happened to Nate in the end. Something went badly wrong didn't it?
Well he got involved with the Endorphin story and he was giving it to patients who were depressed - I think on a one time shot - and that caused a bit of concern. Endorphin was very hard to get but C H Li, who discovered growth hormone, made Endorphin and brought it over and gave it to Nate. Now I think a lot of people in the ACNP and elsewhere felt that it was a bit inappropriate to do this. The preparation had never been tested in any which way at all and it was precious stuff. But Nate finished the study on July the 3rd or 4th and it was read at the Royal College meeting on the 5th and published in Archives in September of the same year. I think he pulled in all his favours to get something published in Archives inside two months. Anyway the FDA looked into it and the upshot was I believe that Nate was not allowed to do any more clinical research.

How did you read the battles between Nate and the Maudsley over Lithium with Michael Shepherd on one side and then Nate and Heinz Lehmann and others on the other side.
I think Nate would always be critical of anybody who questioned his clinical or therapeutic beliefs. When I teach residents about Lithium I always give them the Blackwell and Shepherd paper to say that it doesn't matter that they were wrong because what they did was to provoke people into doing the right study and that is what we needed. There is no excuse for giving treatments that we can show are effective but haven't proven it. I think people felt that Michael Shepherd and Barry Blackwell were a bit highfaluting and anti-therapeutic.

It was extraordinary bitter. I mean there were some very nasty correspondence in one or two journals.
Yes well I think that Nate occasionally liked a good fight. I remember something that Linford Rees wrote about monoamine-oxidase inhibitors and Nate didn't feel he got enough credit and he wrote to Aubrey Lewis to complain about Linford Rees. Now that just seemed a bit childish to me but there it was. But afterwards Nate invited Linford Rees to the Carribean islands for a shindig to which some lady donated annually.

What did you make of the Haiti angle. Did running Institutes there for the poor compensate for charging $500 an hour or whatever was for his private practice.
Well in Haiti, in the late 50s, Nate somehow or other talked a group of pharmaceutical companies into building a hospital and he had a very good film maker do a documentary. I always remember when I saw it Ted Cranswick, an Australian who had been in New Guinea, sort of shuddered and said "that guy has got beri-beri". The patients got perphenazine and multi-vitamins in Haiti. What you saw in the documentary was that before treatment they were living in a ruin and after they were living in a ward and they were washed and clothed and well fed and so on. That was the Haiti connection. People came back and forth. Nate, I think, got decorated but it sort of fizzled. I would just say it was an expedition that Nate went

on and that he enjoyed it. I wouldn't have seen it as the most altruistic thing, even though there was altruism involved. You could say well it doesn't matter what the motivation was, the outcome was important and it was good.

The $500 an hour was much later. I think he was co-opted into that by some of the staff that he was very friendly with. Even though he was a big name, for a long time he did not charge big fees until I think somebody told him that he was making a mistake. At least to begin with he carried a lot of people for years who were difficult patients and he did not raise their fees. Then they had a new broom in the office and raised the fee and there was an exodus of patients. Patients that I had not heard of for years phoned me.

Jack Saunders by the way is still alive. He just retired a year ago and I think he is living up near Nyack. He did a psychiatric residency later but he was never someone that people were very friendly with. Now Nate could be a lot of fun. With Nate you would have told jokes but I can't imagine telling a joke to Jack. There was almost a boyish awkwardness about him whereas Nate had all of the hypomanic characteristics and charisma.

Toward the end he used to go around with a poodle is that right?
Yes he had a dog and of course he grew a huge head of white hair and a huge beard. He looked like Hemmingway at times, though he wasn't quite as robust. He was a bit eccentric with that. On the other hand you always had a feeling that he did a lot of these things very consciously. He would usually dress quite conservatively before that, but somehow or other he got into leather pants or something in his 60s.

So do you think you made the right move ending up over here as opposed to staying in the UK.
I think so. I intended to come back and I just kept postponing it. I did speak to Aubrey Lewis in New York about going to the Maudsley when I had some publications. He said that they were not taking anybody unless they had membership and then Max Hamilton would tell me that I should finish my DPM, do an MD and all of these things. I never did any of them and then when the Royal College was founded they made me a Fellow so I told Max that he had been wrong, which was quite funny, since for once he could not argue.