4 *Frank Ayd*

The discovery of antidepressants

Let's begin with the CINP. If you look at the history the way it's been written these days, people talk about the importance of a meeting that was organized in 1957 by Silvio Garattini, but you and Hanns Hippius have drawn my attention to the fact that there was another meeting in 1957 that was organized by Ciba. Do you want to tell me about that meeting?

To my knowledge, Silvio Garattini's was a scientific meeting at his place. It was not intended to be an organizational meeting. The meeting that Hanns Hippius and I refer to was convened for the express purpose of discussing the formation of an international scientific organization devoted to psychopharmacology. The meeting was held in Milan. It was attended by people from various European countries, North America and Australia. England, for example, definitely had some representatives. Among those from England, Frank Fish stands out in my mind. He was an impressive fellow to meet. Richard Boardman I believe was there. Most of the people that were there actually had done a lot of the early work in psychopharmacology. From the United States there were Sid Cohen, Herman Dember, myself and Nathan Kline . . . I think Fritz Freyhan was there but I'm not really sure. From Austria, there was Hans Hoff and Dr Arnold, who was Hoff's assistant. From Switzerland there were Paul Kielhotz, Jules Angst, Walter Poldinger, from Germany was Hanns Hippius and . . . from France, Pierre Deniker, Jean Delay and Pierre Lambert were there.

Ernest Rothlin?

Yes. He was definitely there. I can't recall who came from the Scandinavian countries. The idea was to assemble a group to discuss formation of an international organization to enhance communication between researchers.

So this was almost completely clinical.

Yes, definitely. We met in Milan for about four days and at the end, there was a decision to organize. The Swiss were given most of the organiz-

ational duties because they were right there and could deal with the people at WHO and also deal with Ciba, although Ciba did not try to control the organization in any way. Ciba's major function was to contribute the money to fund the travel expenses for the people who participated.

The decision was made that not only would we organize but we would start right off with an international meeting that was to be held in Rome. Since it was to be held in Rome the decision was made to extend an invitation to Pope Pius XII to address the meeting and indeed he did. The meeting was held in the fall of 1958 and that was the beginning of the CINP.

How did the Pope end up being at CINP?

Well, the invitation was extended to him and he accepted it. He was provided with copies and reprints of a number of articles because he wrote his own speeches. He was particularly interested in medicine which was one of the reasons why he agreed to do this. After his death, all his addresses – about 200 different talks to medical organizations – were published, and there were several hundred pages. The Pope was supplied with information and he wrote his own speech. It was a remarkable speech for a Pontiff and particularly for a layman, in that he appreciated immediately the potential of the psychoactive drugs – he spoke primarily on chlorpromazine, some on reserpine but not a great deal and of course by then we were in the early days of the anxiolytics. So he had some idea of what the potential was.

The importance of that meeting was that, for the first time, we assembled, not only psychiatrists but pharmacologists, psychologists, and a number of basic science people. The idea was to have an exchange of information between the clinicians and the basic scientists and so this was a revolutionary meeting. It attracted a large number of people and really provided a basic membership for the CINP. It, to me, was perhaps the most important meeting in the early days of psychopharmacology.

It also gave people a chance to meet each other. I was one of the fortunate ones. I had already travelled. I had been to England, Ireland, Germany, France, Italy, Switzerland, Spain and Portugal. So I had covered Europe pretty well and I knew many of the pioneers in psychopharmacology, but very few Americans knew them outside of Will Sargant, who frequently came to the United States. This meeting started an interchange and so now Hanns Hippius was no longer a name, he was a person that you could relate to and that was true for Angst and for Poldinger and for other colleagues.

It makes a big difference doesn't it? Its curious how often you can be hostile to a person's ideas, when you see them put on paper, but when you meet the person you get a completely different perspective.

Sure, for example, Mike Shepherd was there. Now my initial reaction to

Mike reading his papers was that he's negative. At that meeting, the first day we sat next to each other on the bus from the hotel to the meeting centre, so we had a half hour to talk and my impression of him changed completely. Also Pichot was there and my initial reaction to him was also negative – until I met him and then it changed. And I think that probably happened to others, when they met me. The meeting led to a lot of useful exchange of ideas, as well as a formation of mutual respect for people. In my judgement, it was most important thing that happened to psychopharmacology in the 1950s from the standpoint of really having a dissemination of respected material.

In the early days the CINP hit problems. When the meeting was held to found the ACNP you hinted at some of these problems, some of the clashes of personality, you mentioned I think that you had been left off the membership list and . . .

Yes, but whether that was deliberate or accidental who knows. There were some power struggles. Some of the early men in psychopharmacology were somewaht vain and looking for promotions and prestige. You would expect there would be some conflicts and a power struggle, but that was true also within the ACNP.

Well, can I ask you about ACNP? It appears that one of the reasons to organize the ACNP was because CINP was seen as being too European – and very much linked to the major European companies.

Well, we were thousands of miles away. That made a big difference and you have to look at it from the perspective of the people who wanted to participate actively in things. They had to get funded, which in those days was not yet an accepted thing. They either had to persuade the institution where they worked to pick up the tab or pay for it themselves. Consider one like myself. I'm in private practice. I have to get a locum while I'm away. I've got to pay him, the plane fare, the hotel bill and other costs. It was not inexpensive to do. And I think it is better to have a national group and that the national become very active in the international. The ACNP now has become a powerful force within the CINP, very much so.

Who were the key people behind getting ACNP going?

Ted Rothman. Ted was an unusual fellow and a very personable gentleman. He was an analyst in Los Angeles, who had an interest in what the drugs were doing to his patients. He felt that there ought to be an organization of people interested in psychopharmacology. He talked to Leo Hollister, to me, and some others about his idea. Then he talked to friends at Ciba in the pharmaceutical industry. The decision was made to get a group together. We met in New York at the Barbizon Plaza Hotel for a weekend. It was a good mixture of people. There were people from academia, State Hospitals, private hospitals, people from

different geographic parts of the United States and Canada, and people who were just starting in psychopharmacology.

There were some very forceful personalities as well.

Some very strong personalities. Ted put together a list. I don't know exactly how he did that. I know he called a few people and asked if you were going to do this who would you want to have at the meeting? When you look at this list, I was in private practice, Henry Brill, of course was working in the Commissioner's office in the State of New York, Bernie Brodie was at the NIMH, Eugene Caffey was with the Veterans' Administration, Jonathan Cole had been at NIMH, Bill Dorfman was a board certified internist with an interest in psychosomatic medicine. He was one of the founders of the Academy of Psychosomatic Medicine and editor of its Journal. Ed Dunlop was connected with a private psychiatric hospital in Vermont. Paul Feldman was from Kansas, Paul Hoch was from New York State Psychiatric Institute, Doug Goldman from the State Hospital in Cincinnati, Bernie Glueck, the Institute of Living. Some were primarily interested in basic science; others had no real interest in basic science.

Heinz Lehmann put it to me that one of the reasons that either Ted or others were keen to have you there was because of your awareness of the legal angles.

Yes. That would be, in part, because when I was at Rome, I taught a course called Modern Medical Moral Problems. My students were ordained priests studying for their Doctorate in Canon Law. Part of the course covered informed consent, making a valid contract, the autonomy of the individual, and human experimentation. I had some pretty strong feelings about doctors giving medicines to patients without telling them anything at all about the risks and benefits. I didn't think that was right or ethical. Anything that could damage psychopharmacology bothered me because I saw this as a really great blessing for mankind.

Think what it was like to be connected with a psychiatric hospital prior to 1952. There were hundreds or thousands of patients for whom you could do very little. You had hydrotherapy, insulin coma, and ECT, a lot of bromides, paraldehyde for controlling some symptoms. You had patients who were in the hospital for 25, 30 or 40 years and they weren't 60 yet. Abandon hope all ye who enter here – you're not going to leave except in a pine box. Then consider the dramatic change that took place when chlorpromazine and other antipsychotics, and the monoamine oxidase inhibitors, were used properly. Although limited to a certain number of patients, MAOIs offered an alternative to ECT. Then came the tricylics. It is difficult to accurately described the remarkable changes that took place in psychiatric hospitals in the 1950s.

One real value of these drugs in the early days to me was they stimulated inquisitiveness. When you swallowed that pill, what happened – where

did it go, what did it do? When I gave ECT, I wondered when the current passed between the temples and crosses through the mid-brain, what did it do? I was so glad Bernie Brodie was there because he had similar interests. Already we were thinking in terms of, what is now the pharmacokinetics and pharmacodynamics of drugs.

Yes, well that comes through quite clearly. I think it's actually probably yourself and Brodie, who actually contributed the most towards the ACNP organizational meeting. If you look at a word count, I'm sure the two of you will come out as . . .

Yes, we were active participants. Bernie was very interested in trying to explain why and how drugs worked. It was very dramatic. Take ECT – a psychotically depressed patient is given 10–12 treatments at most and he's normal. Then you give this very psychotic individual chlorpromazine and the first thing you saw, of course, was sedation and then gradually, particularly if he was acute with what we call today the positive symptoms, these would disappear. Even some patients who had predominantly negative symptoms, did respond. So this revolution was going on, which I saw as being important, not only to the current patients but to the patients of the future, and I give a lot of time to this – that is one thing my wife will tell you. Sometimes she used to say 'you're like John the Baptist – you're out preaching what's coming'. That's true: I lectured all over the place.

What about side effects. You were one of the first to report some of the side effects of these drugs. The whole issue has to have been tricky in terms of you guys weren't really sure what was going to happen. Some people got well, okay, but . . .

We weren't sure. There was minimal animal and human data. Basically it took a lot of courage because we really didn't know what was going to happen. Yes, I had a fatal agranulocytosis and that will wake you up, if you've been kind of cavalier. I will never forget within the first 6 weeks of chlorpromazine, I had 2 patients who got jaundiced. The first one had only gotten 2 doses. He had just been hospitalized – it turned out in fact that he had a viral hepatitis – whether chlorpromazine brought it to the surface I don't know – but it kind of rocks your boat if you've admitted someone to the hospital and he has 2 doses of this medicine you're giving and the nurse calls you up and says 'hey, this fella's turning yellow on us' and you go see him and he's got a full blown jaundice. The second patient who got jaundice, I didn't tell her this was a risk because I wasn't sure in the first patient whether chlorpromazine had any role in the jaundice. This was a woman who had been chronically agitated and so forth and really was more of an agitated depressive than anything else. I gave her chlorpromazine and when she returned for her next appointment she was jaundiced. I said to her 'Mary, how long have you been like this?' and she said 'doctor you've tried so hard to help me and I do feel better,

even though I'm yellow'. So I said 'well I hope you've stopped the medicine' and she said 'oh no, it's helping me'. So I learned that chlorpromazine can cause jaundice but if you keep it up the jaundice doesn't necessarily get any worse. In fact, if you can keep it up, which I did with her, it went away. So it was a transient hepatic reaction to chlorpromazine. But you also get a hint as to how valuable these drugs were to patients.

I also reported the first case of severe dystonia with chlorpromazine. In fact, I filmed this patient and I took it to SmithKline and French and showed it to them. They had never seen or heard of this and they arranged for me to show the film at the annual meeting of the American Neurological Association in Atlantic City. I showed it there and I got everything from hysteria to 'I don't know what this is'. There were a couple who said 'well it looks like torsion dystonia' but there were some differences, in their judgement. Anyway, I realized that I couldn't go around and just extol the benefits of the medication; I had a moral obligation to keep track of the side effects and to try and present a balance; not frighten people away but fulfil my duty to give them as much information as they need and can handle to make an informed decision about their treatment.

I soon realized that if you stop neuroleptics, relapse occurred pretty quickly. So it was obvious that neuroleptic therapy is equivalent to treating an epileptic or a diabetic: long term treatment is going to be important. I got into that very early. I lectured about one year's experience with chlorpromazine, and at the CINP meeting in Munich I reported on 10 years' experience with chlorpromazine. I gave a paper at the World Psychiatric Congress in Montreal on one year's treatment with imipramine patients and then wrote a paper on long-term perphenazine therapy, which the *New England Journal of Medicine* published. This helped psychiatry. Psychiatrists were not publishing in regular medical journals. My paper on drug-induced extrapyramidal symptoms was a lead article in JAMA in 1961, and I'm proud to tell you that when the 100th anniversay of JAMA was celebrated they listed the 100 most frequently quoted articles published in JAMA in 100 years. My paper on EPS was No. 20 (Ayd, 1961). There were only two by psychiatrists among the authors of these 100 publications.

I had an article on chlorpromazine in JAMA showing photographs of patients who were quite severely anorectic, who looked like they were from concentration camps and who after chlorpromazine gained weight. I reported neuroleptic-induced galactorrhoea. I even had the local heath department analyse the breast milk, collected from women who were lactating on chlorpromazine, and it was absolutely the same as normal breast milk in terms of fat content and other constituents. I was one of the first to report false pregnancy tests on phenothiazines. This was all new. We had to really know what were we doing. It really was a puzzle. Here's a drug that can twist a man like a pretzel, can make him stiff as a

board, produce jaundice, cause agranulocytosis, sedate people and people could take a huge amount without dying. It caused all kinds of endocrine changes, some people had total amennorhea, others had galactorrhea. It was very interesting – what's this drug doing in the body and how is it doing it? This led to endocrinologists getting interested in it.

I got letters from all kinds of specialists based on the articles I had in JAMA and the New England Journal. It changed attitudes towards psychiatry and that was a very important thing. I can tell you the pioneers in psychopharmacology were looked upon as quacks and frauds. I was accused of being no different than the guys who sold snake oil in the wild west days. I gave a lecture in New York on my experiences with chlorpromazine and one of the discussants was the Past President of the American Psychiatric Association, Nolan Lewis. Dr Lewis was very gracious and complementary but at the end he said 'I have one word of advice to the audience, hurry up and prescribe this drug while it still works'. There was such scepticism in the early days.

There was more than just that though. There was hostility in certain quarters that the proper treatment is psychotherapy and this is a quick fix that is going to be harmful to both you and the patient.

That's right. You're not really getting to the problem. You're masking the problem. Oh yes that was certainly true. The analysts dominated, and here you're giving a pill and not talking about the Id, the Ego and the SuperEgo. And you're not even considering the psyche and that was just anathema. They missed the point. The point was sure we were enthused, look what was happening, but we weren't forgetting that this was happening in a human being and just as you don't treat a diabetic with insulin and diet alone, there's a whole lot else that's involved in psychopharmacologic therapy. We were doing psychotherapy but not dynamic psychotherapy. You had to explain to patients what this medicine was, what it could do, why they should take it, how we thought it worked and you had to encourage them to be patient because it wasn't miracle medicine. If you give chlorpromazine and the family would say 'oh yes he's quieter but he's still hearing voices and he's talking about the crazy ideas he has' because you don't get an antipsychotic effect early. You had to educate the family as well as the patient.

I personally was convinced of the value of proper pharmacotherapy. Sure I had a bias – you couldn't experience this and not get a bias – but I tried to be balanced about it. But then I attracted a lot of attention, there's no question about that. Here I am, relatively young, out of medical school not even 10 years and I'm testifying before Congress about these drugs and I'm on different programmes. Ciba had a weekly television programme, prime time Sunday afternoon in the US, called 'Medical Horizons'. It originated almost exclusively from hospitals and it covered surgery and obstetrics, internal medicine and so forth. They asked me if

I would do the first one on psychiatry and I did. I did an electric shock treatment on national television and I learned how ill-informed my colleagues were. Some physicians wrote me saying I faked ECT because they didn't see a convulsion. They didn't know what succinylcholine could do, they had no idea what giving brevital sodium meant or what the new equipment was doing in terms of controlling milli-amperage and all the other things that would influence ECT.

I had a neurosurgeon on the programme with me who had done some lobotomies and we had some patients who had had lobotomies. These were not transorbital, they weren't the original pre-frontal, these were stereotactic psychosurgery and these people made quite an impression.

It also provoked a lot of envy and hostility. That didn't just happen to me. Heinz Lehmann was defending psychopharmacology, in the early days, at a public meeting and a guy walked up to him and smashed a pie in his face. Heinz just wiped it away and continued. I could have never done that. I would have been so angry. But this was the kind of hostility that you encountered. There were people who risked their jobs. Henry Brill risked his job.

Henry Brill's move to introduce chlorpromazine to Pilgrim State Hospital was one of the big breakthroughs. Why did he take the risk?

As you know, initially, psychopharmacotherapy was not embraced by the psychoanalysts who dominated American psychiatry. Some viewed psychopharmacology as a threat to be opposed. Their hostility was not verbal. If the introduction of CPZ by Brill resulted in serious adverse effects, the opponents would have gone for his head. Henry knew he was taking a risk but he believed that patient welfare justified the risk.

In the US, 1956 was a big year for psychopharmacology. The annual meeting of the American Psychiatric Association was in Atlantic City. I gave a paper on chlorpromazine and reserpine. The first papers on meprobamate were presented. Now in part, because of some of the promotional efforts, there was a 'whispering' campaign – have you heard about this drug, meprobamate. It's just as good as thorazine but without the side effects – the press got more interested than usual.

Meprobamate is a drug that has vanished at least in the UK but it had a big impact during the 1950s. When the history gets written of this period, it gets written in terms of the antidepressants and in terms of the neuroleptics. Meprobamate is written out. What role did it play?

Oh I thought it played a very important role. Actually first of all it was an effective anxiolytic and it didn't have some of the disadvantages of the barbiturates. It is a barbiturate-like product but it was a little bit different. When it was used initially in lower doses and people were put on it and left on it for long periods, it proved to be a fairly safe drug and there weren't problems with dependance and withdrawal per se. As time went

on that became a problem and it became, in the eyes of many doctors another barbiturate, but the important thing it showed that you can have a non-barbiturate, which can do many of the things that a barbiturate can. So, it actually was responsible for Roche coming up with the benzodiazepines.

So why did Librium replace meprobamate?

Well, there were two reasons. First of all a very small company had meprobamate and when sales began increasing, they had no sales force. They had cross-licenced with Wyeth, who produced it as Serax. The company was in a sense a one-doctor company – Frank Berger. He was a good man, a very fine man but he was doing more administration than research. Eventually, combination products with meprobamate replaced meprobamate.

Getting back to the APA meeting.

Yes, the most important thing was, attending that meeting was Mike Gorman. Mike Gorman was an experienced press man who was national executive director for the National Association of Mental Health. He was a very astute man. He heard the message and he then approached Nathan Kline, Henry Brill and myself and said 'if you doctors will come to Washington I'll arrange for you to appear before Senator Lister Hill's Committee and you can tell your story. Maybe we can get these people to put up some money' because at this point there was little being done in Washington at all in any way to help psychiatric patients. They were considered hopeless, incurable.

We agreed, and Nathan, Henry and I went to Washington. We appeared before the Congressional Committee. We told our story and we asked for funding and for the establishment within the National Institute of Mental Health of a psychopharmacology branch. Senator Hill was impressed. I was not sure when we left how much of a persuasion we had exerted on any of the other Committee members but if you get the powerful Chairman convinced, he can move the rest of his Committee and so money was made available.

There was an organizational meeting held in Washington. That was an interesting meeting because it brought together pharmacologists, statisticians, psychologists, and a good number of psychiatrists. There was a good mix of elderly and young people. Ralph Gerard, from Michigan, who is famous for his statement 'behind every twisted thought is a twisted molecule', chaired the meeting. Ralph had trained Jonathan Cole and so he played a role in the appointment of Jon Cole to head the psychopharmacology branch at NIMH. That was an excellent choice.

Tell me why. Because he was actually pretty young at the time.

He was. Jonathan had a good, open mind. He is energetic. He got

involved in the ACNP and became very active. He, Bernie Brodie, and I formed a committee to discuss issues that we were all interested in. As a matter of fact, we had all been in a meeting in New Jersey that was sponsored by Warner Lambert, which was interested in MAO inhibitors. On a train back to Baltimore and Washington, we talked about some of these issues and expressed concern at the lack of real work going on in this area. We were giving drugs without knowing what we're giving really and why it's working.

There's a feeling now that ACNP may not be going down quite the right route that it may becoming too neuroscientific. It's led Don Klein to form ASCP, what do you think?

Well, I'm not surprised. Don approached me several years ago. We were the young turks when this started and the initial idea was to have an exchange of information between clinicians and basic science people and for a while that was certainly true. But now what's happened is coming from the basic sciences to the clinician with no input from the clinician back to the basic science people. You only have so much time to give to things and if you come to a meeting like this and 80% of it has no real meaning for you in a pragmatic way, as a clinician, you have to ask yourself 'am I investing my time, my money, my energy in the wrong way?' And this is what basically Don was asking and Max Finx was asking. Oakley Ray will tell you that he's heard from me more than once about what I saw coming. It came a little faster than I thought it would and that's both good and it's bad. Don Klein is a very intelligent man and a good man. He has the power to make this new College a very viable and meaningful organization for a lot of young people who will never get in the ACNP. You know we have a restricted membership.

Has that been a bad idea – the idea of a closed membership?

Well, it's one that is been debated off and on for years. In the beginning I thought it was good because if you're going to have a really viable organization people have to know each other and respect each other and have some admiration for each other and be willing to contribute. So the idea was to have a small number of people – almost like old boy club meetings, where everybody got to know each other. There was enough time for the papers and to go out on the beach for an hour or two for nothing more than serendipity. Then we got accused of being exclusionists, so it was decided to enlarge membership, but everytime you increase the membership you had less time for any exchange of ideas. That to me has been the worst thing that has happened. This is a very big meeting now. It's 700 or 800 people.

There are still people who are very upset that ACNP is not taking in any more members. Last year I think we took in four new members; that's because someone has to die or retire. We may have a suggestion

from within the membership and I'm not saying this facetiously 'hey you're getting old, please resign and let somebody else come in' . I've thought about it, I really have. I'll be 75 soon. I miss, what to me was the greatest teaching force of this College, the individuals whom you could challenge and they could challenge you and make you do some thinking.

You were also involved in helping get BAP off the ground.

Well, the first person I really talked seriously to about it was Max Hamilton. Max and I became friends when he came too work at St Elizabeth's in Washington. He would come over to Baltimore with Tony Horden and visit me at home and have dinner with my wife and I. When we were in Rome Max visited us for a couple of days. Max was very interested as to what was going on in the USA. He knew of my role in the ACNP and CINP and he lamented to a certain extent that nothing like this was really happening in England. But he never said that he was going to do something about it.

Then David Wheatley, who I got to know at NCDEU meetings started coming to some of the ACNP meetings; he asked me if I would share my experiences with the founding of the ACNP with him and with Tony and I agreed to do that. I went over to London and met with them and then we did some by correspondence. I encouraged him to go ahead because I felt that it would be important to British psychiatry. I have attended some BAP meetings.

Let me take you back then to the founding of the ACNP again. You say Ted Rothman was one of the key people. Any other key people?

Joel Elkes was important. He was the first President. Joel, of course, was working in Washington at the time. He was at St Elizabeth's Hospital and he had established a fairly good reputation before he came here becasue of his work in England. He was doing controlled studies and this was something that was new. Joel is a very personable fellow and a very articulate and diplomatic man. We needed someone who, in a sense had all of those qualities because we were hoping we were going to have to do a lot of dealing with the public and with the government, a lot of dealing with the industry and even a lot of dealing within the profession. Joel was highly respected and he was going on to become the Professor and Chairman at Hopkins, one of the most prestigious medical schools in this country, so he was really ideal. He fitted the bill and he was enthusiastic but he wasn't overly-enthused; he was a very prudent man and he was a good leader. He was a very good choice.

Talking about the psychopharmacology service centre brings up Gerry Klerman – where did he fit in?

Gerry was a man with a tremendous mind. I envied the clarity of his

thinking and his logic and his courage. Gerry didn't hesitate to speak out, regardless of how unpopular it might be. Gerry initially was not so much interested in the drugs but applying the drug to the right diagnosis. He was very interested in nosology, in establishing good criteria for diagnoses, but he was also very impressed with what he was witnessing. He went from the Carolina's to Washington for a short stay before going from Harvard to Yale. Then came the opportunity for him to be an administrator at NIMH and, American politics being what they are, you had to have a broad based support, I campaigned for Gerry because I felt he was an extremely ethical man, with an awful lot to offer and he got the appointment to ADAMA.

Gerry was very interested in comparing non-drug treatment with drug treatments. He became a champion of the drugs but not to the exclusion of psychotherapy – he was very interested in extracting the best out of both psychotherapy and pharmacotherapy and he devised interpersonal psychotherapy.

And the use of the two together. Whereas it had always been the case of either drugs or therapy one or the other, he introduced the idea that maybe they could help each other.

Absolutely. And that was very important and he funded some very important studies. He took a very strong position – it wasn't a very popular one but it was a strong position – about the shortcomings of psychoanalysis, not because he was anti but he asked where's the proof of its efficacy. He urged and urged that studies be done and he tried to get funding for that but that was rather difficult to do. First of all even designing a controlled study of psychoanalysis is very difficult.

Just from reading the literature in that period, there was a feeling among the analysts in particular that the rating scales were beginning to be used in drug trials were a travesty of evaluation – they argued that you could not evaluate people's responses in this way . . . and it actually took time to change the whole climate of opinion on this one.

Absolutely and Gerry played a major role in that. Methodology was something in which he was very interested. He was very interested in seeking the truth, even though he was not a well man. His diabetes was giving him some trouble but he was tireless. He worked very hard for the good of the psychiatric patient and for the good of psychiatry. He had a capacity to fuse people – to get them to work together. He was a great organizer. You couldn't help but like Gerry. Those who knew him would work hard for him.

What about the role of Nate Kline in all this because he was one of the group who went to Congress and changed their mind to come up with the money.

He came up with a lot of money. He had a lot of influential patients and

he travelled in an influential circle in the New York area. Nathan in my mind contributed very much to the advancement of psychiatry. It's very hard to quantify it. He was a very flamboyant fellow. He tended to be a little hypomanic on occasions and he tended to get carried away. He would embellish things, not greatly but, at times, he would rub people the wrong way – not intentionally, it was just his style. He knew how to persuade people and he knew how to use the press . . . and he used it.

In your article in Neuropsychopharmacology *(Ayd, 1991) you quote the phrase 'that it's not always the person who makes the discovery first, it's the person who persuades the world of the importance of the discovery, who gets credited with a discovery'. In terms of who actually discovered the antidepressant use for iproniazid, did Nate snatch this out from under other people's noses? There are these two articles, which sit side by side in the same journal, one by Nate and the other one by George Crane. Who was really the first?*

Well that's very hard to say. Nate didn't keep the best records in the world. He had a big operation going. He had a very busy private practice and he was working part-time at Rockland State, primarily seeing chronically ill people, and not seeing a lot of true affective disorders – manics maybe or psychotically depressed patients. Be that as it may, he at least recognized that there was more to this than first meets the eye. Now, whether George Crane ever realized that or not – I have my doubts, I don't think he did.

I knew George well. He and I became friends when George left NIH and came to Baltimore. He was an intelligent man there's no question about that and a fairly astute observer. If you read some of his early observations on tardive dyskinesia, you will appreciate how astute he was but he didn't really appreciate the significance of what he saw with iproniazid – Nate did. And Nate grabbed that ball and ran with it. And he deserves a lot of credit because even though there was some initial hepatotoxicity and some fatalities with it and Marsilid was pushed off the market pretty promptly, that didn't deter Nate from still saying MAOIs are good drugs. Otherwise, I think we would have had the death of the MAOIs, in this country at least. It's to Nate's credit that that group of drugs was saved in this country.

Nate got two Lasker awards for his work with reserpine and his work with the MAOIs. That was most unusual and that made a few people envious to say the least. When he was working with reserpine he was dealing with Ciba and with Jack Saunders, who was employed by Ciba. Nate persuaded Saunders to leave Ciba and join him at Rockland State. Jack was very bright. He liked Nate and they worked very hard together. Jack felt he should have received more credit than he did for his work on the MAOIs. Jack sued Nate. That was the beginning of a series of court battles over who really made this discovery.

As you know, in 1970 Barry Blackwell and I organized *Discoveries in Biological Psychiatry*, to which I invited all the people who had made the

major discoveries in biological psychiatry up until that time. Now here I was faced with George Crane and Nate Kline – and how do you decide what is the truth? Frankly, I talked to the Roche people and it was their impression that it really was Nate. I did that because I didn't want to offend George Crane and deny him an honour if it really was his. I was quite convinced that it was not George who had made the important observations here. No doubt he saw the effects and he may have contributed some input but on his own he would have never taken it to where it was taken by Nate. That was my impression; it's still my impression. So I decided to go ahead and we had Nate on the programme.

I had a similar problem, also at that same meeting, and that was who really was the fellow who made the true clinical observations and really could be considered responsible for chlordiazepoxide – Librium – being known as more than just another barbiturate. There were two people who had done early work. Joe Tobin out in Eau Claire, Wisconsin – a friend of mine, a very nice fellow, and Irv Cohen. At that time Irv had moved to Houston but when he did the chlordiazepoxide work he was at Galveston, Texas. Again, it was Irv who really capitalized on what he observed. His paper was published in JAMA – it went to a peer reviewed prestigous journal and it got accepted. In those days, it was unusual for a psychiatric report to be published in a leading non-psychiatric medical journal. Maybe to ourselves we were coming a long way but to the rest of the medical world we were still suspect. Joe Tobin's article was in a non-peer reviewed journal. I approached Roche for their view and they used Cohen's data. Irv was the first, who presented the data in a persuasive way. So, we finally decided on Irv Cohen and thank God that decision was accepted by Joe.

Before Nate and George set to, the idea that the MAOIs might be euphoriant was around, wasn't it? You have an early publication on these 'side effects'.

That's right, Dr Serra who was Chief of Medicine at Franklin Square Hospital where I was Chief of Psychiatry was interested in tuberculosis. He worked part-time at a hospital which had a large TB Unit. He said to me one day, 'Frank', have you ever looked at this drug isoniazid'. I said 'no', he said 'well, that's a pretty good drug for tuberculosis but there's another one called iproniazid, which I'm not convinced is very good for tuberculosis, but it sure peps up patients, you might want to try that for some of your depressed patients'. So, he told me how it had been widely used and that it seemed to be reasonably safe.

And this was before Nate had come out with his paper.

Oh, yes. In those days you could accumulate drug naive patients who had not been exposed to anything pretty quickly, because there wasn't a whole lot being done yet. I frequently would call general practitioners who referred patients to me and say 'if you've got someone who's depressed,

who would be willing to be a participant in a study, I can take care of them and it won't cost them anything' – that's how you got patients. I submitted this one-page report to the *American Journal of Psychiatry* which published it (Ayd, 1957) and Nate Kline blew his cork. He wrote me a letter; he felt that I was stealing some of his thunder. And I wrote back and said 'Nate, the truth of the matter is I didn't know you were working with iproniazid. This was an idea that came from the Chief of Medicine who works with TB patients and I just tried it'. And it was more of an energizer than really a true antidepressant. If it had been a really good antidepressant, I don't think Roche would have capitulated as quickly as they did, when the few cases of hepatitis came along.

To change from one group of antidepressants to the other, you were at the talk that Kuhn gave in 1957 on imipramine – one of the few people still around I'd imagine because there were about 12 people there, as I understand it.

You're right there were very very few people there. Now, I have to tell you one of the reasons I was interested. I had a relative who was manic – depressive and who had his first depressive episode at college. Within a year he had a spontaneous remission and went back to school. He graduated and was very successful. In 1929 he had another severe depression and was ill for three years. He had to be tube fed to keep him alive and he had to be kept from killing himself. The next serious episode occurred when I graduated from medical school. I was determined he wasn't going to go back to a hospital if I could prevent it because of what I had seen of psychiatric hospitals as a medical student.

You had absolutely no interest at this stage in doing psychiatry.

None whatsoever. There was a psychiatrist in Baltimore who was doing ECT. I called him. He came and saw my relative and said 'yes, he's got to have ECT'. David, the first ECT treatment I ever saw was on one of my own relatives. I was at St Joseph's Hospital in Baltimore then, and the ECT was done in the radiology department with sandbags under his back. There was no ECT machine as we have now, no succinylcholine, no Brevital sodium, nothing. You saw what a real grand mal seizure was and the scream, not really a scream of pain, but as the air was inspired. Quite an experience. It was a horrible one for me.

Your relative was prepared to have the treatment, was he?

If I had to say we got informed consent, no. I made the decision to go ahead. He was in no condition to at all. ECT worked. Eight treatments and he was out of it. He had mild memory impairment for a while. You know if you're a classical unipolar or bipolar, episodes get closer and closer together, as you get older, and tend to be a little bit more severe and so forth. Two and a half years later, my relative had another episode and again he received ECT. This time it was started earlier and the psychiatrist

who was doing it had the latest machine. We had succinylcholine and brevital sodium. He recovered very nicely, some memory impairment but within six months he was back at work. So that's why I was interested in antidepressant treatments.

Tell me about Kuhn's talk at the World Congress first.

Well, it was dramatic. There were very few people in the room. Kuhn is a rather tall man, slender, very soft spoken, very cultured, very dignified and very erudite. He gave a very, very nice description of the clinical manifestations of the illness he was treating. He didn't say, 'this is a good antidepressant'. He said 'this is a good drug for depressed patients who have *these* symptoms'. That was basically his message. He was very impressive. He mentioned the more common side effects, primarily the anticholinergic and some of the sedative effects of imipramine. He gave a very convincing talk.

I'm not sure how many people in that room really appreciated that we were hearing the first announcement of a drug that was going to revolutionize the treatment of affective disorders – and do more than that. If one thinks of what imipramine can do. It's not just an antidepressant, it's an anxiolytic, it's an anti-panic. We would have never had all these things if Kuhn hadn't given a very lucid and convincing paper. I'll tell you David you want to read the English translation of his first paper – it's as good as the Gettysburg address.

Why did it take Geigy so long to market this compound. They did the studies in 1956, in 1959 they marketed it – which was a long time compared to chlorpromazine.

The important thing about Kuhn's paper was not that he said that imipramine is an antidepressant, although that was very important, but he said in what kind of depression it is most likely to work. Kuhn was not well known then. I didn't know who he was. No one I asked prior to the meeting knew anything about him at all. And I think in part that would have been one of the reasons why there were not a whole lot of people there to hear this history-making paper. I subsequently came to know him. He is a man who's basically a philosophical psychodynamic psychiatrist who is a very ethical physician who has devoted his life to working with the mentally ill in a public hospital in a little out of the way location in Switzerland. He had not done any drug studies before imipramine, but had been carefully observing patients and keeping meticulous notes on them.

If you look at the structure of imipramine it looks very much like a phenothiazine. The early neuroleptics were selling like hot cakes then. Geigy's animal data suggested that imipramine had phenothiazine-like properties and therefore they felt it possibly could be another phenothiazine anti-schizophrenic drug. They looked for investigators, who had access

to a fair number of schizophrenic patients. They borrowed, I think from Rhône-Poulenc's experience, that the best way to get this done is to go to the guys who work in the large public hospitals – Pierre Deniker and Jean Delay in France and certainly in the United States chlorpromazine got on the map when the work was done in the large state hospitals.

Kuhn was working at this mental hospital with a fair number of patients, who were not exposed to any medications yet, and I presumed that played a role in the decision to ask him to test imipramine. Kuhn did that. He was a very careful observer and he noticed that some improved and some didn't and to him the question was, what was the difference between them. He found that the difference between them was that those who had depression did reasonably well compared to those who were without any depressive symptoms. Then he asked himself, what kind of depressive symptoms and he looked at the vegetative symptoms and concluded that if they had predominantly vegetative symptoms and particularly the basic biologic things – disturbances in sleep, appetite, sexual drive, etc. that these were the people who were more likely to respond.

Kuhn clearly also realized this was not the only thing: that dose played a role and that low doses were ineffective – you had to give a minimum of 75– 150 mg and in some patients even a little bit more. He made these observations and he reported them to Geigy.

Was the idea there that you couldn't have an antidepressant because analytic theories suggested there was an object loss and drugs can't replace objects?

Well, that certainly played a role in some of the people's thinking because there were analytically orientated people in Switzerland, as everywhere else, and Kuhn himself was analytically inclined. Now the other question that immediately came up was 'well, what do we have for depression now'. And the answer was simple. We had ECT and the only drugs that had any possible antidepressant effects were the psychostimulants, mainly amphetamines at that time. Ciba had already had a bit of work done on methylphenidate. The question was with what would imipramine be competing? Are we going to have a pill that will do what ECT does? Nobody thought that. Is it going to do anything more or less than the amphetamines? Is it a drug that could become addictive? For the business people, the central issue was, okay, let's say that this an antidepressant in a pill, how many people get depression, how widespread is the illness depression? No one had any answers for that. These business people were sharp enough to realize that. You might say 'oh, it's very common', but how common, how many cases are there per year.

In a sense, at the time depression was quite rare because the only people who had depression were the ones who were so bad that they ended up in hospital. No one else was prepared to admit to it. At least in Europe there wasn't the outpatient psychiatry that you had in private practice in the US.

Well, let me tell you how I got involved in this. I published in 1961 a book called *Recognising the Depressed Patient*, and this was based on 500 patients who I saw in a general hospital, not in a psychiatric hospital. I became well known for that – it got very good reviews and as a matter of fact, Merck Sharp and Dohme bought 50 000 copies of it and distributed it, not just to psychiatrists, but to family doctors and internists and so forth. It was translated by Jean Delay into French and then subsequently into a German edition and it did very well. That brought attention to me in this area. Now no one really knew the answer to the question of how common depression was. There were no epidemiological studies worth a tinker's damn. In fact, epidemiology as we know it today in psychiatry didn't exist then. So here you have men whose livelihood depended on making the right decision for the company because if the company succeeded, they succeeded and if they made the wrong decisions they were fairly certain that their days were going to be limited in a highly competitive industry, as it was becoming then. So they asked some very pointed questions.

The advent of imipramine sparked many studies, including some done by WHO, which culminated in Sartorius' very well-known paper, in which he said on any one day there are at least a 100 million people in the world with clinically recognizable and possibly treatable depression. Well 100 million people, that's a big market. That's a very big market but in 1957, that was a way off. Unless there was a motive for doing these kind of things, which had never been done, are we going to market a drug that's only going to be good for a few hundred, or possibly millions?

Let me move on and ask you, since you were also involved here. As is often the case, the first drug in the field helps to make the field but the second drug becomes the best-selling one, and you were involved with amitriptyline, do you want to tell me about that?

Well, amitriptyline's animal's data suggested it too had phenothiazine-like effects. Merck approached me, along with Doug Goldman and Fritz Freyhan and Nate Kline, and asked us to look at this. It could have been 1957/58, I don't remember the exact date. I made the observation that it had some antidepressant effects. In part, I was stimulated to look for that because this is what Kuhn said and here's a drug, structurally almost identical to imipramine except for a slight change in the nucleus. So I reported my observations to Merck and that stimulated Merck to investigate further.

Hoffman La-Roche also had amitriptyline. In fact, they had synthesized amitriptyline in Europe as a possible antipsychotic. When Merck applied for the patent, they applied for the patent as an antidepressant, not as an antipsychotic. So they got the patent in the United States – and once you get it here it's world-wide basically. My understanding of what transpired then was that there was a gentleman's agreement between Merck and

Roche that they would, literally split the world market. Merck got the United States and Canada and they got Australia and I think the other countries were areas that both companies could compete and essentially that's what happened. That was a very satisfactory arrangement for both companies apparently, until Schering and Merck entered into an agreement with the combination of perphenazine and amitriptyline, which Schering marketed as Etrafon in the United States and Merck marketed as Triavil. Well that product turned out to be a huge commercial success. Family doctors loved it because it was sedative, it had some definite antianxiety as well as antidepressant properties and the amitriptyline protected against perphenazine's potential of causing extrapyramidal symptoms.

It wasn't long after that when Roche filed a patent suit in the Federal Courts in the United States. I was deposed in it, mainly because I said it was an antidepressant. The decision favoured Merck. I have never seen the court decision.

As I was saying to you, I think Linford Rees even found in a trial that he did that it wasn't superior to placebo which caused him quite a surprise because he clearly believed that it was an antidepressant.

Oh yes, I know Linford did because I gave lectures in the UK under Merck's sponsorship and he was the man who introduced me at many of these dinner meetings that were held around England, except in Max Hamilton's territory, where Max did the introductions. And there was Tony Horden, who did a huge study with amitriptyline and showed that it was an antidepressant drug. But there again even though you said to the company, look this is an antidepressant, the pragmatic questions were 'how common is this illness? – we don't want to market an orphan drug so to speak'. Nobody really had any idea. That's one of the reasons why Merck picked up on my book. Here at least was something that showed that this is not something that's unknown in the non-psychiatric hospital world. It's a very common thing and, in fact, these people are numerous in medical and surgical clinics. So now you've got something that you could advertise.

I did another thing. I made a film on the depressed patient, which was very well received. Not only was it done in English but we got people at the United Nations to do a simultaneous translation and it was sent around the world in 12 languages. It also won an award at a film festival in Tokyo. This was an unusual film in that it showed patients in a doctor's office. What we did was the patients agreed that they would be filmed but they didn't know when. A hole was put through the wall, over my shoulder and back but the camera was between books and unless you were really looking for it you wouldn't see it. The filming was done on a random basis. The patients may have come in three times and the setting was always the same but sometimes no film was made. And then the

relatives sat with them and described what these people were like at home. It was a quite successful film as a teaching instrument.

Is there a sense in which drug therapies are always going to have the advantage on things like cognitive or behavioural therapy because there's not going to be an industry doing that kind of thing. Could you see a video which shows what the cognitive therapist does being sold in blocks of 50 000? Is there a sense in which the dice is loaded toward drug therapy because there's money to be made out of it in the way that there isn't for other therapies.

Probably. After all, if you're a business man and you've been funded by investors, you've got to produce a return for them. And it's the old story, success breeds success too. If products do well, you get more investors, you get more money to do things. That's why it took lithium a little while to get on the market – there was no one fighting for it. No drug company could get a patent on it. There was a big question of medico-legal issues associated with its use.

So you picked amitriptyline out and when you looked back and it was the people who were depressed that were the ones that seemed to pick up . . . but did you actually test it out on people who were depressed before the patent?

Initially no. Initially these were all presumed schizophrenic patients or schizo-affective, and once I became convinced that this drug did have some antidepressant properties, I switched over and looked at it now in people who were specifically diagnosed as having an endogenous depression. I did not give it to people with neurotic depression.

What did the others think – Kline, Goldman and all.

Well, initially they hadn't made the same observations. Later they did. They didn't attack my findings at all. I think there was some scepticism and probably if I were in the room and somebody else was saying this I might be sceptical as well. But I think that the people who needed the most convincing at that time were first, the medical people and then secondly the management people who had to make that important decision – how much money do you invest in this new product?

There are so many complexities to what's behind a drug getting on a market and for what indication and so forth. Temaril, for example, is a phenothiazine drug – I looked at it for SmithKline French and it turned out to be predominantly an antipruritic type product and not an antipsychotic. Fritz Freyhan did a fairly large study in schizophrenics at Delaware State Hospital and got negative results basically except for the sedative effects, but I found the antipruritic effects and how did I find them? Well, I had a patient to whom I had given this drug who had had an allergic condition with a lot of itching before starting Temaril, and suddenly the itching stopped. The historical truth is, at that same time

three of my children came down with chickenpox and they were driving my wife and me crazy. So I gave it to them. And they stopped itching.

Remarkable.

I reported this to SmithKline – in fact I wrote a paper on it – because I then gave it to a number of patients who had various pruritic conditions and it worked. Here was a drug that was originally looked at for a psychiatric use and it ends up being used by the dermatologist. Just simple clinical observations.

You've also met one of the other key people – John Cade. Can you tell me about John and about the problems trying to get lithium into the US because it's been quite a saga.

Well, John Cade was a host for me in Melbourne when I was on a lecture tour. John met me at the airport and we hit it off. We had a mutual interest. We were both Catholic, both Jesuit-trained. I happened to be interested in beautiful scenery and nature and John was very much interested in that and he took me to see some lovely gardens. We went out to some State parks together. He was very very good to me.

What were the problems he had using lithium then – because they didn't have the brand name forms that we had.

Well, first of all it's a naturally occurring product that couldn't be patented. The real problems were that he hadn't done much in the way of human studies. His work had been with his guinea pigs. He gave the lithium to some chronically manic patients – not really full blown mania, thank God, because if he had it wouldn't have worked. We know that severe mania is not responsive to lithium but hypomania or low grade mania is responsive. That took a lot of courage because there was no way to measure blood levels. It was just careful observation; he was fortunate in that he guessed, so to speak, the right doses. He was very prudent. He started with a very low dose and depending on response he gradually escalated. He carefully observed and kept good notes on those patients. I've seen all his notes. They were meticulous. Then he wrote his famous paper which was published in the *Medical Journal of Australia* (John Cade, 1949). Up to this point John Cade was unknown outside of Melbourne.

In this country, as you know, we had had the problem of lithium being marketed as a salt substitute for cardiac patients resulting in a lot of lithium retention, lithium intoxiciation and a number of fatalities. So much so that lithium was banned.

Mogen Schou deserves a lot of credit because he picked up the ball and ran with it. He did the very important controlled studies and the good observational studies. John was not interested in becoming a great research man. He was a very happy administrator of a public hospital. A very devoted family man. Limelight did not appeal to John Cade. He was

a very humble person and as a matter of fact he was somewhat reluctant to be on the programme for *Discoveries in Biological Psychiatry* (Ayd and Blackwell, 1970). When I first wrote and asked him to come, his reply was 'it's not on the market. Why do you want me to come over and talk about the discovery of a drug you can't even get in the United States'.

But at that point I knew there was a good possibility that it could get on the market. A fellow by the name of Paul Blatchley had picked it up. He was a fine psychiatrist, very much dedicated to alleviating suffering in his patients. He was a pioneer in multi-monitored ECT. He worked primarily with affective disorders, therefore the antipsychotics did not particularly appeal to him. Antidepressant drugs did but his real interest was lithium. He was convinced from what he had read and from what he had done on his own with a local pharmacist making it up for him and by careful clinical observation, he became quite convinced that lithium was an extremely important drug. I was doing the same thing in Baltimore but not on the scale he was doing it.

Paul wrote letters to Congress but got nowhere. He decided to take the next step and that was to turn to the media. He called me and asked me to join him. We did a series of interviews with some media people and that really generated some real interest in lithium because actually when you stop and think about it, you had two choices for a severe manic. One was ECT, but the number of treatments you would have to give almost invariably is going to cause some memory impairment. The other one was to use the neuroleptics, which meant that if you use the high potency ones you're going to get some extra pyramidal symptoms and if you use the low potency ones like chlorpromazine you're going to get a lot of sedation and a lot of postural hypotension. So we really didn't have a good treatment. That's why I willingly joined Paul Blatchley.

He picked some magazine with a national circulation and that really got to families who were faced with the problem of what do you do for a relative who's manic and you don't want any more ECT and you don't want to make zombies out of them as you would with fairly heavy doses of neuroleptics. So there was pressure brought to bear and in the meantime, fortunately, Schou was doing what he was doing in Aarhus and also ways of measuring lithium were developed, so the stage was set and people began writing to their congressmen. Actually SmithKline was the first to market lithium in this country. In part, because they felt they had a duty to it. They wanted to maintain their image as a leader in psychopharmacology. They were making money on all their other products, so this was a chance to make available what could be called an orphan drug to people. That's how we got lithium.

There were two or three other people who played a part in helping raise awareness, one was Nate Kline.

Oh, yes. Very much so. And there again it's another testimony to Nate

really fundamentally wanting to advance the science of psychiatry and to provide alleviation of suffering to people. Admittedly he could be quite dramatic and so forth but in actual fact he was highly ethical and a highly motivated person, so again Nate picked up the ball. I never published on lithium. I had no reason to. My interest was being able to help a few of my patients.

In the early days the person who prescribed the drug would be seen as the 'druggist' and often in quite a few of the hospitals the medical people would try to make sure they were uncontaminated by prescribing. I seem to remember something about you being the only person prepared to prescribe when you were in the Navy.

Yes, at Perry Point. I was in the Navy and was assigned to the VA Hospital at Perry Point. I was giving ECT. And that gave me an idea of what could be expected before we got the drugs. Syphilis was around and we had Pick's disease and Alzheimer's and a lot of organic patients and you really got a pretty good idea of what uncontrolled mania is like, what a severe depression is like and the people who get very negativistic and almost catatonic. There was a certain feeling of frustration that there were so few things you could do.

Isn't it curious though that in a sense although the neuroleptics don't cure schizophrenia, they go very close to curing some forms of it. You don't see classic schizophrenia anymore – you don't see the same hebephrenias or catatonic pictures any more, that I still saw when I entered medical training, in the early 1970s.

That's right. I now go down to Eastern State Hospital in Virginia, as a consultant. There I see psychopathology that I will never see in my office. I saw a first case of acute neurosyphillis with a delirium recently, the first since I left Perry Point. I've seen Pick's disease there. I have seen some very bizarre forms of excessive reactivity, over-activity. One patient there that we've checked now for three months has never slept more than two hours a night. He has a pervasive developmental disorder. He has been in that hospital since age 6 and he's now 60 but he's never had a physical illness and suddenly he developed this very peculiar syndrome, which has been totally refractory to all interventions. Now I am sure he has some organic lesion but the CAT Scan and MRI were negative.

Do we need an asylum yet? The answer is yes we do. There are patients who will never be able to live in the community regardless of what kind of medications are developed. There are people who are refractory to antipsychotics and there are those who can't tolerate or don't respond to Clozaril or Risperdal. The number has wittled down a little bit more with each new entity but we've got a long way to go. I think one of the things that the ACNP is going to have to do is to now champion hospitals – you can't care for all patients in the community. We are going to have a renaissance of the hospital. They will be different from the old days; we're not going to warehouse large numbers of people but we are going

to have to provide humane care for people who just cannot care for themselves in the community. I think the future is bright. I may be too sanguine but I think there are going to be technological breakthroughs. I think we are getting closer to treating the true psychopathology or a pathophysiology of schizophrenia.

I wonder; I have my doubts. The industry needs to make money.

Well, the hope lies in the industry's needs to make money. The hope also lies in that there are non-industry people, who are motivated by what has been accomplished, to carry on to improve on what we have. And there is a better educated public, so Congress is not going to be able to cut off all funds. They may prudently want to withhold certain funding and the people at the NIMH are going to have to say we've put our funds in those areas which are most likely to produce some concrete results. The public expects that. But the one thing that I think psychopharmacology has done is that it has made the public realize that psychiatric patients are sick people and that they are entitled to treatment.

There are now powerful national organizations that are influential advocates for the mentally ill. They are collaborating with psychiatrists to ensure government support for psychiatric patients and to ensure government approval for new psychoactive drugs. But drugs must be prescribed prudently. Doctors who are pill dispensers shouldn't prescribe psychoactive drugs. To be a good psychopharmacotherapist, one has to be a good physician who does a good diagnostic work-up, takes a good personal and family drug history, who knows the physical status of the patient, and who carefully observes the patient's response to drug therapy.

How did you get into psychiatry Frank?

Well, I graduated from medical school in 1945, when the War was on. I did a rotating internship and started a residency in paediatrics at the University of Maryland Hospital in Baltimore. After six months into the residency I got called for active duty by the Navy. I was assigned to the Bethesda Naval Hospital for surgery. I have no manual dexterity. The only exposure to surgery I had was during my internship. When I learned my assignment, I said 'my God I'll kill more people than the War will'. I didn't have any hesitancy to ask for another assignment. At that time the Army and Navy were staffing VA hospitals. Hence I was assigned on loan to the Veterans' Hospital at Perry Point, Maryland, a large psychiatric hospital.

David, to be honest, to me that sounded like a fate worse than death. My memory of psychiatry was a few lectures from people who talked about the unconscious and things of this sort and then we would visit the State Hospital and be taken on a tour like through a zoo. You really got no feel for it. Well there was another doctor at Bethesda who had been a friend of my father. I went to talk to him because I was really down. I

thought I should have kept my big mouth shut and he said 'Frank, go up there, you only have to be there for two years and why don't you just decide that you will take care of all the physical problems of the patients. You be a physician and you won't lose the touch'. So he gave me a very good pep talk and I went to Perry Point with an open mind. There were a couple of thousand patients at that hospital and only eight doctors and that's why the Army and the Navy were pouring extra doctors in. After a very quick indoctrination, you were sort of turned loose, like during the internship during the War.

I was there only a short time working on the admision service when I was transferred to, what was called, the continuous treatment service. There were 800 patients in that service, who had been in that hospital on average anywhere from 20–40 years and none of them were yet 65. So these were really chronic patients. What did we have? Paraldehyde, bromides, barbiturates, cold packs, tubs, all kinds of hydrotherapy, some insulin coma therapy and ECT and that was it. I quickly learned that schizophrenics are really different people. Their pain and temperature senses are different.

I remember one fellow vividly who stuffed himself with newspapers and set himself on fire. When I got there they had put that out and here he is sitting, burned pretty badly, still hallucinating and responding to the voices, but we didn't have to give any narcotics at all. It was just amazing to me. There was a fellow who escaped from the shower. It was about 4@o that night and the old attendant who was in charge of that ward called me, as I was the Officer of the Day, and told me this fellow had escaped. In my naivety I said 'he won't be gone long, it's so damn cold out there, he's going to come back in'. I'll never forget it but he said 'Doc, you don't know schizophrenics, we've got to find that fellow, if we don't he's going to freeze to death'. So we started a search party and we found him. He was hypothermic but we saved him and that made me do some real thinking.

What's wrong with these people? And I'll be honest, the people who were training us were basically psychoanalysts and I could never get a satisfactory answer to questions such as 'You can explain to me why this fellow thinks he's George Washington instead of Abraham Lincoln but why does he have this delusion in the first place?'. Well, they didn't have the answers for that. And I felt that sure you could give what seemed to be plausible explanations but that doesn't really explain anything. So my perennial desire to ask a question why and look for a answer got me interested in psychiatry. I willingly got involved with ECT because I could see what it could do for some people, even people who were called schizophrenic, who probably were schizoaffective or bipolar patients, who were misdiagnosed as schizophrenic.

By the time I had resolved that I was going to be a psychiatrist and had taken my boards and passed them, my time at Perry Point was up. I had

stayed on longer than I was required to stay on because I wanted to get the extra training. That hospital was a museum of psychopathology. You could see everything – all kinds of organic brain diseases.

One of the things that I know David Wheatley was very concerned to get right at the start of BAP, which he says he picked up from looking at ACNP, were the links between the organization and the industry. Now, let me just broaden this out to ask you generally about the industry. You've mentioned issues to do with the editors of various journals having to be, not so much industry friendly, but the next best thing.

Well, to a certain extent that's true. This is not a new one. I was subpoenaed to testify before the Blacknick Committee in Congress at the House of Representatives. It was an official congressional investigation into pharmaceutical advertising. How did I get involved? Well, Congress has a lot of power and they can hire people to investigate things and one of their investigators went through some journals that were suspect and made the interesting observations that the summary and conclusions from a paper I had written were not published, but they were in a reprint. So I got subpoenaed to come over there and explain this thing. What came out of that hearing, not just from me but from others that they subpoenaed, was that when you submitted an article to certain journals, before they send it out for any peer review, if they did send it out for peer review, they sent it to the manufacturer and said 'look, we're thinking of publishing this article on your drug, do you want to buy advertising space in the same issue?'

This was when?

In the late 1950s, early 1960s. Now, what came out was if the company said no don't publish that or we'll stop advertising, that article was rejected. Or in the case of mine it turned out that it was sent to the company and the company deleted the summary and conclusion, which is what most people look at. That's still happening. Some of our prestigious journals have by inference, without proof, lately been considered guilty in this area – that they don't want to publish anything that's not going to please their advertisers. Senator Kennedy has raised this issue a couple of times.

All of this is grist to mill of someone like Peter Breggin – look at Toxic Psychiatry (see Glossary).

You're right. He picks this stuff up and there's a certain element of truth to it and you know money is a poweful motivator. I think anybody who does what I do or who does research has to be very, very careful about having a distant relationship from the company because they can increase your bias, there's no question about that and I've sat in on enough meetings to see that actually happen. The industry has changed. When I first started, and you ask anybody, what it was like 35–40 years ago, you

dealt with physicians. They ran the pharmaceutical industry. Today they aren't running the industry, they have some input but not a major input. Decisions are made by the business people who think in terms of the bottom line and that's their prime interest, there's no question about that. Some companies are a little bit more aggressive than others and I think all Colleges have to be very careful.

There have been some publications recently about, for example, journal supplements and certain journals have been identified now as taking huge sums of money from the industry and publishing supplements. How peer reviewed these are is a big question and how much are they really used for promotion rather than scientific purposes is another concern. And if a company wants to get a speaker on a programme they can do it. You've seen this in England and it happens almost everywhere.

It's a very fine line, because Peter Breggin won't be taken seriously other than by people who are on the fringes.

Yes, it is. We're all human and it's very difficult not to become biased. You really have to say consciously in advance I am going to do my best to avoid that, which means that you say no to certain invitations however nice they might be. I'm well aware of the other problems that have been going on and the gifts that have been given to influence reviewers and teachers here and in England.

Now, in 1970 you organized the 'Discoveries in Biological Psychiatry' meeting, why? We work in a profession that's not terribly interested in history.

I had worked at the Vatican from 1962 to 1965 and you cannot work in that environment without becoming very conscious of history. You're living in a city where everything is older than the country where you were born and raised. I have been very fortunate. I have met a lot of the people who were pioneers in psychiatry and it was a pleasure to meet them. As I say, you put a face to an article and so on. I had been instrumental in getting Barry Blackwell to come to the United States because I was a consultant for Merrell Dow Pharmaceuticals and they were looking for a psychiatrist so I suggested Barry. He was famous for the cheese reaction observations. I met him at a CINP meeting in Washington, where he gave a paper on the MAOIs and I was very impressed with him and we corresponded. So I suggested Barry and they asked me if I would call him and ask if he'd come over for an interview. I called Barry and he was interested. He was interviewed and, as I expected, they were very favourably impressed with him and they offered him a job.

Barry came and we are good friends, although I don't see him as much now because he's interested in the homeless and does a lot of work in the area of the homeless and their psychiatric needs in Wisconsin. Anyway we were both at an APA meeting and we had been to dinner and met with Mogen Schou. Barry and I sat around and talked for a while and

concluded it would be a good idea if we got together all the men who made these discoveries in biological psychiatry, while they are still alive so they could tell the story in their own words. And we kicked it around and that to me was the end of it for a while.

Then I got thinking about this idea and this was another example of picking up the ball and running with it. I called Barry. I then proposed this to Taylor Manor and they agreed to fund it. Barry and I discussed things by phone – primarily who we ought to invite and so on. What he really did was he helped greatly with the editing of the book. One of the things we wanted was early publication. Two weeks after that meeting was over the first copy was out. The man from Lippincott stayed over the weekend, attended the meeting, and then came round to my house and had dinner with me and left with the galleys to take on Monday morning to the printer. We had page proofs within five or six days and within a few weeks the book was published.

Let me ask you – it seems almost that the era of drug discovery is over. There are some drugs coming through but at nothing like the same rate. The golden era was 1954 through to 1974 or thereabouts. In last 20 years, there have been great advances in neuroscience but not clinical advances to anything like the same extent: why is this?

Well, for a long time of course there was a search for me-too drugs, which is understandable. You've got to have money from something to do research on another area and me-too research is relatively inexpensive. One thing about chemists is that they are molecule manipulators and they can produce an awful lot for you but as you know you've got to screen a whole lot before you get one that looks like it's worth doing work beyond an animal stage. So the end result was we got a lot of tricylics, got a lot of phenothiazines, a lot of thioxanthenes and so on. The real change came with clozaril and now risperidol in the antipsychotic field. The serotonin uptake inhibitors are an advance to a certain extent. Whether venlafaxine is going to be another breakthrough in the sense that it may have all the assests and none of the liabilities of amitiptyline, we'll have to wait and see, but that's a possibility. Wellbutrin still has some promise and nefazadone is about to be approved.

There has been a real change in the industry. I have already said to you that 30 years ago, the industry was run by the scientists and that's no longer true, it's the business man who runs the industry. I've seen large companies take and put all their eggs in one basket – gambling because their hope is that this product is going to be a megabuck product and therefore other things fall by the wayside. Look what's happened. Squibb at one time was very active in the CNS field: they decided to go into cardiology because it's a much bigger market. That didn't materialize. They had to merge with Bristol-Myers. Now Bristol-Myers gets into cancer drugs and later the AIDS market, which was a big market at that

time. So money that was being used for CNS research and development was diverted and we had drugs like nefazadone, which was approved almost two years now and in England it's still not on the market.

This is the change. Management looks at that bottom line first. This is why there are all these mergers, in my judgement. I can understand that. They do have to make some return on their investment for their stockholders. Merck and SmithKline have bought into the pharmacy business and they're all getting into managed care one way or another. It's a very interesting time to see what's going on. It's got to be of interest to this College because there are fewer and fewer companies looking at the psychiatric field as a field where there's going to be a big return. In part because it is true that for many people, the tricyclics are still very good drugs and I can treat many patients with them as safely as I can treat them with the serotonin uptake inhibitors, with no greater risk of unpleasant side effects really and there's a big difference in price. The industry are going to have to come up with some very good products if they are going to produce a lot of money from them.

The cost of doing research for the industry has just escalated. I think I did the first 100 patients on chlorpromazine for $1000. Of course everything was cheap then. But the requirements of the baseline data you've got to get, the EEGs, ECGs, the ophthalmological and all these other things. There's no way someone like me can do this kind of research now.

You've been an independent practitioner through this period, which hits me as a drawback in this respect in that the way politics works within any scientific community, you've got to be part of one of the powerblocks and you're not. If you read reviews of things the reviewer cites 'our' guys and doesn't cite the other guys. But being in the middle, the way you've been, you're not going to get that recognition.

That doesn't bother me. As a matter of fact I've been fortunate. I've got five honorary degrees, for 4 Doctor of Laws and one of Science. I've been honoured twice by the ACNP and I've received other awards and honours. So I've gotten my recognition but my most important thing is I go to bed every night with a clear conscience and with a sense of satisfaction that, thank God, today I did the best I could to help some people, somehow. I have lectured extensively and that took a lot of time, lot of effort, sacrifice and you're away from your family, fighting all the vicissitudes of travel. And why do it? What I do it for is, if I can lecture to 50 physicians and convince 10% of them to do a little better, I've helped more patients that day than I would staying in Baltimore in my office and if it weren't for people who were kind to me and shared their knowledge with me I would not have been able to do what I did. Knowledge gives you strength. It really does. It gives you the courage of your convictions and it makes you willing to roll up your sleeves and take legitimate risks for the benefit of your fellow man. That's been my motive.

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