

**Leo Hollister: From Hypertension to Psychopharmacology
- A Serendipitous Career
David Healy's Interview***

Why did you go into medicine?

During the 1930s an American journalist, Paul de Kruif, wrote a series of books such as Men Against Death, and The Microbe Hunters, largely about the advances in medicine such as the development of the concept of bacterial diseases and nutritional deficiency diseases. I thought it was tremendously inspirational to see how research could make a difference in the lives of many people. So that was one of the influences. I had had a tendency to think in terms of law because my stepfather was a judge. I will never forget sitting in the judge's chair when I was about 9 or 10 looking over the majesty of the court room thinking "God what a powerful thing the concept of Government by laws is." But I later came to the conclusion that lawyers tended to try to distort the truth whereas scientists tried to find it. I found the latter much more appealing.

So, despite considerable obstacles, because I didn't have a whole lot of financial backing and had to work through both my pre-medical and medical career as well as go to school, I decided to go into medicine. It was curious that the work I did then had a later influence on my career. During the pre-medical years, I worked in a pharmacy and learned a lot about drugs. And then during my medical school I worked in a neuropathology laboratory, where we had quite a number of interesting people who would come by for seminars including Albert Sabin of the Sabin vaccine. This was exciting - it indicated the complexities of the brain. So those two things, drugs and the brain, tended to jell and ultimately more or less by accident influenced my career. It is strange what influences can occur that you are not even aware of but later on play a role in your choice of career.

In the recent History of the CINP, you reviewed the 1955 Paris Colloquium on Chlorpromazine that was organised by Jean Delay - essentially the first meeting of the new era; were you at it?

No. I had occasion to review that meeting for a book Toward the CINP written by Tom Ban and Oakley Ray, but I was not at the meeting. My beginnings in psychopharmacology were quite fortuitous. I was working as an internist in a Veterans' Administration Hospital largely devoted to psychiatric patients. A detail man, one of the salesmen who come around to tell you about drugs, from Ciba Pharmaceuticals came by my office one day and said, "We have a new drug that is we think is going to be very useful for treating hypertension" and I said "Gee, I know every hypertensive in the hospital and I've had a long interest in hypertension. Why don't you give me some and let me try it"? So, he merely walked out to his automobile, pulled out some reserpine tablets from the trunk and gave them to me. About two days later the first patient was being treated with reserpine. So much simpler to do clinical research than it is today.

Somewhat to my surprise the drug worked. It was a very effective treatment. I had already tried many other drugs to treat hypertension and saw nothing like this before. About three

months later he came by and said, “We have some reports that this drug may also be useful for psychiatric patients.”

This was when?

This was in 1953. I don’t precisely remember the month. So, I said “Well psychiatric patients are not my cup of tea but let me see what I can do.” I went to the chief of psychiatry and told him the story. He somewhat patronisingly said “Leo, you know, in psychiatry we have had these drugs come and go and nothing ever has come of them, I wouldn’t waste my time.” So obviously he wasn’t interested. Then I asked him if it would be all right if I asked some of the psychiatric staff, most of whom were golfing buddies, if they would mind trying the drug under my direction. He said “No, not at all, go right ahead.” What I proposed to the psychiatric staff was that they would send me their schizophrenics to my medical ward and I would keep them there as long as we needed to get them started on their treatment, then send them back with a supply of oral medication. It was their duty to tell me whether the patients were improved or not. I didn’t feel confident to make that judgment. What I did then was to treat some of the patients with the active drug and some with placebo. I believe that these were the first parallel-group double-blind studies that were ever done with antipsychotics.

Curiously enough, I had already done two placebo-controlled double-blind trials in patients with what I then called “psychoses associated with old age.” The first was with oral pentylenetetrazole (Metrazole) and the other was with combined hydrogenated alkaloids of ergot, known better as Hydergine. Metrazole was not very effective. Neither was Hydergine with the exception of two patients who had what was then called “hypertensive brain disease.” So, I wasn’t exactly a novice, although I felt more competent to judge progress in patients with senile psychoses than in those with schizophrenia.

Where did you get that idea from? Because that was very early to be...

The idea of doing double-blind studies originated in the 1940s, largely propelled by Harry Gold, a pharmacologist at Cornell University. It was widely used in the post-war period to evaluate the new drugs for tuberculosis. So, I was familiar with these developments and I thought this was one occasion when it would be very informative to try. Needless to say, we did not have to make too many passes. Some of the staff were coming back to me and saying, “I don’t know what you’re doing over there but some of the patients you sent back are vastly changed.” I said, “Well that is good news.” We kept that up until we had accumulated a reasonable number - 30 or 40 - patients treated that way.

Why was there no difficulty with the other psychiatrists whose patients you gave reserpine to?

It is curious but despite the pessimism of the chief of psychiatry, the other staff were fairly amenable to joining me in this. As I said most of them were people with whom I played golf, so we were on friendly terms. They were willing to go along with me although I don’t know what they expected. It didn’t take too many turnarounds after they sent their patients to my ward and I sent them back before they knew something was going on. And quite correctly they said only some of them got better but not all of them. So, in a way I was lucky. I guess if they had turned me down I would never have pursued the idea. But it turned out that I was fortunate. So many things happen in your life that you can’t predict.

By this time, it was 1954 and I had heard rumours of another drug, called chlorpromazine, which might be equally effective in such patients. In those days it was ridiculously simple. I just contacted SmithKline French and in no time at all I had chlorpromazine and placebo. We could then do the same thing with that drug as we did with reserpine.

By the end of 1954, a meeting of the American Association for the Advancement of Science (AAAS) was to be held in Berkeley California. I had been invited to tell of our work with these two drugs. At that meeting I gave a rather brief paper describing what we had done but pointing out that this seemed to be a revolution in the treatment of mentally ill patients and that undoubtedly there would be a lot more work done with these drugs. One can't be entirely sure but this sight might have been the first meeting sponsored by a major scientific group that dealt with the new antipsychotics. Others whom I recall being at that meeting were Nate Kline, John Kinross-Wright, who later became a drinking buddy, and Murray Jarvik.

How did you get asked to that meeting? How had people heard about your work?

I suppose the organisers, Jonathan Cole and Ralph Gerard, must have found out through the drug company because up till that point I had never published anything on the work. I was extraordinarily naive in those days. I thought that having given the paper at AAAS meeting and knowing eventually the proceedings would be published that there was no need to publish any further. The proceedings came out in 1957 in a small book which probably only 15 people ever read, so my pioneering work remained widely unknown.

If you had published them as early as you could have done, would you have published before Nate Kline?

No. Nate had used reserpine before we did. He had used a very small dose, doses that were usually appropriate for treating hypertension. In his initial study he had not seen a whole lot change. But by that time Ciba had come to the conclusion that you needed much higher doses. By that time Ciba had a research physician, Dick Roberts, who came to the West Coast and was charged with setting up studies of the drug on the West Coast. He was invaluable in telling us what the proper doses should be. The dosage schedule that we used started with a 5mg loading dose intramuscularly given for several days, followed by subsequent oral doses of the same magnitude. This increased dosage schedule was much more effective than the smaller dose that Nate had used. Of course, Nate got the same word so by the time we were using that dose he was also using it. A third chap, Robert Noce, working at one of the California State hospitals, had also started using reserpine in his patients.

By the middle of the 1950s the New York Academy of Sciences, prompted by Ciba, held a meeting in New York to get together the people who had studied reserpine. I was invited to that meeting where I reported work we had previously done plus the work we did subsequently. This report was the only one at that meeting that involved a controlled study. This approach attracted a great deal of interest on the part of the press, so the study was widely reported throughout the country via the wire services. There were articles in almost every newspaper in the country about reserpine and schizophrenia.

This was a sobering experience because subsequently I received literally piles of correspondence from various people throughout the country saying that they had a husband,

son, daughter or whatever who had schizophrenia and they were looking for something to do for them. I made it a point to answer personally all these letters, telling them that essentially there was no need to send people to California to get the treatment because there were very few secrets in medicine and the drug would be widely available throughout the country. It was a rather sobering experience to see what tremendous effect the press had on stirring up hopes for a cure among people who suffer dire diseases.

Again, I hadn't published any of this work in regular journals. The New York Academy of Sciences usually produced annals that published the papers of their meetings. In 1957, a couple of years after the meeting, the Annals appeared and my paper was in there. So, in a nut shell this was the strange beginning of my career in psychopharmacology. I always liken it to the saying attributed to some well-known writer who said "When I started writing I really didn't think I had much talent but after I sold a few books and was making a pretty good living out of it, I decided to keep it up." In that sense I was hooked on psychopharmacology and proceeded after that to study many drugs in the field. We studied prochlorperazine, Compazine, which was the next SmithKline & French entity, which was an effective anti-psychotic drug. But what is a company going to do with two drugs competing with each other for the same indication? So SKF promoted it as an anti-emetic drug. It was highly effective for that indication, as most anti-psychotic drugs at the time were.

Later Sandoz had a drug, thioridazine - Mellaril. We studied that one and it proved to be as effective as chlorpromazine. Mellaril may very well have been the first so-called atypical antipsychotic. Like the current group it was a weak dopamine receptor blocking drug. In fact, many basic pharmacologists at the time doubted that it would be an effective antipsychotic. But it was. The weak effect on D-2 receptors also made the drug unlikely to produce extrapyramidal motor reactions, though most of us at the time believed that this difference was due to its strong anticholinergic effect.

Didn't Sandoz very early on market it almost as much for mood disorders as for schizophrenia? It had an anti-depressant flavour to it.

I think that came later. I may have contributed to that notion. Because it was a phenothiazine, and generally speaking drugs within a chemical group have somewhat similar actions, it was tried as an anti-psychotic. The remarkable thing about thioridazine was that it rarely produced the extra-pyramidal reactions associated with other drugs. By this time, of course, reserpine, which was not under a patent because of being a natural substance, fell into disuse because the phenothiazines seemed to do as well or perhaps even better than reserpine with fewer disagreeable side-effects. Reserpine produced a kind of flu-like syndrome! Diarrhoea, aching, feeling rather unpleasant including a somewhat depressed mood. So by that time the pendulum was swinging towards the phenothiazines.

We studied another SKF drug trifluoperazine - Stelazine - and again it looked to be like an effective anti-psychotic. With this drug, we used a variant on the double-blind technique. Patients were all started on trifluoperazine and then, after having responded, were continued on treatment under blind controls with either the same drug or an active placebo - a small dose of phenobarbital. This technique was somewhat different from what Joel Elkes had done early in the game with chlorpromazine in which patients were simply crossed over to placebos.

The impetus for Mellaril being tried as an anti-depressant came from clinical experience in Europe. People were using it for that purpose. We did a controlled study under what might be called triple-blind conditions - because the participating physicians didn't really know what drugs were being used - Mellaril versus Imipramine both in schizophrenics and depressed patients. In the schizophrenic patients Mellaril was clearly superior but in depressed patients the two drugs looked somewhat similar. This result gave a considerable boost to the idea that Mellaril could be used for treating depression. I'm not sure whether that was a correct conclusion - there were probably many reasons why we couldn't show a difference.

When was that because it sounds something similar to what Don Klein and Max Fink did in Hillside where they randomised everyone regardless of diagnosis to Imipramine or Chlorpromazine?¹

Yes. That would have been probably around 1958. I remember both Max and Don approaching me and saying, "Why don't we do our studies together." I said that mine was already underway and I was happy with the design so why didn't we do them independently which would probably give more force anyway to whatever consistent conclusions emerged. But you're correct that it was about the same time.

There was then the large Veterans study of chlorpromazine that you were involved with.

Yes, by 1959 the Veterans Administration had decided that, because they were the biggest operator of psychiatric beds in the country - they had more psychiatric patients than perhaps all the institutions put together - that they should look into these new drugs in a systematic way. I was approached to join the planning group which included a multidisciplinary group of statisticians, psychiatrists, psychologists, neuroscientists and so on. We then planned a series of cooperative studies among a group of many hospitals. The first study was a comparison between chlorpromazine and another phenothiazine, mepazine - Pacatal, that had been reputed to be an anti-psychotic. At my insistence we used phenobarbital as a kind of active placebo. Much to our gratification this study showed that chlorpromazine was effective, that Pacatal was almost ineffective, and that placebo was totally ineffective. So we had a technique that was sensitive enough to distinguish between phenothiazines with different levels of antipsychotic action which was really encouraging. From then on a series of studies over the next several years extended the first one and we started the study of anti-depressants. So, the VA co-operative studies group was a highly productive group in defining the uses of these drugs.

There were also a number of studies done by some of the larger State hospitals in New York and California, modelled on the VA studies which came to virtually the same conclusion. Then the National Institute of Mental Health (NIMH), under a sub-unit called the Psychopharmacology Service Centre, had planned to do a study in acutely admitted schizophrenics - people who were presumably having their first break - and I was invited to consult with that group as well. That study got more publicity and more references in the literature than any of the VA studies, which many of us found somewhat offensive. But because the Psychopharmacology Service Centre had the purse strings for grants obviously

¹Klein DF. Reaction patterns to psychotropic drugs and the discovery of panic disorder. The Psychopharmacologists Vol 1, Chapman & Hall; 1996, pp. 300-300.

people wanted to cite their studies. Their study was somewhat similar in the sense that they studied two phenothiazines, both of which were effective compared with placebo².

The NIMH study indicated a high number of these patients, perhaps 20%, spontaneously remitted. This result led to the erroneous conclusion that there is a high placebo effect in schizophrenics. The fact of the matter is that in those days it was not easy to make a diagnosis. I am quite sure that a lot of those so-called acute schizophrenics were really manics who probably went into spontaneous remission. Besides for everyone who got better an equal number got worse. The net effect of placebo on these so-called schizophrenics was essentially a stand-off. The study has been misinterpreted in respect of placebo effects.

When the Psychopharmacology Service Centre began, they held a large meeting in Washington in September of '56 which was convened by Ralph Gerard and Seymour Kety; were you at that?

Yes. When I mentioned the multidisciplinary group that had been associated with the VA studies, Ralph Gerard was a consultant to the VA group before he became a consultant to the NIMH group. When I used the word neuroscientist among the disciplines represented, I was thinking of Ralph, who of course was well known for his wonderful aphorism that behind every twisted thought is a twisted molecule. In a way that was the essence of biochemical psychopharmacology in those days. He consulted with the VA group in 1956 and the NIMH group in 1959. I don't recall Kety's participation in either group.

The 1956 meeting I was referring to was organised when the funding came through from Congress and it was out of that meeting that the psychopharmacology centre came.

I may be wrong. I was commuting back and forth to Washington to both the VA and the Psychopharmacology Service Centre groups. The latter was then honchoed by Jonathan Cole, who had been one of Ralph Gerard's proteges. The psychopharmacology service centre aided immeasurably in elucidating the mechanism of action of these drugs because of their grant funding. Their first grant programme was for the study of acutely newly ill schizophrenics. They recruited about 10 or 11 hospitals and gave them a considerable amount of money to participate. From that point on they had a more open grant system where investigators could apply. I don't know when I first actually got a grant, but it was probably not until around 1961 or thereabouts. That grant went over 27 years. I remember that in my last reapplication I said, "I am not trying to get the largest numerical suffix on my grant but if you give me two more years I promise never to come back."

Those were exciting days. You might wonder why all these different agencies, the VA, the NIMH, the State systems and numerous independent investigators worked so hard, using controlled studies to prove these drugs were effective. All you had to do was look at your patients and improvement was obvious. People who were mute began talking. People who were attacking ward personnel were no longer hitting people. Even now when I hear about the older drugs not being effective for negative symptoms, I don't believe it. I remember quite well very early in the game I asked one of the psychiatrists participating in my study "Would you like to have some more of your patients treated with chlorpromazine?" And he said "Leo, I have so many patients talking to me now who never talked to me before that it's all I

²Cole JO. The evaluation of psychotropic drugs. in *The Psychopharmacologists*, Vol 1, Chapman & Hall; 1996, pp. 200-200.

can handle to keep up with them.” Now if that is not improving a negative symptom, I don’t know what is.

Some years back I pointed out to John Overall, my long-time colleague, that we had we had abundant data showing that negative symptoms as well as positive symptoms were amenable to improvement although they did not improve as much as the positive symptoms. I wanted to resurrect some of our old data and write a paper about it but John was even more lukewarm about publishing than I was, so we never did that.

Can I ask you about John since you have introduced him?

John and I first met in 1960 at one of the annual VA meetings on chemotherapy in psychiatry. These meetings described the progress of the co-operative studies as well as other studies being done within the system. I had never known him before, but we hit it off very well. We both liked to drink a bit and over a few drinks we managed to generate all kinds of possible ideas. So that began a collaboration that exists up to the present time. I recently joined the University of Texas in Houston Medical Faculty where John is also a member, so we are now together. He was the main reason I came from Stanford to Houston. It was an excellent collaboration because he knew everything I didn’t about how rating patients. Of course, his Brief Psychiatric Rating Scale has become the most widely used rating scale...

Where did that come from?

It was a derivative of a scale called the In-patient Multi-dimensional Psychotherapy Scale (IMPS) that Morrie Lorr had brought out a few years before. In this scale the domains of psychopathology were rated in a more particulate way and what John and Don Gorhim, his colleague, did was simply to take the same domains and make rating them more global. That made it a much more useful scale, but it was somewhat derivative from the IMPS. Subsequently John and Don made some other refinements by putting in two or three other domains. John knew about psychometrics as well as being a superb statistician. I knew something about drugs, medicine and experimental design, so we meshed very well. Once when we were having some conversation and I pointed out something about the statistics of the situation and he was pointing out about something about the drugs, we seemed to have learnt much from each other. I refer to John as one of our national treasures as they do in Japan, because he is an outstanding researcher. I feel very fortunate to have had a chance to work with him over the years. Most of the time, not having the credentials of psychiatry, I have felt that I have needed psychiatrists or psychologists to evaluate patients.

Did you not ever go back and get a psychiatric training or did you just stay straight medical?

No, I never felt the need to. I’m a great believer in self teaching - you can learn on your own a lot of things. Sometimes I point out to students, trying to give them an idea that learning is a never-ending process, that I am probably the only person who has been a Professor of Psychiatry and Pharmacology at two different medical schools who has had absolutely no formal training in either discipline. These days you simply have to keep learning all the time and be willing to cross disciplines. After some years I began to feel confident that I could make diagnoses and make appraisals of patients. In fact, having come from internal medicine, where we are more precise about our diagnoses, I was more conscious for the need of accurate diagnosis than most of my psychiatric colleagues. At the New York Academy of

Science meeting on reserpine, people were talking about “150 psychiatric patients” - no diagnoses at all. Psychiatric diagnosis is terribly imprecise and, despite setting up various diagnostic criteria it is still so. Further it has become increasingly evident that diagnoses don't exist in pure culture. You see a patient and you can make three or four diagnoses on him - personality disorder, psychosis and affective disorder. So, there is a tremendous amount of overlap due to comorbidity, which is still rather vexing. One of my colleagues at the University of Texas, whom I think is a very able clinician, said “When I see patients, I don't know what to call them.” There is such a mixture. So, there are many remaining problems in regard to diagnosis.

Let me take you back to the late 1950s, what was the impact of Nate Kline at the time?

Well, Nate was a very opportunistic fellow who wanted to make a big name for himself, which he did. He also had a great deal of showmanship - I wouldn't say charisma because he was not universally liked. But he was able to project himself in the public eye - like going to Haiti to start a psychiatric system where of course most people didn't have enough food, clothing or shelter. But he did a lot to put psychiatry in the public eye in a somewhat favourable way. He didn't stay too long in academic psychiatry or at least investigative psychiatry. He had been director of research at the Rockland State Hospital in New York and had done very well. But by the early 1960s, the mental hospital system was beginning to shift to an out-patient mode, so Nate started a private practice in New York.

My first encounter with Nate was rather unusual. The physician from Ciba, Dick Roberts, had also helped Nate. At the AAAS meeting Dick and I were sitting together when just before the meeting was to begin Nate came in. Dick stood up, which he did it with some difficulty because he had a residual of polio in one of his lower extremities, and I did too, to greet Nate. Dick introduced me to him. Nate was very high handed - he acted like we were peasants gathering crumbs from the master. As he departed to go up toward the podium, I turned to Dick and said, “Who the hell does that guy think he is? Does he think he is going to get the Nobel Prize simply because he used your drug?” Well, it turns out that might not have been too fanciful an idea. A couple of years later Nate got one of the first Lasker awards for using reserpine.

And why not you?

Because Nate knew how to cultivate people. He got to know Mary Lasker very well and she was interested in psychiatric illnesses, so I am sure that contributed to the selections. In those days the Lasker was not nearly as prestigious as it became later on. Mary alone could name the awardees. Heinz Lehmann who was another of the awardees at that time as well as Bob Noce, whom no-one has heard of since.

Anyway, Nate was always somewhat controversial. After my rather rocky beginning with him, it remained rocky throughout the course of my acquaintance with him - sometimes it was pleasant sometimes not. He was that way with many people. He always seemed to have a provocative approach. If there was a chance to get into an argument, he would do so rather than try to resolve differences. Despite these character faults, he certainly had a big impact on psychiatry and hastened the acceptance of biological psychiatry into the mainstream. At that time psychoanalytic theory dominated the area and virtually every chairman of a department of psychiatry in the US was either a psychoanalyst or psychodynamically oriented. Now of course the pendulum has swung completely in the opposite direction. One

current chairman, Joe Coyle at Harvard, has also been president of the Society for Neuroscience.

As far as the Collegium, the CINP, is concerned I missed the first two or three meetings. Finally, my family was getting old enough to enjoy a trip abroad so I took my wife and three of the children to Birmingham England for the 1964 meeting. After that I have attended most meetings. When you are president you have a big say as to who comes next. I lobbied for Arvid Carlsson to be my successor and next for Paul Janssen, two indisputable choices. Later, I was influential in having Ole Rafaelsen, one of the brightest people I have ever met in medicine named as president. My last influence was to support Paul Kielholz. We have had some excellent people as president and I feel very fortunate to count myself among them.

What role do you think the CINP has played - there are certain strains at the moment, but I guess there always have been various strains?

There are all kinds of neuropsychopharmacology groups formed around nations or regions. The first of these was the American College of Neuropsychopharmacology. One of the prime movers in getting that organisation started called me up and asked me if I would like to join. I said, "Oh God, we have so many organisations now, who needs another? But if you insist put me down as a member."

Who actually called you?

Ted Rothman. Ted was a very nice man who suffered from rheumatoid spondylitis but that did not impair his sense of humour a bit. At one ACNP meeting we shared digs. He was one of the prime movers in getting ACNP started. I missed the first two meetings which according to the by-laws should cause you to lose your membership. But I went to the third meeting in Washington. As we were signing out of the hotel, Ted was nearby and I walked over to him and said, "Ted, I was dead wrong, I am so happy you persisted in getting me as a member of this organisation because I think its great and it will become even greater." Since 1962 I have not missed a meeting. The next such society was the German-speaking one. The Canadians had their own society and I just learned at this meeting that there is one in Latin America, in which one of my former foreign students is now the president. The CINP serves the purpose of integrating all of these groups by bringing everyone to share a wider viewpoint.

I used to give a lot of papers and I have done as much travelling as anybody giving lectures to medical schools, societies and various other groups. Now I rarely give a paper. One of the problems with a meeting like this is that only so much is new. Most has already been published somewhere and is old hat. But maybe it isn't old hat to everybody and even repetition may serve some purpose.

In the US, ACNP and psychopharmacology has seemed to be more an East Coast than a West Coast thing.

It may have started off that way, but I don't think it's that way now. In fact, there have only been four people from the US who have been president of both the ACNP and CINP. The first was Paul Hoch from New York but the next three were me, Biff Bunney and the current ex-president, Lew Judd. I was pointing out to Biff yesterday that the only three living people who have been President of both societies are all from California. So, things have shifted a

bit from the East Coast. This may be just part of the general demographical redistribution over the last 30 years - with an enormous amount shift towards the West Coast.

You were one of the first people to describe a benzodiazepine withdrawal phenomenon. Can you tell me how that came about?

That was a fortuitous situation. In 1960, just before the introduction of chlordiazepoxide, Roche had a closed meeting in Princeton New Jersey where the people who had been studying this drug reported on it. I had been invited to the meeting, not because I had studied the drug, but as an outside impartial observer. All the reports were quite favourable. As I listened to them, I kept thinking if this drug is as good as these people say its going to be abused. So, I thought how can we study this possible problem. One of the studies not yet done was to use it in large doses for schizophrenia. Thus, we could justify larger doses not only to test this indication but also to study any withdrawal syndrome. We pushed doses up to 300mgs and 600mgs a day, at which time most people were ataxic. Then under very carefully supervised conditions we would switch them to a placebo while taking blood for measurements of plasma concentrations, EEGs and a number of clinical observations. We only tested 11 patients but 10 or the 11 showed a very clear-cut withdrawal reaction comparable qualitatively to that which had been discovered a few years earlier for alcohol and barbiturates. The big difference was it was attenuated in time. For the first couple of days after withdrawal not much happened and then about the third day patients began to develop clinical symptoms which generally peaked at about the fifth day. We had two patients with seizures on the eighth day. This timing was quite different from short-acting barbiturates or alcohol, where seizures usually occur within the first 48 hours.

We had drawn blood for measurements of plasma concentrations which in those days were rather primitive compared to current measurements. The data were not complete because I had no idea we should follow plasma concentrations for eight or nine days. However, we deduced that the half-life of this drug after discontinuation was approximately 48 hours. Consequently, the delayed onset of withdrawal and the late occurrence of seizures was attributable to the long half-life of the drug. Incidentally, although chlordiazepoxide alleviated some of the behavioural symptoms of schizophrenia, it was not truly an antipsychotic.

These results were published in *Psychopharmacologia*, in 1961. I was fully confident that nature would imitate art and that a lot of spontaneous withdrawal reactions would be subsequently reported. One of the reasons for the paucity of reports was doubtless the attenuated time course. Many patients resumed taking the drug and managed to abort the full withdrawal reaction. Or some of them probably went through without knowing what was happening, as the withdrawal reaction was relatively mild. Much later in the 1970s and 1980s it became a much bigger issue but by that time my original report was somewhat forgotten.

Possibly of much more clinical significance was the concept of therapeutic dose dependence - that even smaller doses multiplied by a long period of exposure could lead to some sort of modified but definite withdrawal reaction. This recognition came during the 1980s.

Had you thought right from the start that these drugs would cause a withdrawal reaction?

Oh yes, that was the hypothesis. If they were going to be abused they would cause a reaction. The surprising thing was the time course. Earlier we had studied withdrawal reactions from

meprobamate. These were much more like the classical ones, with early onset. We figured the half-life to be in the order of 11 hours, which is comparable to the short-acting barbiturates. Later when the meprobamate congener, tybamate, came out we tried to produce withdrawal reactions, but we couldn't because tybamate has a half-life of 2-3 hours. There was no way short of keeping patients awake during the whole 24 hours of the day to sustain a high level of the drug. This experience led to a formulation which I think has held up pretty well; that is that the onset and severity of withdrawal reactions are a function of the half-life of a drug. Those with a shorter half-life will have a more abrupt onset and a more severe reaction and those with a longer half-life have a delayed onset and are less severe. There had, for instance, been a lot of clinical use for phenobarbitone before the newer sedatives came along, but withdrawal reactions were never a problem. Phenobarbitone had such a long half-life, in the order of 96 hours, that it had a built-in tapering-off action. That formulation has generally held over the years.

What response did you get from Roche when you showed this potentially significant drawback to their treatment?

They were not particularly happy about it. I just told them that I wasn't trying to kill their drug but that it was worth knowing about the possible withdrawal reaction before the drug was marketed so that people could be aware that following long-term use of the drug they might taper it as they stopped it. A couple of years later, in one of my small collaborative groups, we were also studying diazepam in schizophrenics, again with large doses. Unbeknownst to me one of the hospitals decided they would run all patients up to the maximum dose with 120mgs a day and then abruptly stop the drug. It turned out that diazepam produced exactly the same withdrawal reaction - with a somewhat delayed onset and late-developing seizures. We reported that in a little paragraph on adverse effects in the original paper but never as a separate publication. But that too was known before diazepam was put on the market.

There was another observation of withdrawal reactions which I neglected to publicize. I can't imagine how naive I was in those days. Sidney Raffel, a professor of microbiology at Stanford, had done some *in vitro* experiments where he showed that chlorpromazine in concentrations of about 5 micrograms per ml could kill *Mycobacterium tuberculosis*. Now in the 1950s, we didn't have too many drugs for tuberculosis, so we decided to add chlorpromazine to the existing regimen of isoniazid and other drugs that tuberculous patients were being treated with. We did that for six months with two three-month evaluations and saw absolutely no change in the progress of the tuberculosis. Our doses were 300mgs a day of chlorpromazine. We then said okay, let's quit. It was a placebo-controlled study. None of the placebo-treated patients had a bit of trouble stopping but 5 of 17 chlorpromazine patients had a clear-cut withdrawal reaction which was mitigated by either restarting chlorpromazine or starting another sedative drug. I reported those findings in a very brief paragraph in a paper reporting the whole study - again not publishing it separately. In retrospect it was an unusual situation. First, it was the only placebo-controlled withdrawal study. Second, it was the first study in which a withdrawal reaction occurred with therapeutic doses of the drug. And third, it was the first study in which a withdrawal reaction occurred in the absence of any abuse potential, because nobody in their right mind would ever abuse chlorpromazine. I missed the boat.

What do you think the withdrawal syndrome with Chlorpromazine is?

Well, I suspect that at any time you disturb the chemical equilibrium in the brain, some compensatory mechanism will try to overcome it. Then when the drug is stopped the over-developed compensatory mechanism produces the opposite effect. That's been shown for tricyclic antidepressants and I am sure it would be the case for many drugs that affect the brain. The manifestations in the case of chlorpromazine were somewhat the opposite to the therapeutic effects - nausea and vomiting as well as restlessness and sleeplessness. So, I suspect that this is a generalisable phenomenon. It goes back to a number of theories about tolerance and withdrawal that were adduced in the late 1940s from a number of groups.

Talking about withdrawal brings Abe Wikler to mind. You reviewed his book Pharmacology and Psychiatry which came out in 1955 for the recent History of CINP and called one of the key early texts in the field.

I didn't know Abe at the time because he worked at Lexington and I never had any experience there but his book on the relationship between psychiatry and pharmacology was a monumental effort and it certainly opened my eyes. Having come into this thing with no training in either pharmacology or psychiatry his book not only helped bring the two together but summarised the state of the art as it existed in 1955. I always felt that it was rather strange that Abe whose primary interest was in substance abuse would come up with such a complete volume covering all of psychopharmacology, but he was an avid student and he had many interests. Even today his theory of conditioned abstinence is very useful in treating substance abuse and explaining it. Later on, I got to know him but at the time I read his book I had no idea who this chap was who was doing such a comprehensive job. The paperback version is still on my bookshelf.

In fact, the work of the group at Lexington provided the model for most of the studies we did. They did some studies in the early 1950s on alcohol which proved that alcohol withdrawal was exactly that and not some mysterious ailment caused by some toxin or whatever. They also did studies on the withdrawal to barbiturates, mostly the short-acting ones, so when I started my study on meprobamate the essential model was what they had done at Lexington with the barbiturates. It was a great group at Lexington. Harris Isbell was there. He was a remarkably quiet and unassuming man who had a wealth of knowledge.

In a book called Storming Heaven which is about the LSD phenomenon in the US in the '50s and '60s, there is a minor mention that Ken Kesey of One Flew Over the Cuckoo's Nest fame was an orderly on one of your wards at one point and got some of his ideas from your work on LSD

Around 1960 I had a look at the literature on LSD. At that time there was a lot of talk about LSD producing a model psychosis and that it was a way to understand schizophrenia. I wasn't very happy with the work I saw published and I thought maybe I could do a little better. So, over the next 5 or 6 years, up to 1966, we did a series of studies on various types of so-called hallucinogens or psychotomimetics. We studied not only LSD but also mescaline and psilocybin, which in a series of clinical and biochemical comparisons were essentially identical, give or take a few orders of magnitude difference in the dose, so we presumed they must have rather similar modes of action. We studied LSD as a therapeutic agent in alcoholics - we compared it with dexamphetamine - and found that while there were minimal benefits after 3 months this was gone after 6 months. The idea of curing alcoholism with LSD perhaps now sounds naive but we demonstrated that there wasn't much clinical benefit there.

Ken Kesey approached me early in our studies, saying he was writing a book and needed to know what it might be like to have schizophrenia. He thought the psychotomimetic drugs would provide such an experience. I told him I wasn't so sure but that if he wanted to try some, I'd enlist him as a volunteer subject. I was very interested at the time in delineating clearly the clinical syndromes produced by such drugs. We would leave a tape recorder in the testing room and periodically I would venture in after giving a time cue to ask about what was being experienced. Later, in a labour-intensive fashion, it was possible to reconstruct the sequence of the clinical phenomena. Most subjects needed such promptings but not Kesey. He was at the recorder constantly, dictating what later turned out when listened to them to be the most beautifully written and imaginative descriptions. There was no doubt that he was a master of words. He later took a job as an orderly at the hospital to gain more first-hand experience. His subsequent novel, *One Flew Over the Cuckoo's Nest*, became one of the most magnificent and successful first novels in history. Alas, he became hooked on the drug culture and despite his enormous talent never produced anything of note thereafter. In retrospect, I consider him to represent the worst result of our studies with psychotomimetics.

What was the idea behind using LSD - was it that it allowed you to cut into the depths of an individual's fantasy life and this might allow you to undo the complexes that were leading to alcoholism?

There were probably various rationales at the time. What prompted me to do the study was there was an off-beat group headed by an engineer, who was not medically trained, who was going round the country giving 600 microgram dose of LSD to alcoholics and charging them \$1,500 or some astronomical amount for this treatment. This sounded rather phoney to me and that's why we subjected it to a controlled clinical trial. Curiously enough at the same time there were two other groups also working on the problem and independently we all came to the same conclusion, which I think stands up pretty well. One group was Arnold Ludwig and Jerry Levine. We all came to a meeting in 1964 and presented our papers independently. All came to the same conclusion, even though we used vastly different techniques to test the hypothesis.

You alluded to the possibility that LSD or similar drugs might be useful for facilitating psychotherapy - we tried our hand at that too. We gave people who were already in psychotherapy a series of trials where they were randomly assigned to either LSD, mescaline, psilocybin, placebo or no treatment and we taped their interviews and had them rated independently and blindly by experts in psychotherapy as to what they thought the productivity of the interview was. There again we could find very little evidence that these drugs increased insight or brought about a confronting of problems or any of the other things you try to achieve in psychotherapy.

Another of our experiments was to test the model psychosis hypothesis - did the LSD state have any resemblance to schizophrenia? What we did there was to record interviews with schizophrenics as well as interviews with people who were under the influence of these drugs and edited out any reference to drug action in either group. We then had them audited by psychiatrists who were experts in diagnosis and the batting average was almost 100% in terms of distinguishing between who were schizophrenics and who were not. We went to psychologists and they did just as well. We went to social workers and they did as well, as did the nurses. It seemed that almost anyone could tell the difference between the line of thinking of a schizophrenic and the line of thinking people had under the influence of these

drugs. To my mind that scotched the model psychosis hypothesis. Danny Freedman and I used to quibble about that because he was in favour of the model psychoses. He thought it might be more applicable in first-break or newer schizophrenics than it might be in the older ones that we were studying but this hasn't been followed up very much.

Just about the time we were ready to sign off on our studies of hallucinogens it became possible to get synthetic delta-9-tetrahydrocannabinol (THC). To illustrate how things can happen by accident and how casual things were in those days, I was in Washington for a meeting and I ran into a chap named Milton Joffe who was with the Food and Drug Administration. He said "We have a big problem with something called STP out in San Francisco - we really don't know what its all about. I have some in my desk drawer." I said, "give me your supply of STP and we'll study it," which he did. It turned out to be one of the amphetamine homologues. Sol Snyder also started studying it, but he had a grant for it. I had a protocol set up for LSD, so we simply switched to studying STP instead. Within a few weeks we had shown that it was a hallucinogen very similar to mescaline and LSD and that group, secondly that tolerance could develop very quickly to it and that it was not amenable to treatment with chlorpromazine or any of the antipsychotics. Because Sol had also done some work, he and I decided to publish jointly and a first account came out in *Science*. Subsequently we each gave more detailed separate accounts.

My last excursion into hallucinogens was when synthetic delta-9-THC came along. Again, it was very simple, I just had to go to Washington and ask them for it. I remembered that there was a compound called synhexyl which was a THC-like structure which had been studied very extensively in the 1940s on the assumption that it was equivalent to marijuana. Nobody ever had a chance to compare it directly with THC. I was working then with a pharmacologist friend who had retired from Abbott Laboratories and he said, "we had some of that in the refrigerator for a long while." He was able to put his hands on some 25-year-old synhexyl which looked like a bit of tar. We reconstituted it in aqueous alcoholic solution and gave it to subjects in a blind comparison with THC and what we found essentially was that they were the same even though structural differences existed between the two compounds. Synhexyl was somewhat weaker than THC and had a lag-time in its onset of action but qualitatively it was quite similar.

Marijuana is more of a political issue these days than a scientific issue. Ten years ago I published a review in *Pharmacological Reviews on Health Aspects of Cannabis*, looking at the possible adverse effects but also the possible medicinal uses of it. At that time, I was roundly criticised by Gabriel Nahas, who is on the ultra-conservative wing of the substance abuse question. I and the editors of *Pharmacological Review* pointed out to him that I had tried my best to be impartial and fair but that didn't satisfy him. I have become acquainted with the philosophy of trying to turn an enemy into a friend and over the years we have started to collaborate. One project is a re-review some eleven years later covering the literature that has appeared in the interlude. This may be very timely now that there is a big push in the US to liberalise its use in the medical field and possible first step in a campaign to legalise the drug. I anticipate there is still some interest in what the health aspects of cannabis really are.

I have belonged to several organisations, but I think the one I was most effective in was the Committee on Problems of Drug Dependence which was the oldest scientific organisation set up for drugs of dependence in the US. I was invited to join it by Nathan Eddy after my study on STP came out. Within a few years I became chairman of the committee while it was still

under the National Academy of Sciences. Owing to some political shenanigans within the Academy they decided to drop some committees including that one and it was my job to shepherd it along through another channel, which has now evolved into the College on Problems of Drug Dependence, which is continuing the tradition of good science in this field.

How much have the behavioural pharmacologists contributed to the field of drug dependence?

I am not terribly impressed with this. One of the thrusts of the Committee on Problems of Drug Dependence was to make sure we didn't market any opioid analgesic that might be abused. God knows how many were turned down because monkeys would self-administer them. I often wonder whether we didn't keep a lot of potentially useful drugs off the market. When you look at it, it isn't the medical use of opioids that causes the addiction, it's the social use. It has little if anything to do with medical use. You could count the number of medically addicted people on your fingers and toes, so I wonder if the thrust of that committee wasn't misplaced.

Furthermore, it seems to me that a lot of behavioural studies have shown that drugs that will be abused by man will be self-administered by animals which is no surprise. It's usually been that way around rather than the other way. They have contributed something to the clarification of the tendency to abuse a drug by tests such as determining how hard an animal will work to get a reinforcement, but I see that more as cleaning up the situation after it's already known. Maybe I have a biased view on that.

Did you meet up with Jim Olds at any point?

No, he died shortly after his work on the reward centres in the brain. That was one of the seminal discoveries in the whole of neuroscience. Had he lived I'm sure he would have been a candidate for a Nobel Prize. Here I am contradicting myself because that was behavioural pharmacology. But I'm sure it was completely unexpected. In so far as one can get it from the history they were just feeling around in the brain, putting in these probes to see how animals responded without any idea that there would be this systematic division between reinforcement and punishment. That's the way so many discoveries are made.

I didn't think I would pursue a career in psychopharmacology. I would have bet that it would have been in hypertension. Sometimes I wonder which would have been better. By and large we can treat hypertension somewhat better than we can mental disorders as well as having a better idea of the pathogenesis. But it's not all that different. I think the interesting thing about being in psychopharmacology has been the multidisciplinary nature of the field and the fact that we are dealing with an extraordinarily complicated mechanism compared to what causes your blood pressure to elevate. What causes the brain to go awry is much more complex. So, I don't think we need to hang our heads.

A book published in 1954 called *American Medical Research At Mid-Century* reviewed progress in 10 major public health problems, including schizophrenia. After comparing progress in schizophrenia to progress in other areas my conclusion is that schizophrenia isn't all that far behind. It has been an exciting 50 years, but I expect in another 50 years people will consider our current approach primitive. But that is the nature of science.

Let me float this past you. In the case of hypertension, there was a study from Newcastle about 14 years ago which showed that from the point of view of the physician treating hypertension treatments worked awfully well - blood pressure fell - but the patients were not so happy because they were not clearly aware of any subjective improvement in how they were feeling and quite a few felt worse. But from the point of view of the relatives treatment was a disaster because the patient had been converted into a hypochondriac and they had symptoms that they never had before. Does that apply to psychopharmacology?

No, I don't think so. The paradox about hypertension is that it has no symptoms. You can have fairly severe hypertension, which puts you at risk for a myocardial infarction or stroke, and never know it. Furthermore, hypertension is absurdly simple to diagnose. Unfortunately, many of these drugs that we use to treat hypertension produce side-effects, so a patient who is feeling pretty good starts on these drugs and they develop new symptoms that they don't particularly relish. Nevertheless, the complications of hypertension have been enormously reduced over the years due to the fact that we do have effective treatment. It is hard to think these days that there is any kind of hypertension that could not be managed by drugs. When I was younger, we used to have people with malignant hypertension whose life expectancy was measured in months. But you hardly ever see those patients anymore. We don't have any less hypertension than before, nor do we have any less schizophrenia, but we can treat both of them better.

What role did Gerald Klerman have in the field?

I first ran into Gerry when he was a Fellow at Jonathan Cole's Psychopharmacology Service Centre while they were planning the first NIMH collaborative study on schizophrenia. Gerry was very sharp, very much with it on the development of the study. He probably had more influence than any other single individual on the form that it ultimately took. Gerry had an amazing good humour about him - he could always tell some joke or find something to laugh about. He also had a facility for a good phrase - such as "Pharmaceutical Calvinism." We were in Geneva a few years ago at a panic disorder meeting and somebody mentioned that term without giving it an attribution. I told Gerry that this place might be the most appropriate to use that term, but I objected that he was not given the credit for the statement.

I was sorry to see him get so disabled in the latter years of his life. His diabetes caused a lot of complications so that in the last two or three years of his life he had to get around in a wheelchair. Despite that he travelled all over the world. His second wife, Myrna Weissman, was an angel so far as he was concerned. When he died, I wrote Myrna and told her how much I admired what she had done for him, because without her I don't think he would have been anywhere near as productive as he was. The other gratifying experience in this field is that over the years you meet so many bright nice people. People you admire, people you value as personal friends and sometimes who have an influence on broadening your own perspective. Gerry is just one of many that I can think of.

Anyone else you want to include there as the people who have influenced you?

I have always had a tremendous amount of respect for Arvid Carlsson. We were at a reception a couple of nights ago and I told Arvid that a few years ago I had a chance to nominate somebody for the Japan prize and I nominated him. He said "Gee, that is maybe why I got it." I thought he was kidding. The next day Brian Leonard introduced him for a Guest Lecture and said that he had won it. I was dumbfounded because I would have

congratulated him the night before if I'd taken his statement seriously. Arvid has been an enormously fertile thinker. I have always said his genius was that he knows just how far beyond his data he can extrapolate to come up with novel ideas. Another genius is Paul Janssen. Janssen has been a genius in business as well as in science. I had a chance to nominate some people for the Nobel prize for several years running. One of my nominations was a trio of Black, George Hitchings and Paul Janssen for developing drugs, each one with a different approach. Hitchings used them as anti-metabolites, Black used homologues for receptors, and Janssen exploited structure-activity relationships. Well, those two won it and Paul didn't. Paul is one of the richest men in Belgium which probably turned the Nobel committee off, because the theory behind the Nobel prize is that it is to help people who need help. Paul certainly didn't need help financially. He is a very modest man, very congenial and very bright. I could go on and on but those are two of the giants in the field.

I got to know Julius Axelrod tangentially. I never worked in his lab, but I knew a lot of people who had. I knew Bernard Brodie whose heart must have been broken when Julius got the prize and he didn't. I remember a pharmacologist friend of mine came up one morning and said, "Guess who won the Nobel prize?" I said, "von Euler, Sutherland and Brodie." He said, "You're close, von Euler, Katz and Axelrod." I said, "Oh my God, Brodie must be shaken to his core." But they were virtually equal. Very pioneering in their work. Brodie was the founder of biochemical pharmacology. But these were the top dogs in the field. There are many many others who aren't that prestigious but who also had very good ideas and were quite influential.

Anyone else who stands out for you?

Frank Ayd is one. He and I became acquainted early in the game and have long been friends. My favourite story about Frank concerns the Christmas cards he sent while he was resident at the Vatican. One Christmas, my secretary after sorting out the mail said, "you have a card from the Vatican." I replied, "no doubt that's from Frank Ayd and if it isn't a signed photograph of the Pope, I'll be disappointed." It turned out not to be - merely an appropriate Christmas card. The following summer in 1964, while attending the CINP meeting in Birmingham, I lunched with Frank and told him the story. He remained rather non-committal. The following Christmas another card arrived somewhat different from the previous one. It was a photograph of Frank, his wife and 12 of their 14 children with Pope Paul. Talk about one-upmanship. I think my second son still has the photograph.

I have on occasion co-authored papers with persons who, though great in their own fields, were not close colleagues. These came about because of my belief that one paper on a subject is better than two. For instance, in the early 1960s, there was a flurry of excitement about a "pink spot" in the urine of schizophrenics. As it turned out to be a compound closely related chemically to mescaline, the thought was that this represented the residue of some endogenous psychotogen. Arnie Friedhoff had been investigating it in animals, but I decided to see what it would do in humans. I was the first human to take it. It did nothing to me or subsequent volunteers, it turned out given in progressively higher doses. Arnie found that it was immediately metabolized accounting for its inactivity. Arnie and I published jointly two papers, one on the clinical activity of the compound and the other on the reasons for it. Nearly at the same time, there were implications that alphanethyltyrosine, a specific blocker of tyrosine hydroxylase, might be useful in treating schizophrenia. We found it not to be so and so did Sam Gershon, who was working with it at the same time. Our studies were halted prematurely because dogs formed renal stones when given the drug - they have highly

alkaline urine. So, Sam and I decided to combine our two incomplete studies and publish together. I commented elsewhere on the impromptu collaboration with Sol Snyder. One would think that these collaborations would be encouraged, especially in this day of universal and rapid communications.

One of my greatest regrets is that I did not leave a greater legacy of students. Only two have become major successes. Ken Davis returned to his Alma Mater, Mt Sinai and turned it from a backwater into a major department of psychiatry in the US. John Csernansky was offered an endowed Chair at Washington University. I have no doubt that both would have succeeded without me. Perhaps the most a mentor can do is to provide encouragement and support early in the careers of rising students.

How does the field look after 35 years?

I must confess it is frustrating because the rate of progress has been so rapid with the neurosciences in the last 15-20 years. We have a totally new vocabulary spawned by molecular pharmacology and molecular biology - it's almost impossible for any individual to keep up with it. Much of the program at an ACNP or CINP meeting these days, perhaps 80%, would be as appropriate at the Society for Neuroscience. The promises of this new knowledge are so important in allowing us to have a fundamental understanding of mental disorders and the rationale for using drugs that nobody can short-change the possibility that we will soon have very selective drugs for these disorders in contrast to the non-selective and accidentally discovered drugs we had in the past.

But on that score the evidence of the last 35 years is somewhat discouraging. The difference between not having chlorpromazine and having it was enormous. The difference between having chlorpromazine and risperidone, clozapine or olanzapine is not that great. There is a lot of hype now about the new drugs for depression and schizophrenia. But if you look at them from a historical point of view, they don't represent a benchmark advance. I have only been present in three medical miracles - in my internship I had a patient with bacterial endocarditis who was one of the first treated with adequate doses of penicillin. She survived an otherwise totally fatal illness. The second one was having a patient wheelchair-bound from rheumatoid arthritis being able within a week to walk around the ward after getting corticosteroids. Though corticosteroids are not now the treatment of choice, they certainly had a tremendous impact. The third was the marked changes seen in schizophrenic patients with the anti-psychotic drugs.

I don't think we have reached another point that is as sharp as not having chlorpromazine and reserpine and having them. Risperidone may have less side-effects but there is a very very narrow margin between the therapeutic dose and the dose that will produce extra-pyramidal reactions. Clozapine perhaps over the long pull has some effect on re-socialisation and of course it works for many patients who don't respond to traditional drugs but that's always been the case - every time you get a new drug you find people who respond that did not respond to something before. And as far as the atypicality of the profiles I am not quite sure what all this means. Nobody has ever been able to claim that a D1 receptor antagonism has anything to do with schizophrenia and the purest 5HT2 antagonist, ritanserin, has been of little use in schizophrenia. So, it is pretty hard to believe that D1 or serotonin receptors are all that important in the action of atypical antipsychotics.

You're saying the neuroscience has advanced but the therapy hasn't.

No, I don't think the therapy has and in that sense that's perhaps why the balance of the program for these societies has moved more in the direction of neuroscience than clinical science because there is nothing so terribly new coming along clinically. Thirty-five years ago, before anybody was sure how to study these drugs and John Overall and I were trying controlled trials and objective measurements of change and so on. He provided many novel statistical analyses. You had some feeling of contributing something but these days that's all old hat. Every drug company has its staff that will produce an excellent protocol that will fly through the regulatory agencies. They have the statistical help in-house to process the data. They farm it out to some professional writing house to write up the manuscript. So, these days the clinical investigator is relegated to data gathering, which is a dull enterprise if you ask me. We really ought to be more experimental in trying to break out of the traditional parallel group double-blind design which thirty-five years ago was news but is news no longer and find ways that may be more expeditious and cheaper to screen these drugs and get them on the market.

What these drugs have done, which is a not inconsiderable advantage, is that they have reduced some of the side-effects and possibly produced a more specific profile of pharmacological effects. I may be too pessimistic, but I don't think that we have yet crossed into a new era. But we have so many leads now in affecting messenger systems at different receptors and so on that it may very well be that we will have new drugs soon. Arvid, in his lecture, made an indirect plug for his presynaptic drug, 3-PPP, but that has been kicking round for ten years now and not made the grade. If you want to work presynaptically, why not go back to reserpine?

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*Adapted from *The Psychopharmacologists, Volume I. Interviews by David Healy*. London, Weinham, New York, Tokyo, Melbourne, Madrid: Altman. An Imprint of Chapman and Hall; 1996, pp. 215-236.

February 17, 2022