

## FROM HALOPERIDOL TO RISPERIDONE

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**You've written a number of accounts of the way Haloperidol came to be discovered. The account in Discoveries in Biological Psychiatry, following the meeting that Frank Ayd put together in 1970 was one of the first. In this you said that when you came to write the piece it was hard to know whether to give an outline of the principles involved in the actual discovery or to give the emotional feel for what happened. I think in that account you looked more at the principles. Perhaps we could look at the discovery more from the emotional feel of what happened?**

The whole story probably starts with a friend of mine by the name of Arnold Beckett of Chelsea Polytechnic. He told me something that later on turned out to be wrong but anyway he claimed that Pethidine itself was not active but that it entered the CNS and was then demethylated to Norpethidine and that this was the active analgesic.

This was something he believed in and he made me believe it for a while so I came home and said if this is true then it should be possible to increase the potency of Pethidine easily by putting a Mannich base tail on it like this -

The new compound R951 is called a propiophenone. We lengthened the carbon chain by reacting the ketone, acetophenone, with formaldehyde to form R951. And indeed when injected into mice it turned out to be a few hundred times more potent than pethidine. Now why did I anticipate this high potency? Simply because chemically speaking the older compound pethidine is more stable than this new compound R951, which is also much more lipophilic. In those days we were still believers in the theory that lipophilic compounds somehow had an easier time entering the brain than hydrophilic compounds, which again is wrong but anyway that is what was believed then.

**Its curious how things can move forward even though all the ideas behind them are wrong, isn't it?**

Yes, the theory was wrong but in those days we were simply synthesizing new compounds, which we injected into animals and asked the question what kind of a compound is this? What does it do? Does it act like morphine, does it act like atropine? We had a small battery of screening tests. But one of the ideas that we had been working on - no more than a dream - was to find one day an amphetamine antagonist. You know the story behind that probably.

**There are a few different stories.**

Well I had seen a number of cyclists who, hoping to enhance their performance, had taken very large doses of amphetamine and was told by a friend that their amphetamine induced symptoms were indistinguishable from those of paranoid schizophrenia. I knew very little about psychiatry but these cyclists were hallucinating, they were stereotyped in their

behaviour, they had delusions and, when asked a question, they would always give the same stereotyped nonsensical answer. They were more or less excited. Clinically the syndrome was reminiscent of an acute attack of paranoid schizophrenia. So the idea was: let us try to find an antagonist of amphetamine - it would certainly be of help for the treatment of amphetamine intoxication and with some luck it might even work in the real disease. So we started to look systematically for amphetamine antagonists.

**1953/54 was extremely early to be thinking that a drug that could be used to antagonize amphetamine might be useful for schizophrenia. The whole idea of the amphetamine model had not been born at that time.**

No this was so-called original but it was simply the direct consequence of this observation in the cyclists. But the fact that amphetamine poisoning resembled paranoid schizophrenia was not completely unknown even then. To me it became very obvious and my friend, Fries Claes had seen many such cases because in those days cyclists in Europe were swallowing very large doses of amphetamine. Subsequently in the chemistry lab we started modifying the structure of R951 and one of the modifications was simply a lengthened side-chain with one extra CH<sub>2</sub> group, giving a butyrophenone.

When this compound, which we called R1187, was injected into animals something strange happened. The first effect seemed to be morphine-like but relatively short lived. This was followed by an effect resembling the effect of chlorpromazine. In those days chlorpromazine was new and its pharmacology was mysterious but sedation or what we called, catalepsy, was a prominent feature of this butyrophenone. We tested it as an amphetamine antagonist and, sure enough, it showed amphetamine antagonistic properties - for the first time.

What we then did was to chemically modify this structure (R1187), trying to increase the anti-amphetamine effect and to get rid of the morphine-like effects. This was achieved by putting an extra fluorine group on the phenyl group leaving the rest of the molecule intact and then replacing the ethylester moiety with a tertiary alcohol group - all very simple, straightforward chemistry. In order to make it long acting we put an extra chlorine group in the para position. The product was called R1625.

The difference between R1625 and R951 gives you an idea of the number of compounds that had to be synthesized because each time we tested a new compound it was given the next number. R1625 was then given the generic name Haloperidol. When injected into mice and rats, it was very potent as an amphetamine antagonist. We fiddled around a little bit but this was the best we could achieve.

Then we approached a few psychiatrists, one of them was Jean Bobon in Liege, trying to convince them to test my hypothesis in man - which they did but rather reluctantly. For six months they left the ampoules on the shelf. But in the middle of one night Andre Pinchard, one of the assistants in Liege, didn't have much to do and when a son of a local practitioner was brought in at night with symptoms of what appeared to be acute paranoid schizophrenia and severe agitation, he gave him 10mg of Haloperidol I/V, around 3 o'clock in the morning.

That had the effect we know well today. He was very impressed and phoned me, urging me to come to Liege. When I arrived around 9 o'clock the next morning, all I could see was a young boy asleep. His father, a local general practitioner, was there as well as Jean Bobon and Andre Pinchard. We discussed what had happened.

Jean Bobon decided to test the effect of 5mg I.V. of Haloperidol in approximately 50 acutely agitated patients. Agitation of any origin, schizophrenia, mania even delirium tremens. His first paper describes the effect of Haloperidol on psychomotor agitation not on schizophrenia. It simply states that the intravenous administration of 5 mg of haloperidol is quite active in calming down acutely agitated patients - that's all. Because even then he had not really tested the new compound in schizophrenia or by the oral route. This was done by Paquay, who was a psychiatrist working in Namur.

The first patient, the young man, treated by Andre Pinchard, was studying architecture. He had never previously had symptoms. His acute attack was completely unexpected. When he woke up the next day he was completely normal as far as one could tell. And then we started talking about what to do next - to continue treatment or what? A compromise was reached which was: 10mg is a heck of a dose, let us try a much smaller oral daily dose. The patient was given 1mg in drops in his coffee, I believe, or his tea which he drank daily.

He completed his studies, married and had two children. He had no psychiatric symptoms. Every year I was invited by the father, with Bobon and Pinchard to discuss the case and the question was always the same: was this really an attack of paranoid schizophrenia or was it maybe what French psychiatrists refer to as "bouffee delirante" because he had no symptoms and therefore shall we continue treatment or stop it? For six or eight years the treatment was continued because there were absolutely no side-effects and no symptoms. In the meantime what is today called biological psychiatry had been born. I was of the opinion that it was safer to continue treatment than to interrupt it, because there was obviously no harm done. It could have been paranoid schizophrenia and of course if the 1mg was really doing what it appeared to do then interruption could lead to relapse.

After about 7 years it was unfortunately decided to advise the boy to stop taking the drug. He did and lo and behold, three weeks later, in the middle of the night, he was brought back to the ward with exactly the same symptoms of paranoid schizophrenia. This came as a shock to the whole family and to the patient because he had studied and had a family and he was not convinced that he was suffering from schizophrenia, this ugly word and neither was the family. But now with the second attack, the diagnosis was obvious and it ruined his life. After his relapse the dose had to be increased to 3mg daily and he became more difficult to manage because compliance became a problem.

Paquay, knowing of this case said - well haloperidol is obviously very potent against hallucinations and delusions - I am going to try it in chronic cases. He tried low doses - 1-7mgs daily. The objective was very clear - to make the hallucinations and delusions disappear, to control the agitation if necessary and to re-establish normal human contact. These were considered the core symptoms of paranoid schizophrenia.

Haloperidol was not seriously tested in the other types of schizophrenia like hebephrenia, which I always thought was a different disease - it did not resemble amphetamine intoxication. We only tested it in patients that looked like amphetamine abusers - for want of a better word we called it paranoid schizophrenia. The closer the clinical picture was to amphetamine poisoning the more interesting was the patient. This is the reason why hebephrenia was not seriously considered. And even today I still believe that hebephrenia has a completely different etiology.

Paquay's success rate was very high. His main objective was not to produce side-effects. Patients who would not respond to 1-7 mg daily were considered non-responders. He thought that extra-pyramidal side-effects were awful: patients hate them and become very poor at compliance. Paquay was careful and patient and I believe that what he concluded in his first article on Haloperidol is still true. It was much later that, under the influence of American psychiatrists in particular, very high doses of Haloperidol were given in therapy-resistant patients.

**Do you not think the Dopamine hypotheses of schizophrenia had some part to play in the fact that people went up to extremely high doses. The idea that if Dopamine is abnormal in schizophrenia then if they fail to get well the answer is to increase the dose?**

Well, the Dopamine theory was not the same then as it is today. Again the whole thing started with amphetamine. I always thought that phenethylamine was the endogenous amphetamine and still believe that. Pharmacologically these compounds have similar properties and chemically the only difference between the two is the extra methyl group in amphetamine.

Phenethylamine, like amphetamine, releases Dopamine from the vesicular dopamine storage proteins. When phenethylamine or amphetamine are injected into the brain, dopamine is released from these proteins and this is why dopamine concentration increases locally. Now phenethylamine is a normal constituent of the brain. So even today I believe that the story of paranoid schizophrenia is relatively straightforward. My preferred theory is that for some queer reason, in certain regions of the brain, there is increased enzyme activity converting phenylalanine to phenethylamine or decreased MAO activity. This leads to an increase of phenethylamine concentrations and thus increased dopamine release. The rest is really the classical story. Neuroleptics are active against some symptoms of what is called paranoid schizophrenia but also in mania as well and mania and schizophrenia are certainly two different diseases.

**But they can also be used for people who are anxious.**

There is a problem with anxiety because the English word anxiety is untranslatable. There is the French word anxiete but anxiete doesn't mean anxiety. It is a difficult linguistic problem.

Later on we realised that there were two big problems with Haloperidol. One was the problem of compliance and the most obvious reason for lack of compliance was forgetfulness. Another reason was the fact that patients on too high a dose experienced side-effects and actually spit out their pills. And this is why Haloperidol decanoate was eventually developed: to improve compliance. When properly used Haldol decanoate gives better results in terms of control of symptoms and certainly in terms of relapse rate reduction.

We then made numerous haloperidol-like butyrophenones and diphenylbutylpiperidines and other neuroleptics, literally thousands of them and many were tested in schizophrenic patients. Always pursuing the same obsessive idea. Most of them were rejected, not because they were inferior but because they were not superior or significantly different. An important exception was R3345, which we tested a long time ago because it was such a powerful drug in the tryptamine test.

After the success of this anti-amphetamine story, it occurred to me that amphetamine is not the only compound producing symptoms that resemble schizophrenia. There is also LSD, which was thought to be a serotonin-like agonist. So we started looking for an LSD antagonist hoping that it would somehow complement the amphetamine story. But this was not an easy task. It was even difficult to set up a screening test that would mimic LSD. The best we find was the tryptamine test in rats.

We screened compound after compound after compound until R3345 emerged, which is dipiperone or pipamperone. Pipamperone turned out in the clinic to be very well tolerated and free of side-effects. It resembles Risperdal. The problem was the Americans didn't like it. Not the psychiatrists but the marketing people. They thought that Haloperidol was enough - that it could take care of everything - in spite of the fact that in America, certainly at the beginning, there was a very strong and long lasting anti-Haloperidol period. This was a direct consequence of the first publication on Haloperidol in the American Journal of Psychiatry, by Herman Denber, which you will have trouble believing.

**Denber is a fairly famous name in the early history CINP etc.**

But he did something unbelievable. He was responsible for research work in Manhattan State Hospital where he had 60 beds. But he did not get along well with his colleagues, who tended to give him the most untreatable patients. So his whole research ward was full of what we call chronic hebephrenics and they are resistant to whatever. Anyway he spent all his time touring the world looking for new compounds to be tested in his patients because his ambition was to be the first to publish on new compounds in America.

He came to see me after having visited Jean Bobon in Liege to see what Haloperidol was doing in patients there. He came to see me asking for samples. I was very pleased because I had never seen an American psychiatrist before. Being very honoured, I gave him all the samples he wanted. He went back home but what he did then was to give the samples to one of his nurses by the name of Mrs Kauffman. And Mrs Kauffman was instructed by Denber to give the new compound to 10 patients in increasing doses to see what would happen. Denber went on another trip probably. He actually never saw the patients. He came back and he asked Mrs Kauffman what is your experience with Haloperidol and she said it doesn't do anything at all. It is like water. It does not even induce side-effects. So he took his pen and he wrote a paper which basically says that Haloperidol is a very effective drug in Europeans but, for genetic reasons, completely inactive in Americans.

I jumped on a plane and I went to see his 10 chronic hebephrenic patients and to my amazement 2 or 3 of them were black, 2 or 3 were Hispanics, one came from Russia, the other from Germany. Ridiculous! But he had never seen these patients. He must have been as surprised as I was. But it was published. The other Americans including the managing director of McNeil, a sister company supposed to sell Haloperidol, said : well Haloperidol is a dead fish. It will never make it. Look at Denber, who says it doesn't work in Americans, it only works in Europeans. As a result from 1960-1964, I believe, nobody gave even one dose of Haloperidol in the States. In the meantime, the drug became generally available in Europe and in Japan. It was a real horror story - until in 1964, a psychiatrist of Italian extraction published an open study on Haloperidol in about 250 patients treated in a state hospital in California describing "European" results in American patients. It didn't bring anything new because it was simply an open study and it confirmed well-known observations. But in America this had an effect because it showed that after all Haloperidol was doing something. The doses he gave were small doses. He was dosing his patients like Paquay more or less, so the side-effect profile was okay. This is how interest in Haloperidol in America emerged in 1965 approximately. Then eventually it was marketed and today it is the most widely used neuroleptic in America and elsewhere.

Then dipiperone was put on the market in Europe. In hindsight you could say dipiperone is interesting because it is the first D-2/S2 antagonist. In those days the serotonin story was completely unknown. There is one publication by an American psychiatrist, Sugerman, on dipiperone which is like reading a paper on Risperidone. It is almost the same story. Sugerman was very satisfied but McNeil did not want it. Therefore the "world" never heard of it. It is a pity because if McNeil had marketed dipiperone, I believe that what is called biological psychiatry would have changed completely. Today the serotonin story is a relatively new story. But it is true that dipiperone was not particularly potent. The doses to be given were high - 60 - 240mgs per day but well tolerated and effective. Ever since, therefore, we have tried to find a more potent and "better" dipiperone and for me Risperidone is just that - a better dipiperone.

Risperidone is not an atypical neuroleptic. It is a typical neuroleptic but it has very strong effect on S2 receptors which probably explains the fact that many people who take it sleep better and because they sleep better they are probably less depressed. In recent years I have been interviewing lots of patients and my impression is that a patient who responds better to Risperidone than to Haloperidol is a typical schizophrenic who over and above his schizophrenic symptoms is rather depressed and claims not to sleep well. This patient is likely to respond better simply because of this obvious effect on deep sleep. I don't like the claims that are being made about negative symptoms. I don't really know what they mean but I know what it means not to sleep well. That I can understand easily - to feel lousy in the morning because you have not slept well. This effect on sleep is probably the additional benefit in my opinion of Risperidone plus the fact that fortunately enough from the very first the recommended doses were low and therefore EPS occurs only in a minority of patients but EPS can be induced with Risperidone as with all other neuroleptics if the daily dose is increased.

**You had the first meeting on Haloperidol here in Belgium, in 1959, a year after it had been launched. At this there were 17 papers describing the full range of uses for the drug. Its usefulness for Tic disorders and other conditions had been picked up even then. This all seems extraordinarily rapid.**

Well it took six months. The story is as follows. I knew very little about psychiatry. I had no contacts with psychiatrists whatsoever. And I was very sceptical. My father who was an MD told me to beware of psychiatrists. He was convinced that most of what they had to say was simply not true - that they were very good at inventing all kinds of fancy stories. But my father was too skeptical. It took him quite some time to believe that penicillin was doing what it was doing.

Thinking about the problem and feeling convinced that Haloperidol was indeed effective - on the basis of very few patients actually and without double blind evidence at all but based on the notion of obviousness, a recognition of what was obviously effective. In those days the notion of obviousness still existed and was accepted. Like in anaesthesiology, the intravenous use of an opiate is obviously effective. Nobody ever asked me to prove it double blind test.

What I did, with the help of friends, was to find 8 of the best known psychiatrists in Europe. Jean Delay was quite helpful and we became very good friends. I was very young and he took an interest in what I was doing and helped me as much as he could. He told me I should go to Professor so and so - Lopez-Ibor in Spain, for instance, and a few others in Germany and so on. We asked all 8 to test Haloperidol, on an open basis. They didn't know that they were a group of 8. They all thought that they were the only ones who were doing it and there were no contacts between them. Six months later, we asked them to come to Beerse and to give us their impressions, which we published (references). What really convinced me was that all 8 had exactly the same clinical impressions. This is quite clear from the book. I said well it is statistically highly improbable that 8 completely independent

psychiatrists, who had not been influenced at all, living in completely different environments, using different languages, customs and even concepts of psychiatry would arrive at exactly the same opinion in the course of six months. So it must be true and that was the end of clinical investigations. Practically all we know about Haloperidol can be found in that first publication.

**The fact that people picked up its usefulness for Tic disorders so early was quite striking.**

Well this was based on an observation by Jean Bobon I believe. Simply in a mental a schizophrenic patient with tics, probably a case of Gilles de la Tourette's disease. He responded very well to low doses of Haloperidol and other patients with tics were then treated with small doses and in general the effects were quite obvious and published.

**Out of that you could deduce potentially the idea that some of the delusions in Haloperidol responsive forms of schizophrenia are mental tics.**

Well yes. This is the stereotypy hypothesis which is in my opinion more than a hypothesis - its obvious.

**On that point, one of the arguments you get from someone like Tom Ban is that 40 years ago what we ought to have done when we found that drugs like Chlorpromazine and Haloperidol worked was to have defined much more clearly which were the groups of people that they worked for and tried to work out the psychopathological consequences of that. Instead the industry hurled compound after compound at us and we have never had a chance to actually take stock.**

We tried very hard using all kinds of tricks and internally it worked very well. One of my pet ideas has always been that schizophrenics for whom haloperidol works well are stereotyped in their movements and their thinking and in their behaviour. As if they have no internal inhibition in the Pavlovian sense of the word. As if they cannot shift from one idea to another very easily. This is a feature of amphetamine poisoning too.

I remember the construction of a small gadget with 10 knobs numbered 1 - 10. Volunteers in the laboratory were asked to push these knobs at random following the rhythm of a metronome 200 times consecutively and this was then analysed statistically for randomness. These volunteers were able to maintain randomness but a schizophrenic was asked then he could only do it for a short period of time. After five or six times or so, he would push do three and then four, three-four, three-four, three-four. He couldn't do it but if you give him a neuroleptic his performance improved.

I also remember playing around with stimulating the pupil of individuals with invisible light but light of sufficient intensity to create measurable miosis. If you do that there is rapid extinction - in other words the first stimulus produces miosis, the second less, the third even less and after four or five stimuli there is no miosis anymore - except in schizophrenics. In schizophrenics the miotic response continues without extinction. They don't seem to be able to distinguish between what is relevant and what is irrelevant. They seem to be unable to extinguish irrelevant stimuli. In this sense it is the opposite of Parkinsonism. When I talk to Parkinson's patients about their movements, they all claim the same thing which is that there is a considerable delay between the decision to start the movement and the actual start of the movement. It takes a long time for a Parkinson's patient to actually start doing what is intended. It seems to me that with the untreated schizophrenic it is exactly the opposite - that he cannot but respond to every stimulus and of course being forced to respond it is no wonder that his response is stereotyped. This is the way I see it.

This is probably the reason why the striatum plays such an important role in mechanism of action of neuroleptics. Because it is in the striatum that internal inhibition is created - not in the cortex. This is why I have always believed that the real therapeutic effect of a

neuroleptic is indeed a neurological effect. If you do it right internal inhibition is restored. If you over do it you get something that resembles Parkinson's disease.

### **What was Jean Delay like?**

Jean Delay was a very famous psychiatrist but he was really more interested in literature and in the French academy than he was in psychiatry. He was in charge of the Department of Psychiatry at Hopital Saint Anne in Paris but in fact he delegated a lot to Deniker and Pichot.

### **Did he see patients.**

That was far below his dignity. He spent most of his time writing books on Andre Gide and attending meetings of the French Academy. His main interest was the French language. He was really an academician above all. Not only did he not like psychiatry, he actually disliked it. It was not easy to come in contact with Jean Delay.

### **So he is not then the person who actually discovered Chlorpromazine.**

The way it happened as far as I can figure out is that Rhone-Poulenc synthesized Chlorpromazine as an extension of the anti-histamine series, I suppose everybody knows that story. When the pharmacology was done and published by Mlle Courvoisier it was obvious that this was something completely new. Mlle Courvoisier was thinking of a possible application in anaesthesiology because the compound was first given to an anaesthesiologist by the name of Henri Laborit who tested it in patients and noticed, because he was a good observer, that they became indifferent. That was the main effect he observed - the fact that it made people indifferent. He had a brilliant idea which was simply that this could conceivably be beneficial in the treatment of certain psychiatric disorders. So he convinced Rhone-Poulenc that it would be a good idea to test it in psychiatry. But in those days, the idea of treating psychosis was considered ridiculous, because psychosis by definition was an incurable disease. When I was young one of the definitions of psychosis included incurability. If the psychosis disappeared, this was indicative of a misdiagnosis. The idea that it could be cured with a pill was ridiculed as simply too childish an idea.

I really do not know how Rhone-Poulenc established contact with Jean Delay but he must have somehow accepted the idea of having this compound tested. His contribution was to coin the word neuroleptic, a very nice word in my opinion with a very clear meaning implying a compound inducing striatal effects. This was, as far as I can tell, Jean Delay's main contribution to the field because he delegated the clinical investigation of Chlorpromazine to one of his two principal assistants.

He had two assistants Deniker and Pichot; Deniker got chlorpromazine. This created of course problems within his own service because Pichot was not very pleased. Deniker was somewhat older than Pichot and that is probably why it went to him. Deniker, of course, didn't test chlorpromazine himself but he had another psychiatrist working for him who then reported to him and this is probably how the whole picture emerged. The Haloperidol part of the story, is of course better known to me because I was a witness. Haloperidol, a little bit later, was given to Pichot, Deniker's rival in a certain sense.

### **Did Pichot actually see the patients or..**

Pichot saw patients but not very many. Fortunately he had a very good assistant, a woman by the name of Mlle Lemperiere. She was really a very good observer and she took care of the patients and reported back to Pichot. Most of the actual work and the observations were done by Mlle Lemperiere as far as I can figure out. When I wanted to know something about the clinical effects of Haloperidol, after a very short period of time I realised that the most effective way of knowing was to talk to Mme Lemperiere.



I have always been convinced that the quality of the observation in psychiatry in particular is much more important than the quantity. The Goldstein double-blind test work on Chlorpromazine versus Placebo convinced me of this.

### **How was that?**

Well briefly one of the first double blind studies published in the American literature was a study by a psychiatrist working in Miami called Goldstein. He compared 4 Grams of chlorpromazine per day with placebo in what he called chronic schizophrenic patients. And the conclusion was that there was no difference in efficacy - not even in side-effects.

I went to see him because we ran into similar problems with Haloperidol, where American patients apparently were said to be very different from European patients. I said well this is strange, what on earth is going on on the other side of the ocean. So I went to Miami. I saw Dr Goldstein for the first time sitting behind a large beautiful mahogany desk on one side of the street. On the other side, there was a State Hospital and a large building filled with computers. This was in the 1960s: huge computers with punch cards and lots of girls punching cards and filling boxes.

I asked Dr Goldstein to show me the patients because I could not believe that there were patients who could tolerate 4 Grams of chlorpromazine without side-effects more serious than those observed with placebo. I simply could not believe the story. There was something wrong. Goldstein when he entered the State Hospital did not even know how to open the doors and it was obvious that he did not know his observers. It also became evident that he had hardly ever seen the patients. He had a small army of paid observers who were walking around the wards from morning to evening, filling in cards and rating the patients. But they could hardly read or write and they were obviously quite indifferent - they could not care less. They hardly knew what they were doing and it was very monotonous to rate patients always the same patients, always the same ratings. I had the impression that they filled in the cards practically at random because they knew that it was all blind and that the quality of their work was impossible to control. Then the raw data sheets went from the observers to the girls who punched the cards and of course it became very clear this was "garbage in and garbage out". It was so crude and unreliable that even a difference between 4 Grams chlorpromazine and placebo was not detected.

From that day on I have always been very sceptical when it comes to double blind trials because the same risk exists everywhere. I don't know of any learned professor or any very good observer who takes the trouble of doing what the protocols require in terms of observing. Certainly not in psychiatry. But what is the reliability of a psychiatric observation if it is done by somebody who does not know anything about psychiatry? I am not talking about theoretical psychiatry, I am talking about someone who knows how to observe psychiatric patients.

### **Did the Goldstein study have much impact at the time.**

Well chlorpromazine was first approved in the United States by the Food and Drug Administration as an antiemetic. Even Smith-Kline and French who had the rights to sell it under a licence agreement with Rhone-Poulenc did not believe in its activity in psychiatric patients. They thought that this was an invention of some queer French Psychiatrist. It was only after the compound was marketed as an antiemetic that it was used more and more by psychiatrists. A few years later it was officially approved for that use in the United States. But even then as far as I can remember, there was no double blind evidence for its use in psychiatry. In order to get something approved double blind tests were not always required as they are today. I presume, but I am not sure, that the FDA approved chlorpromazine because they were pressured by family members and various pressure groups. We had pimozide approved in the States for Gilles de la Tourette's disease for the same reason not because we had so much double blind evidence but because the associations of parents of

patients were actually pushing very hard on the basis that in some patients the effect was so obvious, they claimed, that they could not do without it.

**Was the Goldstein study then picked up by the psychotherapists as evidence that neuroleptics did not work as they had always said.**

When Rhone-Poulenc asked Deniker to go to the States and promote chlorpromazine for the first time, he was ridiculed by the psychoanalysts because psychiatry in the States in those days was dominated particularly in the large cities by very expensive psychoanalysts and the idea that a simple pill without psychoanalysis could actually be beneficial to patients with delusions and with hallucinations was ridiculed. So much so that Deniker came back completely exasperated after about two weeks.

**But wasn't there something similar to some extent from psychiatrists here. Divry, Bobon's boss, was never convinced that Haloperidol was effective despite the evidence?**

Well Divry was the Professor of psychiatry in Liege and he was super-sceptical. He would practically never use the word schizophrenia. I remember that he once told me: don't believe Bobon, I am telling you, young man, nobody will ever cure schizophrenia. What he really meant was chronic hebephrenia because only patients with a very low IQ who were chronically ill were in his opinion probably suffering from schizophrenia. All the others were doubtful and he was not interested. He was constantly looking at slides of brains and he was more interested in the shape of the brain of a human being than in psychiatry. He was a strange man and he played no role at all in the development of haloperidol.

But Jean Bobon, who was his first assistant, was eager of course to get Divry's job because Divry was approaching retirement. He was very eager to publish something because he had never published and that played a role. I had never been in contact with psychiatrists and I was very pleased that there was at least somebody who was willing to look at Haloperidol.

**You had problems with your licensing in the States....**

With Searle yes. Searle was a large company in Skokie Illinois, run by its founder, Jack Searle, who described himself as a glorified book-keeper. They were doing very well and they were good licensees for one of our anti-diarrhoeals - Lomotil. That was doing very well and we got substantial royalty income from them. But we had signed a contract and under the contract Searle had the right of first refusal on anything that came out of our research laboratory.

The day came when Jack Searle had to make up his mind whether or not to exercise his right of first refusal for Haloperidol in the United States. His decision was negative. His argument was I am only a glorified book keeper but we have tried twice to launch a psychotropic drug in the States and we failed twice. First with Dartal and then with Mornidine. Dartal, chemically speaking, was simply acetylated perphenazine or Trilafon. Trilafon has a terminal -OH group which can be acetylated and when you do this you get Dartal. Its main metabolite is trilafon so there is absolutely no difference between the two. Trilafon had been on the market for a long time and was relatively successful and sold by Schering. Searle with their new compound had nothing to add and they didn't know the field and therefore they didn't sell much.

Mornidine was also a phenothiazine and anti-emetic. But it had a very powerful alpha-blocking action and therefore orthostatic hypotension was a common side-effect. This is the main reason why it failed. So Searle said he was not going to make the same mistake three times. In England, in Australia, in South Africa, in Japan, all right, but not with Searle in the States. And this is why Haloperidol is still sold by Searle in part of the world under the trade name Serenace but not in the US.

This refusal to me was like Searle planning to kill my brain child in a certain sense. I said anything you want but not that. So we discontinued our relationship with Searle and as a result we eventually merged with Johnson and Johnson a few years later. That shows how important one seemingly minor misjudgement can be. Otherwise we would probably have merged with Searle. It is very strange. The fact that Denber had published these negative articles of course strengthened Searle's hand because Jack Searle was led to believe that Americans reacted differently to Haloperidol than Europeans did. It is unbelievable but true and I could not really convince him unfortunately.

**From all you have said one could draw the conclusion that you believe that the escalation of doses that we had during the 60s and 70s and 80s has been one of the great crimes. Why did it happen?**

Yes it did a lot of harm. It happened under the influence of American psychiatrists, some of whom I know, who thought that drug resistant schizophrenics were not given sufficient doses and that more must be better. This, of course, was not resisted by marketing people because the more they sell the better. So this was in a certain sense a conspiracy between psychiatrists who expected to see better results with higher doses of Haloperidol and the marketing people, particularly at McNeil, who were pushing the use of these high doses in order to sell as much as possible, in my opinion. This is something that should never have happened because first of all the results were not better except maybe in a few cases. And secondly the whole world became scared of so called tardive dyskinesia and all kinds of other irreversible extra-pyramidal side-effects or EPS.

**Could one argue as well that to some extent the drugs have been used punitively almost in that they have been used as a means of behavioural control at times in perhaps wards where say the ratio of nurses to patients is not all that it should be.**

I have always been a strong believer in the fact that in order to get good results with neuroleptics one had to determine what I call the optimal dose, because the difference between a low ineffective dose and a high over-dose is small. The optimal dose concept is rather crucial in my opinion. If a patient needs 3mgs don't give him 5. If he only needs 1mg don't give him 3. I have always been a strong believer in the usefulness of the handwriting test as described by the German psychiatrist, HJ Haase, more than three decades ago.

**Hanns Hippus put it to me that yourself and Jean Delay and Haase between you were the people who came up with the idea that in order to have a neuroleptic you have to have a compound that produces extra-pyramidal side-effects, while he held out for the possibility of a non-neuroleptic antipsychotic - like Clozapine.**

I think I know the Clozapine story from the beginning to the end. It is not a very nice story. Clozapine was synthesized for the first time by a chemist working for the Swiss company Wander. Stille did the pharmacology and he realised that it was a weak sedative neuroleptic but in his opinion not interesting enough to be tested clinically, so it was shelved. Then Wander was bought by Sandoz, who hoped to find lots of interesting new compounds at Wander but didn't find anything. They started scratching and scratching and found compounds that had been shelved like clozapine. They asked Stille - who later became a good friend - why on earth didn't you test this compound clinically and he answered because it is not interesting enough in my opinion. Sandoz said well we have paid a lot of money for Wander and we need something out of it and as marketing people we know that if we can make the world believe that this compound is maybe not as potent as chlorpromazine or haloperidol but free of EPS, then some psychiatrists at least will prescribe it. Because in these days EPS was already something that people were very afraid of.

Psychologically they were right. They approached people like Hippus and convinced him to test clozapine clinically and to start spreading the gospel that this was an atypical neuroleptic free of EPS. It is true that tolerated doses are virtually free of EPS side-effects. It is a

neuroleptic in the sense of Delay but only at very high doses. It is above all a very potent Alpha blocker. It is a relatively weak S2 antagonist.

Hanns Hippus is a very good friend of mine. His photograph is over there but if he were sitting here I would tell you exactly the same story. Actually I met him in Munich some months ago and we discussed this very openly. He did not contradict my story. Hanns was working in a famous clinic in Munich in charge of the administration and patients were seen as a rule by assistants - Herr Professor did not see many patients. But he went to all congresses you can think of trying to spread the gospel that clozapine actually was an atypical neuroleptic and had no effect on the striatal system and was free of EPS. It was completely different and not a neuroleptic but very potent. Sandoz then marketed the compound until it was found to produce agranulocytosis and then it was withdrawn from the market.

That, I thought, was the end of clozapine. Then, several years later, under the influence of Meltzer, the same story was spread all over again in the States. When Meltzer talks, he pronounces the word clozapine at least once in every sentence if not twice. He tries to make the whole world believe that it is in the patient's benefit to be treated with clozapine in spite of the fact that his blood has to be monitored every week.

**But it does seem to do something for some patients that some of the others...**

It sedates. In my opinion this is all. I would very much like to see these fantastic patients that they are always referring to. I have been looking for them but I have never seen them. It all depends on what we want and what we are talking about. In my opinion a good compound for the treatment of patients with symptoms resembling amphetamine poisoning are drugs that will have a very clear cut effect on hallucinations, delusions, improve human contact and are active if necessary against psychomotor agitation without side-effects. This is what we should be looking for and this is not at all the case with clozapine. It is practically impossible to treat acute cases with clozapine without running into terrible problems with alpha blockade for instance. Most of the clozapine patients I have seen are severely sedated. This is not what we want. But it is understandable that if patients are troublesome in a hospital setting and if they are being treated with heavily sedating neuroleptics that the nurses have an easier time and are satisfied. Well if this is the criterion, then yes. I may be exaggerating a little but in my opinion this whole field of the so-called "atypical neuroleptic" is a pure invention. I would not know how to define an atypical neuroleptic; what on earth does that mean? The word neuroleptic, as coined by Jean Delay, has a very specific meaning. It is by definition a compound that can induce extra-pyramidal side-effects.

**So can you have an anti-psychotic that is not a neuroleptic.**

This is what we have been looking for for 50 years now. We and others have never found it. I don't like the word anti-psychotic. What are the drugs that we know to be of interest in the treatment of severely diseased psychiatric patients? - the typical neuroleptics and reserpine. What else? I don't know of anything else. Everybody and his brother has tried to find drugs devoid of neuroleptic activity but active in the clinic but each time we have tested such compounds in the clinic we have failed - like everybody else unfortunately. If the dopamine story is correct then we should not be surprised.

**If it is correct why do we need the 5HT 2 input?**

Well what always struck me was that so many chronic schizophrenics not only hallucinate and have delusions and difficulty to establish human contact but they also complain of sleep disturbances and if we actually objectively measure their EEG it is very abnormal. Many of them even sleep during the day and walk around at night or wake up repeatedly. And many of them claim to feel rotten because they have not slept well. This is very common. There is the same symptomatology in dysthymic patients. You don't have to be a schizophrenic to have these symptoms.

When we started looking for pure centrally active serotonin antagonist, the first compound we discovered was ritanserin, which is not on the market. We did not really have the slightest idea of what a serotonin antagonist would do - except of course antagonize some of the effects of LSD. To our enormous surprise the most obvious effect of this compound, in animals at least, was an effect on sleep. In man it doubled deep sleep - phase 3 and 4 sleep - from 2 hours a night to 4 hours. In these days we had a sleep lab in England with Chris Idzikowski doing most of the work. We studied this compound in normal volunteers and in dysthymic patients - most of these dysthymic patients are seen by GP's not by psychiatrists. Ian Oswald in Edinburgh looked at this and he became convinced that this compound was very active in the treatment of what the Americans called neurotic depression but what many others prefer to call dysthymia - basically patients who claim not to sleep well. They are not able to have deep sleep - stages 3 and 4 - and when they wake up in the morning they feel lousy. If this goes on for a while, they get depressed. If you make these people sleep better with ritanserin, objectively deep sleep reappears and their complaints disappear. They stop claiming that they have not slept well and they start feeling fit in the morning. They are less depressed, life becomes more bearable and even pleasurable. This is very unusual for these patients because typical dysthymic patients in my experience have forgotten what pleasure really is. Many of them even end up committing suicide.

So for reasons that are not clear to me, dysthymia in schizophrenic patients is very common. Typical dopamine receptor blockers like Haloperidol have virtually no effect on sleep. Sleep does not get better or worse: one of the shortcomings of typical neuroleptics. And I believe we have learned that sleep disturbances can be improved with at least some S2 antagonists like ritanserin. But instead of launching ritanserin plus Haloperidol, we tried to find a drug which has the two properties, hoping to have less trouble with compliance. On hindsight, this was probably a mistake because we had done studies with patients who were receiving Haldol decanoate optimum dose plus ritanserin and the effects were the same as with risperidone.

In the meantime, I have learned that patients with sleep disturbances when treated with S2 blockers, like ritanserin or risperidone, fairly often feel very much better. They actually like these drugs. This to me is new because as you know many schizophrenics when treated with haldol don't like it at all. I actually have rarely seen a patient saying I like to take your Haloperidol but I have seen many patients and I have received even more letters from patients and their family members about risperidone saying: I feel so very much better, this is changing my life and thank you very much for having discovered it. So there must be something new and this has nothing to do with the schizophrenia itself but with the fact, in my view, that these patients simply sleep better and as a result feel much better, can cope much better and can be more easily reintegrated into society.

**Would the market conditions have been as good for Risperdal as they have if Clozapine had not been re-invented. It helped to push out the D2-S2 story.**

Well I simply expect clozapine to completely disappear and I am very surprised it hasn't disappeared already because to test the patient's blood every week is not very pleasant. An incidence of agranulocytosis of 1% is not to be taken lightly. To me the word agranulocytosis is more frightening than EPS. Maybe I am blind but when I compare patients treated with Risperdal to those who are treated with Clozapine the difference is so huge that even a blind psychiatrist must see it. That is one reason. The second is simply an economical reason. The treatment of patients with Clozapine is very much more expensive. So these are two reasons and then purely from a scientific point of view I would like this confusing story to disappear.

**Up till about 1988 people seemed to be proceeding down the lines of producing more specific compounds, more specific D2 blockers in particular and that has all been thrown open now. Was clozapine not responsible for that?**

I have never been influenced by clozapine. Clozapine has created an enormous amount of confusion - enormous. It has set psychiatry back, I believe, for a decade or two. All I am saying is only what I am convinced of by the way. I hope it is right.

**Let me hop back to 1957. At the time you seem to have been interested to enter the psychiatric market which was unusual because companies then weren't terribly interested in psychiatry. It took someone like Jean Delay to force Rhone-Poulenc to develop chlorpromazine for mental illness, without him they would not have been interested it seems to me. So why were you open to the idea.**

Don't forget in those days we were not a pharmaceutical company we were a research company. In 1953, my objective was not to create an international pharmaceutical company but to create an independent research company. Marketing did not even enter the field. I knew nothing about marketing. We were not selling anything. Everything was sold under licence by others. McNeil, for instance, was our licensee but before that Smith-Kline & French was our first licensee, second was Searle with Lomotil and the third was McNeil and in Japan we have had lots of licensees. So marketing considerations did not play a role.

For instance when we started looking for these very potent morphine-like drugs this was not because of marketing considerations. On the contrary everybody was saying: what are you going to do with these things. After we had found them, we discovered that they were useful in anaesthesiology. Today they are very widely used and we have a kind of monopoly because marketingwise they are not very profitable. One of our compounds, sufentanyl, a very potent morphine-like compound, is used in at least 80% of all cases of cardiac surgery worldwide. Without it, I don't believe that cardiac surgery would have achieved what it has done. So these were considerations that did not even enter my mind - fortunately, because otherwise we wouldn't have done it.

Or, take synthetic antidiarrhoeals, we have a kind of monopoly in this field. They are morphine-like drugs that do not enter the CNS and so are better than codeine because they produce absolutely no CNS effects and their abuse liability is zero. All of this came out of our morphine research but this was not anticipated. We were trying to find active compounds and after having found active compounds we tried to answer the question what could they be used for and not the other way around. Not first a marketing consideration and then research but first research and then marketing considerations.

I always thought from the very first day when we started this research company in 1953 that somebody who would be better than anybody else in finding novel and better compounds would have an easy time - would practically automatically become rich. This was true because today we have approximately 34 Janssen companies all over the world selling most of the compounds we discovered on a large scale. Until very recently we still were a research oriented company where research was really calling the shots and marketing was simply doing what research suggested.

Research can be looked upon as a goal or as a means. I have always considered research as a goal in itself - like playing chess or any other game. And I have always tried to be the world champion in a certain field. Today more and more people in the pharmaceutical industry are looking at research just as a means to make more money, literally speaking. This usually doesn't work and I have no sympathy for it. I believe drug research only makes sense when it benefits patients. To put it in other words I am not ashamed to make a lot of money but only when the drugs we have discovered offer great benefits to patients - it is only reasonable that these patients should pay some money for what we are doing for them. It is

like a medical doctor asking for a fee. I am not ashamed of that but I would really be ashamed of selling clozapine for instance. I would never do that never.

**There is a feeling you get from some people who work within the industry these days that there has been a change within the pharmaceutical industry. Whereas before people who were researchers or clinical people headed up the companies. Now it is the MBAs and this is not helpful development.**

What is paralysing the industry in general as far as I can tell are these regulations called good laboratory practices, good manufacturing practices, good clinical practices etc. In other words everything seems to be based on the assumption that we are all cheating and lying and we have to prove almost daily that we are not. Unfortunately some people are cheating and lying and therefore it's understandable. But today, people in industry are complaining that they are spending more and more time filling in all kinds of forms and protocols and they have less and less time to do research. This is true because if you really have to follow good clinical practice, for instance, then you have to fill in I don't know how many pages per patient.

**Is there more than just that though. For instance, I can see the role that GCP plays in all this but if you take a company like Ciba-Geigy who in the early 1970s had a string of compounds in the pipeline. Early SSRIs, interesting neuroleptics and a whole range of other compounds but none of them ever came to the market. There seems to have been some corporate failure there.**

The case of Ciba-Geigy I can explain because Ciba-Geigy is one of our best licensees in the field of plant protection. In the field of plant protection we have always done research and other companies the selling until recently. We have been very successful in finding the most widely used anti-mycotics for instance in plant protection and Ciba-Geigy has always been one of our licensee. Now what was wrong with Ciba-Geigy? What was wrong is that the bureaucracy was even worse than here. They had one big tower called research, another tower called development, a third tower called sales, another tower called production and there was too little contact between these towers. The man who was in charge of the development of plant protection was the late Professor Franz Schwinn who became a very good friend after a while. He was frustrated because he didn't get anything of interest out of research and if development doesn't get anything interesting out of research what can it hope to do? Management, of course, was constantly complaining that Franz Schwinn wasn't doing a good job.

He learned that there were some azoles available here in Beerse that, in his opinion and in ours of course, were promising drugs for the treatment of fungal diseases in plants. So when we met, he asked whether we would be willing to work with him. He "jumped" at our azoles and developed them like nobody else ever did. He was very good at it and in a certain sense saved Ciba-Geigy. Now what was his motivation? His motivation was to show that there was nothing wrong with his development group but that there was everything wrong with the research group at Ciba-Geigy. We were both happy of course. We were happy because he was doing such a wonderful job with the compounds we had discovered and he was happy because he saved Ciba-Geigy. Unfortunately the management of Ciba-Geigy is flying so high in the sky, the story as I am telling it to you is probably even today not generally acknowledged.

Then there is something else that I am seeing more and more and that is that it seems to have become fashionable these days to "manage by fear". To manage by saying if you are not going to do what I tell you to do I am going to fire and replace you. It is brutal, it is stupid and it doesn't work. But that is what is going on in the world. It is terrible. I have always tried to convince people. To follow the philosophy that good people need to be convinced and by definition don't need to be controlled.

I always believed that in order to be successful, certainly in a large company, decentralised management is essential. To decentralise and to delegate is very simple if you have good people because good people by definition don't need to be controlled. But today everything is being controlled all the time. Good laboratory practices actually demand that everything should be controlled all the time. Good people don't like to be controlled. I certainly don't. It demotivates. So the system itself I believe is rotten.

**But the system is there because of the individuals who as you say have cheated.**

Yes, criminals should be put in jail but unfortunately we cannot prevent crime. Cheating cannot be prevented. In my opinion it is very stupid to cheat: it is much more clever to be honest. The advantages of virtue are so obvious that people should practice virtue out of self interest. People who cheat are simply being stupid and will be caught sooner or later. They will lose their credibility and they should be severely punished in my opinion. But the idea behind these good laboratory practices is to prevent cheating and that is impossible.

I don't know whether you know the story of Mr Poggiolini in Italy. He is now in jail but he used to be the head of the Italian food and drug administration. He was called Mr 10%. Being the oldest of all of his colleagues in Europe, at one point in time he eventually became number one in Europe. Today he is in prison in Naples and he is telling his story. This was the man who called the shots - who had to control the industry, yet he was a cheat. Who was controlling him? Maybe I am getting too old .....

**One of the other people who began with a very successful drug during the 1950s and his own company to some extent but who didn't develop in the same way as you was Frank Berger.**

I have known Frank Berger quite well and was even present, by pure coincidence, when the word tranquillizer was born. Do you know who the inventor of the word was? Nathan Kline. Frank Berger had invented Miltown, as you know, and he was about to launch it as a modern sedative. He was a friend of mine and we were having dinner in a restaurant in New York with Nathan Kline, who had done some clinical studies with Miltown, seeing sedative effects but nothing very pronounced. Berger was talking about his ideas of how to launch this product. He already had his trade name, Miltown. But he was going to call it a sedative and Nathan Kline said: you are out of your mind. The world doesn't need new sedatives what the world really needs is a "tranquillizer". The world needs tranquillity why don't you call this a tranquillizer you will sell ten times more. Frank Berger was not a fool and he followed the advice of Nathan Kline, called meproamate a tranquillizer and was quite successful for a while.

**Very successful.**

Yes until Roche took the market over with Librium. Randall who did the pharmacology was a good friend and he compared all the new compounds with Miltown, which was the enemy to be beaten. Miltown was only active at high doses and Librium was quickly seen by the whole world as being a big leap in the right direction and now we have the other benzodiazepines and God knows what else.

This is important because when we tried in the United States to introduce the word neuroleptic the Americans did not want to hear the word neuroleptic. It was unknown to them, this invention by a strange Frenchman, Jean Delay. Rather than use the word neuroleptic they preferred to call neuroleptics "major tranquillizers". Minor and major tranquillizers! I have done my utmost to change this but the word tranquillizer although invented for promotional purposes by Nathan Kline and although it had nothing to do with neuroleptics was used in the American literature for a few decades. It is only recently that words like neuroleptics and anti-psychotics are replacing it.

**What did you make of Nathan Kline.**



I liked him. He was funny. He was also one of the first investigators of Haloperidol in the States. He wrote me a letter saying your compound is worthless: I have treated 10 patients giving them 1mg the first day, 2mg the 2nd, 4mg the next 8mg the next, 16 the next. He doubled the dose every day and he said he had to stop treatment in all cases because of side-effects. He was a clown. I liked his jokes and I liked the way he told his stories like how he invented iproniazid for instance. I never knew what was true and not true. We met rather regularly. He used to play a very important role in what was called biological psychiatry.

#### **What was the role.**

Well it was very dangerous to contradict him. He was a good speaker, very outspoken and he was opinionated. To contradict Nathan Kline was politically very dangerous. People were afraid of him and certainly by the end of his life he behaved like a kind of a Pope. At the end he had this habit of coming to congresses with a small dog on his lap and patting it all the time and attracting attention whilst smiling to the speaker. And he liked to ridicule.

There were a few famous psychiatrists at that time who actually never did anything. Max Hamilton, for instance, was even more incredible. He was Professor in Leeds and his only contribution, except for a rating scale, was that each time somebody had something to say Max would stand up and say "my dear friend it's not as simple as you seem to believe. It is much more complicated. You are naive". And he would then sit down. He would actually never make a positive remark. Everybody was very afraid when Max was in the room because he knew how to ridicule people.

**During both the 1960s and 1970s psychiatry and the emerging neurosciences seemed to work quite closely together. Recently things seem to have changed. When you go to the large meetings like the CINP or ACNP, it seems to me that there is an increasing gulf between the two. Neuroscience has become so large so technical - perhaps too large to be constrained within the clinical domain anymore. It seems to me that there is increasing strains in groups like the ACNP where you get the clinical people unable to see the relevance in all of this. Do we need to be going along to meetings where there is so much esoteric neuroscience? Do you think there is a problem.**

It seems to me - this may be a biased view - that the famous gap between clinicians and biochemists or biologists is if anything increasing and the role of slogans is increasing. Slogans in the general sense of the word. When, for instance, I try to explain to our pharmacologists who have never seen patients, how a schizophrenic patient looks like I have the greatest trouble. I try to tell them that schizophrenia is a word invented by Bleuler half a century ago - not a disease but a word. In my way of thinking it is very difficult to accept that this particular word invented by Bleuler can be one disease entity. This is important because we are constantly bombarded with the question: what is the etiology of schizophrenia. And my answer is that the aetiology of schizophrenia is Dr Bleuler.

I am personally very influenced by the fact that in biochemical genetics it becomes more and more obvious that diseases which look like a homogenous entity, when the chips are down are far from homogenous. A good example is retinitis pigmentosa. I always thought it was one inherited disease. But at the moment there are at least 80 different mutations known, all 80 leading to what looks clinically like one disease. So if this is true for retinitis pigmentosa, what odds schizophrenia being one disease.

**But can I put it to you that one of the forces holding schizophrenia together at the moment as just one entity isn't just Bleuler and the grin of the Cheshire Cat that was left behind after he died but the industry. They have got to have a big schizophrenia in order to be able to market compounds. If schizophrenia were to fragment so that the target populations were not as big industry's interest in developing drugs for any of these smaller groups would be much less.**

That is true. We have very often been confronted with the problem of how to promote new drugs and all I can tell you is that if we were to do it using purely scientific language then not a single box would be sold. So in a certain sense the industry is practically forced to use simple language. I call that slogans. Slogans in the sense of hypersimplifications of the truth. It is probably human nature that most people are more interested in slogans than in dry scientific facts.

But the interest of the industry in the treatment of schizophrenia is relatively new. For instance Haloperidol was very difficult to sell in a country like Italy for purely economical reasons. To sell drugs to hospitals in Italy used to be a terrible idea because the inflation was very high and these hospitals would not pay. So there was nobody really interested. In the early 60s in the United States there was practically nobody interested. Rhone-Poulenc, for instance, had a difficult job to find an interested partner in the United States for Chlorpromazine.

Rhone-Poulenc was of course one of the largest pharmaceutical companies in Europe and in those days from a research point of view probably the best. After Laborit had done his work and then Delay and Deniker, Deniker was sent by Rhone-Poulenc to the United States to try to sell the idea of a pill being able to make voices and delusions disappear. In those days psychiatry in the States was dominated by psychoanalysts. They ridiculed Deniker whose English was poor and rather than stay a month in the States he came back after two weeks, and after five conferences rather than the scheduled 20 or 30, completely exhausted and completely disgusted because they systematically ridiculed this "silly Frenchman" with psychotherapeutic arguments. Nobody seemed to believe him.

At the same time Rhone-Poulenc approached the large pharmaceutical companies in the States Upjohn, Parke-Davis, Eli Lilly and quite a number of others but chlorpromazine was turned down by all of them. Because they didn't believe it and because they couldn't see a market. Schizophrenia was completely unknown to them. Don't forget marketing people working in the pharmaceutical industry know nothing about medicine. They know something about existing markets. They have books and there is a market for this and a market for that but in those days there was no market for schizophrenia. They opened their book looking for a schizophrenia market, reported back to management that there was no such market and that was the end of the story. What really saved Rhone-Poulenc was Smith-Kline and French.

SK&F in those days was a small company in Philadelphia exclusively selling amphetamine as Dexedrine. They had a pharmacologist working for them by the name of Leonard Cook. In desperation Rhone-Poulenc had offered Chlorpromazine to SK&F being unable to find a big company. A sample was given to Cook who repeated a few experiments described by Mlle. Courvoisier. One of these was an anti-emetic experiment with apomorphine in dogs and he showed what Mlle Courvoisier claimed in her first publication, namely that chlorpromazine is a very powerful anti-emetic. Cook reported to management - because the company was so small a pharmacologist still had access to the top - and he said well the strange stories these funny psychiatrists are telling may not be true but I can assure you this is a damn potent antiemetic. So the management of SK&F took the decision to develop chlorpromazine as an anti-emetic. They simply forgot psychiatry. For this reason chlorpromazine was first approved as an anti-emetic by the FDA. No psychiatric studies had been conducted - only anti-emetic studies. Officially psychiatrists were not supposed to prescribe chlorpromazine but under the influence of probably European colleagues they started prescribing it and eventually they started to realize that Delay and Deniker were not hallucinating and they slowly started to believe it.

This is where the major tranquillizer story comes in because commercially speaking they could see the success of tranquillizers but they were still not convinced that there was a

market in the treatment of schizophrenia. This is why they started calling chlorpromazine “a major tranquillizer” hoping that it could somehow be used not only in schizophrenia but in as many psychiatric patients as possible. They were even hoping that it would compete with meprobamate, Librium and Valium and other “tranquillizers”. The implication of the expression major tranquillizer is that it is better than a minor tranquillizer. So these were two slogans invented by some people at SK&F and taken over by the psychiatric community and by textbooks, even Goodman and Gillman - everybody.

I was blowing my trumpet saying “this is nonsense” but nobody was listening. It is obvious both pharmacologically and clinically that Librium has absolutely nothing to do with chlorpromazine. If you call the one a minor tranquillizer and the other a major tranquillizer you are only spreading confusion. These are all funny stories - all of these details of course are not very well known.

**Why did your company not get into the antidepressant arena.**

That's my fault. First of all because I had a very hard time - even today I have a very hard time - to accurately define depression. As far as I am concerned there are hundreds of different types of depression. The only disease that I know of that in my opinion deserves the name depression is endogenous depression, in other words a psychosis, or the depressive phase of a manic-depressive illness. That is clearly a depression as far as I can see. But in general practice the common type of depression which is so often seen and which is treated by tricyclics, first of all doesn't respond very well to these tricyclics. I really don't know whether they are not doing more harm than good. Secondly we don't have any animal model to work with. Third many forms of depression, like for instance dysthymia, are seen by general practitioners, not by psychiatrists, and unfortunately the results of clinical work we are doing with general practitioners these days are no longer believed. Dysthymia, or neurotic depression is probably the most common form of “depression” in my opinion.

**You actually made a good case for dysthymia being seen as a disease entity as well with the altered sleep stages.**

Dysthymia as I define it is something that many general practitioners see every day and usually these patients are treated with benzodiazepines and that usually makes it worse. There is no treatment for dysthymia that I know of except ritanserin. But I am really puzzled with the obvious clinical efficacy of Lithium for instance. There is no animal experiment that would make me predict that Lithium would be effective in the treatment of endogenous depression but it is often very effective.

So it is my fault in the sense that in the literature and in our laboratory I have always fought the idea of some of the old pharmacologists who claimed to be interested in making anti-depressants - my question has always been: what is an anti-depressant ? Because the best treatments that I know of for endogenous depression are electroconvulsive therapy and lithium. It may be a biased opinion but for me these two modes of treatment are clinically far more obviously effective than imipramine-like tricyclics.

Imipramine to me is a mysterious drug. I know Kuhn who was the first to test it in the clinic and I know Angst who did I don't know how many double blind studies with it. To the best of my knowledge there are now and then depressed patients who respond well to imipramine but they are the exception rather than the rule. In classical double blind tests for instance comparing anti-depressant A with anti-depressant B, a man like Angst was never able to show a difference between groups treated with A versus with B. Many years ago he told me: well here is what I get with imipramine and here is what I get with this new compound and there is never an obvious therapeutic difference except in side-effect liability. For instance Prozac is better tolerated than most tricyclics but efficacywise it is about the same, not very impressive. Angst never got the permission from the ethical committee to compare imipramine with Placebo and he became more and more convinced that to distinguish

imipramine from placebo with his protocol was impossible. Not because the compound is inactive but because the percentage of good responders is too low.

I have often put the following question to many psychiatrists "how satisfied are you really with whatever you have in the treatment of what you call non-endogenous depression?". And the answer was usually "well I'm satisfied with approximately half of my patients after about 5 weeks". Its far from obvious therefore. I made a mistake also by believing that it would probably be best to no longer use the word depression because it was so confusing but to use more understandable words like dysthymia and to concentrate on certain types of depression that are more easily understood than other types of depression.

**But again the problem will be that if you restrict it and say lets have a drug for melancholia, the response from the marketing division within the company would be well this is too small an entity for us to develop drugs for.**

Well the marketing divisions in such companies are doing much more harm than good then. They kill too many good ideas. One could write a book on it. It usually has to do with the fact that when they hear the first rumours about something completely new, they are scared to death. Because there is no such market, they have never seen such patients and they are completely misled by their own slogans.

For instance, one of the areas this laboratory has great success is in the area of mycology. We started doing research in mycology in 1960 when the Belgian Congo had just become independent. I remember very well that everybody told me in 1961 that this was sheer stupidity because all problems that had something to do with mycology could easily be solved with amphotericin B, with potassium iodine or with griseofulvin. Somebody doing research in this field was out of his mind. Incredible but true. This came from some marketing departments. Fortunately in these days we did not have a marketing department. I was simply listening to doctors and veterinarians and people in plant protection who were trying to solve mycological problems without success and they told me that most problems related to mycological agents could not be adequately solved with what was available. Fortunately, unlike many other people, I was not forced in those days to listen to marketing people otherwise we probably would not have started.

McNeil, a sister company was selling griseofulvin - they were promoting it and one of their slogans was "if you have a mycological problem, griseofulvin will solve it. They believed that as marketing people tend to believe in their own slogans. They first invent a slogan and they repeat it so often that they believe it even when it is a gross exaggeration as is usually the case. They are salesmen - they try to promote drugs just like car salesmen - any argument is good as long as it sells.

**Drugs like Haloperidol were brought out almost forty years ago now and their cost is now virtually nil. Is that getting in the way of being able to develop new compounds.**

Oh yes, of course. In 1953 the cost of research and development of a new chemical entity was a few tens of thousands of dollars approximately. Fortunately for me because that is all I had. In the case of Haloperidol probably even less - maybe \$20,000-\$30,000 everything included which in those days was considered an enormous amount of money. Today the official estimate is something like \$250-\$300 million. In my opinion it is much more than that. Johnson and Johnson is spending \$1.6 billion in 1996 on what is called R&D and I don't know how many new chemical entities will come out per year for this tremendous amount of money - only time will tell.

The reason why this tremendous increase occurred has not much to do with research but practically everything with development. I will give you a simple example. In the 50s and 60s I was so afraid of being misled by clinicians that I refused to work with clinicians who were asking for money. If they were not interested scientifically, I told them to forget it. But

in those days, it was relatively simple to find clinicians who were willing to do whatever was required simply for the sake of their patients and because they were interested. Jean Delay or Jean Bobon, for instance, never asked me for a dime. What was not uncommon was that you would then do clinical investigators a favour after they had done their job. That was a question of being polite and grateful. But to discuss money was simply not done, it was even considered very impolite. Jean Delay I am sure would have been angry if somebody had raised the subject with him.

Today I am not exaggerating when I say that it is simply impossible to do clinical research without discussing money first. And with enough money almost anything can be done apparently. The world has completely changed. As a result of these changes clinical research, or what is called research and development, particularly development is becoming so incredibly expensive that in my opinion in a few years time it will no longer be justifiable to do it.

### **Unless it would happen in the third world?**

Theoretically yes but in practice no. Take the example of malaria, one of the most important diseases of the third world. Technically with the artemisin derivatives and so on, there are quite a few new drugs that should urgently be investigated clinically because they are, in all probability, very potent. But for reasons that are not clear even the Vietnamese or Chinese, where the disease is very common, are not doing enough. Is this because they don't know how to do it or is this because we ignore what they are doing? Is this because they are publishing in journals that we don't read? Is this because we are not interested in malaria anymore? I don't know. The last anti-malarials were discovered and developed for use in the American army during the second world war as a direct consequence of strategical considerations. Most of the work was done in America. Hundreds of thousands of compounds were synthesised and screened at Walter Reed. Walter Reed now has a very interesting research programme and they have published on an impressive series of drugs that, on paper at least, should be very potent but as far as testing is concerned apparently nothing is happening. Is this because the chronic toxicity requirements are so enormous that even Walter Reed finds it too expensive? Is this because there are too many ethical committees who make it impossible? I don't really know.

As well, in actual practice, for instance, in order to convince the US Food and Drug Administration you have to have US data. They claim that they will accept UK data for instance but this is not true. And vice versa. So you have to repeat clinical studies in every important country. That makes it very expensive. Chinese data for instance Vietnamese data in this field are useless because nobody believes them anyway. So it is in a certain sense a loss of time. Again this question of suspicion.

**Can you foresee a day when the cost element will actually bring the production of novel compounds to a halt within an area like the neuroleptic area? What about Alzheimer's, where you could bring in new drugs that cost a lot on which you will be able to recoup the cost because you are not constrained by the fact that there are cheaper drugs there?**

Well Alzheimer's in the scientific sense of the word is a type of dementia which is inherited. There are at least 4 different types of inherited Alzheimer's. It has become fashionable to use the word Alzheimer's instead of dementia but most demented patients are not suffering from Alzheimer's. Furthermore Alzheimer's is a post-mortem diagnosis. So to use drugs specifically for the treatment of Alzheimer's is impossible. But this is a slogan that captures the imagination of practically everybody in the industry - they are all dreaming of selling a drug for Alzheimer's because if the FDA would only allow such a drug to be sold they would make a fortune.

You know better than I do that the treatment of dementia is impossible. The treatment of real Alzheimer's disease is certainly impossible. Patients who don't yet have the lesions would have to swallow pills before the onset of the first symptoms and for the rest of their lives. There is a compliance problem there. This is utopia I think. It is a dream of sales people that has nothing much to do with real medicine in my opinion nor with "patient benefit"..

**Talking about real medicine why, just when we have become able to produce effective medicines, are people getting so alienated from medicine and turning to alternative methods?**

I don't really know but it is a fact with the only exception of Prozac. My wife and some others tell me that it is becoming fashionable among women to claim to be taking Prozac - that is the only exception I know of. Most so called intelligent people I meet take pleasure in saying that they never take drugs - only homeopathic medicine or plant extracts. And they are supposed to be intelligent people. I cannot understand that. Except when one assumes that 99% of the complaints of people disappear spontaneously anyway, whether they take something or not. Then of course it is not so difficult to see that almost anything taken with great conviction can have a very strong psychotherapeutic beneficial effect. So that is maybe the reason. Most complaints these people are talking about are of course complaints of self-limiting diseases. Even these people say that for serious disease like cancer or diabetes alternative medicines don't work. They only "work" for the symptoms like headache or migraine. As a psychiatrist you should be in a better position than I am to explain it. I find it regrettable but it is a fact. I hope I am wrong but I am convinced that the attitude of the world is not only not helping medicine but actually blocking its progress.

**Which attitude.**

The attitude which takes heed of rumours about negative side-effects of a new drug. Everybody believes these rumours without scrutinizing them, without asking questions. People can be made to believe almost anything negative which is scary. The world is becoming more and more sceptical when it comes to accepting positive messages. Except when these positive messages are in the form of slogans. A very good example is Taxol, the anti-cancer drug given to us by "mother nature" coming from these very rare and expensive tropical forests. Three trees per treatment yet it is a simple cytotoxic agent. But if the message can be brought with a slogan that has something to do with "mother nature" or when a slogan starts with bio, then people are ready to listen. But to listen to so called dry scientific or rational arguments is the exception rather than the rule.

I don't know, could it be that we are so influenced by modern propaganda that we only tend to pay attention to slogans and to nothing else anymore? When I say we I mean, statistically speaking, mankind in the Western world. We are bombarded by television messages, by slogans not just for soap but for cars and even for drugs apparently. This is something I feel even in the laboratory where slogans often catch more attention than facts.

It is possible that 50 years ago side-effects were underestimated. When chloroform was killing 1% of patients this was, I wouldn't say accepted it was certainly regretted, but it didn't stop physicians from using chloroform and I never heard of legal consequences when somebody was killed by it. Today for the slightest thing going wrong patients go and see a lawyer. It seems to me that the population at large is expecting almost miracles from the medical profession and if they don't get these miracles they are dissatisfied. All drugs must work 100% of the time, they must be completely free of side-effects, they must be easy to take and cost virtually nothing. That is what people are led to expect these days.

**Talking about side effects prompts me to ask you about the hand-writing test. Who was Haase and when did he come up with the test?**

HJ Haase was a psychiatrist in Bonn who did research on gross and fine movements. His handwriting and tapping tests resolved questions in Parkinson's disease but they also first

defined the neuroleptic threshold in patients treated with chlorpromazine. That work was impressive and obviously important for haloperidol, so I sent him a message and his reply was enthusiastic.

When we talk about the optimal dose in pharmacology we talk in statistical terms. We talk in terms of an ED 50 for dogs or rats or mice. This leads to a kind of irrational conviction that there must be something like an optimal dose for everybody of a new drug. The idea that the drugs have to be titrated patient by patient is only accepted for old-fashioned drugs like digitoxin or insulin but not for neuroleptics for instance. I have the greatest trouble trying to make the point that most neuroleptics have a narrow safety margin of less than 2. It is very easy to overdose or underdose them and to find the individual optimal dose is not easy. This is not a popular idea. Pharmacologists in general and clinicians prefer to think and talk about the optimal dose for a certain disease.

In the case of Risperdal for instance, I have seen the results of extensive studies performed in Germany and the lowest optimal dose in a minority of patients was 1mg per day and the highest was 6mgs with the median about 4mgs. This shows that Risperdal is a very potent neuroleptic and not at all an atypical neuroleptic. It does in the handwriting test exactly what typical neuroleptics do. The reason why psychiatrists are so satisfied with Risperdal is because fortunately we have been stressing the point that the dose of 6mgs per day should not be exceeded. At 6mgs per day the number of patients reacting with EPS is low but not zero. We have done that because over and above 6mgs you get into problems with EPS, sedation and with orthostatic hypotension. Also if a patient's response is not good with 6mgs, the probability that it will be better with a higher dose is low.

I have always been convinced that 1mg of haloperidol is active in some patients. We took 1mg ourselves here. In those days I was rather nervous and I could easily tell the difference between 1mg of Haloperidol and placebo simply because the neuroleptic made me less nervous. I had to guess 8 times and I guessed right 8 times out of 8 which carries a probability of one chance in 256. One of my collaborators was a rather phlegmatic individual who was far from nervous but he was also right 8 times out of 8. Do you know why - because it made him lazy. He could feel it alright but for completely different reasons. So there was an obvious correlation between personality and effect.

**There do seem to be some people who are made very demotivated by a neuroleptic and others who are not. These areas are unexplored really aren't they.**

In recent years virtually nothing has been done. Because this is typically a type of experiment that is no longer allowed by ethical committees. There is no potential clinical benefit expected and therefore we are no longer allowed to do these things. It is a bit strange but there is in my view a great need to do these simple experiments.

**I sense you have a certain scepticism about the history of psychopharmacology. Do you think there is anything we can do in the area of history other than compile lists of who was voted onto which committee and who was at which conference. Can we get beyond those supposedly objective facts.**

In my opinion no. The best you can hope for is to come up with a plausible story. Do you remember a Japanese movie called Rashomon ? From time to time we have been asking ourselves questions that have to do with the history of our company and the various witnesses have different memories. They remember different things and sometimes we really don't know ourselves who is right and who is wrong. There are no obvious reasons for saying a, b or c often. We simply don't know.

There is a small booklet on the history of our company. We tried to keep to the facts as they are remembered by everybody and it was very surprising because we really had to leave out a number of "facts" because we could not reach a consensus. But it is very difficult to write a

book not containing statements that are contradicted by one or another witness - and there are 10 or so remaining witnesses not more. People remember things differently like in Rashomon. So therefore answering your question I believe if you can come up with a plausible story not contradicted by known facts or by witnesses that is the maximum a historian can hope for.

**Yes but that is going beyond the simple list of people. Once you have come up with the plausible story that is not contradicted by the facts - the witness thing is tricky I think you have got to bring the question of judgement in there you obviously can't come up with a story that the majority of witnesses don't agree with but I don't think you can have a criterion which says all the witnesses agree.**

Well for this book we have been very strict. There was fortunately complete agreement on the essential facts and we therefore did not really have major problems. But the less important "facts" are, the more difficult it is to reach agreement. For instance one of the questions would be what is it that motivated the founders of the CINP. Everybody probably has his own opinion of the subject but these are guesses. I don't know for sure. I don't know what went on in the mind of the others. So I will probably never know.

**Can we not go beyond the details to try and get a hold of what are the forces that shaped the field. Sometimes the clash of personalities and things like that can be interesting because of what it reveals of the underlying forces. Obviously one of the big issues has to be something in the area of why have we had this huge change from people being so happy to take risks to the current state where people just are not prepared to take any risks at all. Can this not be traced through the perceptions of people as to what are the important events....**

For instance I made a few rather strong statements about the attitude of what I call the American psychiatrists to the neuroleptics and I realize that these are strong statements and they are not entirely correct. There are exceptions but anyway this is what I generally believe. But the really interesting question would be what was actually going on in the minds of these sceptics that were ridiculing Deniker. He was a good psychiatrist and his interpretation was that they felt threatened. That they were all treating rich widows - talking with them on a couch and charging fortunes. Without much therapeutic success but anyway this is how they made a living. Deniker strongly believes that when he came with his simple story these inexpensive pills threatened their source of income. Who am I to question that? Would it be useful to ask that question to these sceptics? I don't think so because they would probably not give you the right answer.

Why is it that in general terms the US was about 10 years behind Europe in this field, except for purely commercial products, like Librium or Valium. As far as I am concerned Librium and Valium cannot be described as major advances in therapy but they had obvious commercial potential and Roche made a fortune selling Librium and Valium in the States. As for the neuroleptics in my opinion, the sales people there were dominating the scene and could not really care less about patients. They probably didn't even believe the true story and they certainly did not believe that there was a market potential. I know that this was true for Jack Searle and for Harry McNey at McNeil because I have seen it and I have heard the same story told by people from SK&F. I was befriended by quite a number of them.

I don't know why chlorpromazine was turned down by the big companies because I was not a witness. It would probably not even be written down in archives. We have no archives containing information on this subject. Most discussions on new compounds are verbal discussions between two or three people and aren't written down. Maybe these days but I never did.

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