# Jean Thuillier: Ten Years that Changed Psychiatry
# David Healy's Interviews*

***How did it all start?***

It was by chance. Let me take you back to the beginning of the story. In 1950, I was an intern in the Department of Professor Delay in Sainte Anne. I was interested in curarisation and in the curare molecule. Looking back at the early work of Claude Bernard, I found that he had found that the introduction of curare, the drug which paralyses muscles, by the rectal route permitted a light curarisation that allowed muscle relaxation without causing the respiratory muscles to be paralysed. He had done this in the rabbit. I repeated this study in man using the rectal route and have a publication on it in *Nature* – Infracurarisation by Rectal Suppository. At that time in all publications, it was standard practice to put the names of the chiefs of the department first in the list of authors. This is why the names of Professor Delay and Pichot were at the start of an article like this, whereas today they would be at the end (1). Our aim with infracurarisation was to relax the patient. It worked to some extent. So this was an early psychopharmacology.

Even before this, I had met Erik Jacobsen in Copenhagen and he told me his early adventure with Antabuse – disulfiram. He and a colleague had been at a ceremony where they had a drink. They had taken disulfiram as an anti-helminthic in the morning as part of a study to test out its toxicity. During the cocktails at the party, they started to feel hot and breathless and unwell. This was the way in which they found the Antabuse reaction. He sent Germaine, who worked in a chemical department, who later became my wife, the formula for Antabuse. She made the molecule up for me – it was easy to synthesize. I went on to do my post-doctoral thesis on the medical use of Antabuse. It was the first thesis on this in France and the first clinical publications on its use in the management of alcohol abuse (2). I was an assistant at this time in both the pharmacology and psychiatry departments and so I presented the thesis to both Jean Delay and René Hazard, who was the professor of pharmacology. In the course of my presentation, I said to both of them that as one of them was the professor of psychiatry and the other of pharmacology, that therefore this must be a psychopharmacology thesis. This was in 1950. I know of no earlier use of this word psychopharmacology in France.

Anyway, when I gave my publication on curarisation to the French Society for Anaesthesia, I met Pierre Huguenard there. He became a close friend. He was the anaesthetist to Hôpital de Vaugirard. He was also working on occasion with Henri Laborit, who was a surgeon, in Val-de-Grace, the first military hospital in Paris. Now Huguenard had an operation to do on the head nurse of his service. The operation was to fix a nose problem. This made it impossible to put a mask on the person's face. Local anaesthesia was necessary. Huguenard before this, with Laborit, had been trying a series of mixtures, with anti-Parkinsonian drugs and analgesics, aimed at producing a "lytic cocktail" to stabilise the autonomic nervous system. One of these anti-Parkinsonian drugs was a derivative of phenothiazine – Diparcol. It is still used. Anyway, he made a cocktail for this nurse – Diparcol with Dolosal (pethidine). During the operation he

asked the nurse "how are you doing" and the nurse answered "fine, very well" and she was smiling (3). Huguenard was impressed and called this mixture Dip-Dol. He told Laborit about this and suggested he use it for his operations.

At this time Laborit and Huguenard were also studying artificial hibernation. They had found that the autonomic nervous system could be settled down, could be made less reactive, by hypothermia produced by packing the body with ice, along with Dipdol, the mixture of an analgesic and a phenothiazine derivative. Laborit's artifical hibernation and Huguenard's mixtures became well known. Laborit, who tried out new drugs for Rhône Poulenc, replaced Diparcol by a new compound RP 4560, which he later called Largactil. He then suggested to his good friend in charge of the psychiatric department at Val-de-Grace – Dr Hamon – "you know these patients who you have in straitjackets, if you give them this mixture and cool them down with ice, you will not need this jacket." Hamon and his collaborators, Paraire and Velluz, tried this and this was the first publication of artificial hibernation in psychiatry with the new drug 4560 RP, Largactil. But Hamon was a military physician and so he did not pursue this. Val-de-Grace was a military hospital, which only had a few psychiatric patients. Laborit called RP4560 Largactil because even then he thought it would be possible to use this drug in all medical specialities – surgery, obstetrics and even gastroenterology. This is what gave rise to the name, which indicated a broad range of actions. At this time, he was not thinking about a specific action in psychiatry.

But the treatment was taken up by Deniker, who had read the publications of Hamon. This is how Deniker began to hear about this treatment and began to try artificial hibernation with the new phenothiazine derivative, RP4560, that had been synthesised by the chemist Charpentier and studied by Mme Courvoisier, the pharmacologist, which Laborit had recently begun using. So, Deniker took up the work of Laborit but did so in a great psychiatric hospital – Sainte Anne.

In this way, chlorpromazine started to be used in Sainte Anne, but it was in the form of artificial hibernation that it was used first. I was in the same service as Deniker. He was looking after the male inpatients, who needed a locked ward, and I was looking after the male open ward. Anyway, one day, he said to me that he had a week of holidays starting and he asked me if I could visit his patients while he was away. So, each morning I went up to his ward. Now I knew the system and it was clear to me that some of these patients were not getting artificial hibernation. When I passed by the beds, I could see that these patients were not being chilled down, that they were warm. There was no ice there. I turned to the nursing staff and said, "But this is not artificial hibernation." The nurse in charge of the hibernation room said it was not possible to do it because the pharmacist, from whom they used to get the ice, complained that he could not produce enough. The nursing staff were not too bothered by this because they had already decided that the results were the same, whether or not there was ice being used.

Well, well this was a big problem. I asked them to get ice and they did it. When Deniker came back, I told him this – "you know, the pharmacist didn't send up any ice, but the results were the same without it." He was surprised but he confirmed it. He went and talked it over with Delay and that was the beginning of chlorpromazine used alone in psychiatry. There in a nutshell you have the history of the discovery. The merit of Deniker was to have said and to have been the first to insist that chlorpromazine alone without hibernation was active in psychiatry.

It was later that Deniker got acquainted with Laborit and you will know that both of them got the Lasker Prize in 1957. Delay was not included in this Prize. Jean Delay was a gentle professor who left us with the possibility to do many of the things that interested us. He set me up with a laboratory where I was able to do lots of experiments with all sorts of animals and psychotropic drugs. This gave me the opportunity to work with the CNRS – the National Centre for Scientific Research – and to take out patents with them and to create a laboratory of pharmaceutical products in 1960, which in the end allowed me to become independent.

***Are you saying then that it was the nursing staff who made the discovery?***

No. Laborit had been studying RP4560. The first publication was made by Hamon in Val-de-Grace using hibernation. The second, the utilisation of chlorpromazine on its own, was made by Deniker. It was the nursing staff who noticed that hibernation as such was not necessary, but Deniker proved it. I was interested in the pharmacology of the drug. To explain this to you, I need to take you back to my early interests in research.

I had first of all been interested to be a neurosurgeon. After doing medicine, I went into neurosurgery before joining Delay. Professor Baudouin was the Dean of the school at the time. Puech was one of the aspiring neurosurgeons and a student of Baudouin's. Baudouin told him that if he wanted to become the Professor of Neurosurgery, he needed to do the first lobotomy in France. As I was an assistant to Puech, I did this operation with him. I was the person who drilled the two holes in the skull. Puech introduced the blades and did the operation, but he was very upset at having to do it.

I can tell you the history of one of the first patients who had this operation. The man was a peasant from Normandy, whose father had treated him brutally. When the father died, he saw the father everywhere, up in trees etc. It was a hallucinatory psychosis. He was lobotomised. I remember one day some physicians from Belgium and England came to see this first lobotomy. I had to present him to them, so I went to see him that morning and told him that they were coming and that if all went well he would be able to go home in a few days. I asked him was he well and did he still see his father? He said yes, he was well and he was looking forward to going home to his wife and his farm and no he didn't see his father but he could hear him. I got a big shock. I told him immediately that he mustn't mention this when he saw the visiting doctors or he might have to remain in hospital. When they came, they were very impressed. When I asked him did he see his father anymore, he said "no of course not and that he didn't hear him either." Puech did some more operations, about 10 altogether, and then a few months later he had a heart attack and died. His successor brought all his own team, which meant there was no place for me or the rest of the Puech's team.

I knew Delay because he had been sending patients to Puech for this operation. This was my first real contact with psychiatric patients. Wondering what to do, I went to Baudouin who said to me that Delay was a good and clever man. So, I looked for an assistant's job with Delay. At that time, 1949, there were no drugs of any use in psychiatry. They put their patients in hot water or cold water and there was electroshock, insulin therapy, psychoanalysis and now there was lobotomy but what they really needed were some drugs. So Baudouin also sent me to see

Hazard, who was the professor of pharmacology because I wanted to learn something about drugs.

So, in 1949, I became a clinical resident in psychiatry with Delay and an assistant to Hazard in pharmacology. I spent 5 years commuting between Delay and Hazard's departments. I ended up knowing pharmacology, at a time when none of the other psychiatrists knew any pharmacology and really were not interested in it. I left neurosurgery and became a psychiatrist, but I ended up being considered a pharmacologist by psychiatrists and as a psychiatrist by pharmacologists.

Later on, Delay set me up in my own laboratory in the grounds of Sainte-Anne to do psychopharmacology research. In 1960, my contributions in this area were recognised by the Institut National de Sante et Recherche Medicale (INSERM) who made this unit into an INSERM unit and created for me the first department of neuropsychopharmacology in the world. I was the Director from 1955 to 1976.

After this opened up, I was rather proud of this big building. Many people came from abroad to join me there. One of them for instance was Nakajima from Japan, who later became the Director General of WHO. He came on a grant from Tokyo to me. He married, in fact, one of the three assistants of Mme Curie, where my wife Gemaine was also working. Linus Pauling and Daniel Bovet came to visit and Julius Axelrod sent his assistant McDonald for a sabbatical year.

One day in 1957, Nakajima came into my office and said, "you know Professor Trabucchi in Milan, with Cerletti his assistant, is organising a conference on Psychotropic Drugs." The word psychopharmacology at this time was only used by me and my staff. We went to this meeting in Milan, where I met Trabucchi and another assistant Garattini who later became a close friend and they outlined their plans for developing an organisation. All the key people for the later development of the CINP were present at this conference of Garattini and Trabucchi. I was there talking about a classification of psychotropic drugs I had developed and showing a film on my turning mice. This was one of the first screening tests for new drugs. I also have a film from this meeting on the side-effects of the neuroleptics. Before the meeting, Deniker had asked me if we could do one. So, I came over with a camera and we made it. Deniker showed it during the meeting.

Rothlin from Sandoz was also at this meeting. He was only a few years away from retirement. Because of links I already had with him, I had been the first in France to have LSD, which Hofmann who worked with Rothlin had sent me. After the war there had been an episode of poisoning in the South of France, which involved bread made with a flour containing rye contaminated with ergot. Delay was nominated to be the expert to examine this event at Pont Saint-Esprit, which had sent a whole village mad. Delay said to me "Thuillier can you do some research on this." As I read the literature, I came across the paper of Hofmann from Sandoz who had synthesized LSD and I went to Sandoz to see him. After this, he sent me the first gram of LSD sent to France. Nakajima had an apartment near the main reservoir in Paris and I remember him saying to me one day, as a humorous aside, "you know with one gram of LSD put in this reservoir I could disable all of Paris." As it happens, a number of military authorities thought about his kind of thing – to pulverise LSD and drop it army or navy personnel or even to affect a

city. I was also, at this time, able to get hold of mescaline or psilocybin. I was interested in the fact that if we could induce madness in man with drugs then we should also be able to treat it with drugs (4). Psychiatry it seemed to me had now become experimental - we could precipitate psychosis with drugs and we could cure it, so we should be able to tackle the issues scientifically in a way that we hadn't been able to do before.

Anyway, to come back to the Milan meeting, Trabucchi, who was a big and very sympathetic man, convened a dinner with Denber, myself and Rothlin. Denber was the main American representative at this time because he spoke French and he was working in Geneva. Rothlin suggested to Trabucchi that he could arrange a psychopharmacology meeting during the Second Congress of Psychiatry in Zurich in September and that perhaps during that Congress he would try to gather a group together to create a Collegium Internationale Neuropsychopharmacologicum (CINP). This is what he did. He organised a special symposium at the Second International World Congress of Psychiatry in September 1957 and convened a group of people at that to establish the CINP.

Rothlin persuaded Carl Jung to be the *presidence d'honneur* of the meeting. I remember I was travelling with Rothlin along with Carl Jung in the same car to Jung's house near Zurich. He was very old but mentally still very alert. But the car had to stop because Jung being old had to urinate. We stopped near the public gardens in Zurich and had a drink in the LUNETTE. This led Jung to remember a meeting with Freud at the beginning of the century. He said that when he had met Freud near there once, Freud had in his pocket a small packet of cocaine, which he said to Jung helped him with his work. "And now look," Jung said, "Freud could have been presiding over a psychopharmacology congress if he were here."

***Can you tell me about Henri Baruk – he and Delay did not seem to get on? What was the basis for their dispute?***

Dispute is not the right word. Baruk is a Jew. He is alive still even though he was born in 1897[1]. During the period of occupation, Levy-Valensi, who had been the professor of psychiatry at Sainte-Anne, was deported and died in the camps. So, after the War, the position had to be filled. Delay had close friends everywhere and was appointed. Baruk would have been another possibility.

Back in 1939, Baruk had been interested in the use of drugs for nervous disorders. He was the first to use bulbocapnine in experiments. He used it to put animals in catalepsy – experimental catatonia it was called. After these experiments, he went to do psychiatry in Sainte-Anne where he was the senior assistant of Claude and then later Levy-Valensi who was the Professor of Psychiatry who got deported during the war. Baruk used at one point apparently to go round the hospital with a pigeon on his head. The pigeon had been treated with bulbocapnine and so it stayed there perched on his head.

When Delay was appointed the professor at Sainte-Anne, Baruk left and he later created at Charenton, one of the great psychiatric societies in Paris, the "Association of Moreau de Tours." Moreau de Tours was a French psychiatrist of the 19th century who used hashish to study mental

[1] Henri Baruk died in 1999.

illness. This was essentially the first French Society for Psychopharmacology. To this day there is still no other specifically psychopharmacology society in France. I was invited to the meetings each year by Baruk but neither Delay or Deniker were ever invited. Baruk eventually won his own department at Charenton and became the clinical professor as opposed to the university professor, which Delay was. As a professor agrégé rather than a titular professor, Baruk decided to go to Sainte-Anne to give lectures. He was very popular there because he was a very brilliant man, but Delay forbade him to continue with the lectures.

***Did Baruk contribute to psychopharmacology?***

Not really. Before the Second World War, he was the only psychiatrist interested in drugs. At that time, there was psychiatry, psychology and psychoanalysis but no feel for drugs. Electroshock had just been discovered in 1938 but Baruk was against it. He was a Jew and he saw it as being an aggressive treatment and for this reason he was against it. At this time, it was given without muscle relaxants and there were some reports of broken vertebrae. There was also confusion. But when I asked him about all this, he never really explained it to me in a way that made sense.

***You have also known Schou for a long time.***

Yes. I met Joel Elkes in Birmingham in December 1955, where he was working with Bradley and the German psychiatrist Mayer-Gross. Mayer-Gross who was present at the 1955 Conference on Psychotropic Drugs in Paris, had asked my wife and I to visit them in Birmingham and present on psychotropic drugs. Joel Elkes then invited me to one of the first congresses of neurochemistry in Aarhus in 1956. At this I met Mogens Schou. I remember sitting at the dinner and over the sweetened chicken, which they have in Denmark, he said "I must tell you something important. I have found that lithium has a very good effect." I later found out that Cade had been the first to describe this effect and that there had also been two people in France, Despinoy and Romeuf who had experimented with lithium in 1951 or 1952.

Schou anyway said lithium worked but he was having some troubles with it – some kidney problems. He said he was worried about lithaemia – too high a dose of lithium in the blood. Those of us involved in psychopharmacology were interested in all aspects of it and Schou was accordingly invited to every symposium, so that at every meeting since 1956 there was a paper on lithium. It got to the point where even I would react when I saw the program – what Schou still chasing lithium. It was only 10 years later that lithium was recognised. Nobody paid any heed to it for the first 10 years. This was not because it was dangerous if you did not know the blood levels, it just was not very interesting.

***You knew Robert Domenjoz?***

Yes. In 1954, I made with Geigy the first non-barbiturate anaesthetic, G29505. This was how I got to know Domenjoz. After the discovery of RP4560, I remember him telling me that in Geigy they were hoping to make a me-too of 4560 and asking me if I could help them but I was too involved with other things. One day he gave me a call from Basel and said, "I have something

interesting to show you." I met him at the Gare de l'Est in Paris. When he arrived, he said he had a close friend – Kuhn – who was a young psychiatrist who was working in the country. Kuhn, Domenjoz said was the chief in a little department in a little hospital but that when he had new drugs to try he gave them to Kuhn. Now they had been trying to make a me-too for chlorpromazine because of the money involved. This had led them to make G22355 – later Tofranil. And Domenjoz told me that in schizophrenia this didn't work, but that in depressed men it seemed to be working, so much so that Kuhn wasn't using electroshock anymore. So he asked me as a favour to ask my friend Deniker or Delay to try imipramine.

I brought him to Delay's office. Delay had not heard of Geigy. "Geigy", he said, "who are they?" I told him Domenjoz was the co-inventor of DDT along with Muller and also the discoverer of phenylbutazone. Ah, he said, Welcome Mr Domenjoz. Domenjoz had a few hundred tablets of G22355. Delay called in Deniker and he was presented to Domenjoz. At this stage I was over in my new pharmacology laboratory, so it was really up to Deniker to try it out in patients. He said yes, he would try it. But he left it on the shelf. Domenjoz called me "any news?" I checked back with Deniker, who it seems was worried about a possible suicide effects in depressed patients.

Domenjoz asked me if I could approach someone else in France. I asked Laborit who I used to discuss many things with and he suggested the new psychiatric director of the department of psychiatry at Val-de-Grace, Raymond Coirault. So I gave a supply of G22355 to Coirault. Later on there was a series of symposia on Tofranil in Switzerland, Italy and France to which Coirault was invited because he had confirmed the antidepressant effect of Tofranil. Delay said to me "Hey Thuillier, there is a symposium on antidepressants and I have not been invited." "Oh" I said – what could I say? Deniker sent Lempérière to this symposium and she came back and reported that this was a splendid, a formidable development. Delay then said "Telephone Domenjoz and ask why we did not get this Tofranil to test out." I did but Domenjoz said "but Tofranil was G22355." Deniker died recently – on August 17th. In one of his obituaries, curiously, he was credited with introducing imipramine to France.

Muller got the Nobel Prize for the discovery of DDT. Domenjoz told me the story of what happened. The story was that he was working with Muller who noticed that there were a lot of dead insects around his laboratory and very few living ones. He asked Domenjoz, who was the chief of the department of pharmacology, to help him work out what was going on. It was Domenjoz who suggested that there must be some chemical around the laboratory that was producing this effect. But no-one could work out what it might be. Eventually Domenjoz realised that the container for what they thought was simply another adjuvant, DDT, was slightly open and he suggested that it was this which was producing the effects. Domenjoz later discovered phenylbutazone in much the same way. It too was a solvent for some analgesic, which they had previously thought was inert, until they realised that it also was an anti-inflammatory analgesic.

As I said earlier, I developed a general anaesthetic with Domenjoz and Geigy. I also developed another drug. This was meclofenoxate, which Germaine, my wife developed in the laboratory of Paul Rumpf in the CNRS. This was a derivative of a vegetable hormone, acid parachlorphenoxyacetique, which had most unusual properties. It crossed the blood-brain

barrier, where it reversed the effects of aging on the brain cells of aged laboratory animals. It also counteracted the hypothalamic effects of stress, more profoundly it seemed than chlorpromazine or any of the other new tranquillisers (5).

Kety and Elkes organised symposia on neurochemistry each year in different countries. The first was in Varennes in Italy in 1960. An American, Polis, from NASA in Philadephia, who was in charge of the health of the astronauts was at this symposium in Varennes and Kety introduced him to me. He was very secretive. He was interested in meclofenoxate and wondered could he get some. I explained that my wife was at this time in charge of a department of chemistry in the Centre National de la Recherche Scientifique with Rumpf and she could make him some. So I sent him a quantity of meclofenoxate. Six months after Varennes, he phoned to invite me to Philadelphia. I went with my Germaine. It was funny, we had a police escort while we were brought to the NASA centre for research. There Polis told me that meclofenoxate was the only drug they had studied in 5 years which seemed to prevent deaths from g-acceleration in laboratory animals. I was invited to inspect the centrifuges where they did this work.

When I came back to France, I told the secret chemical service here – I was a scientific director of INSERM at this point. So, a general, General Grognot, came to me and said that they had the same centrifuges in France and said that they would repeat the experiments. They found that when they gave it to rats, who were exercising very vigorously that hypothalamic secretions which would otherwise flood the pituitary were blocked. This made the rat more resistant to stress it seemed. Lately I have been told that this drug has been used in Alzheimer's disease with apparently good results. Various different companies have sold this world-wide. The name it has here is Lucidril. It has also been used to help people recover from comas. The son of Jeanne Moreau was in a coma after a car crash many years ago and it was given to him and he recovered. It is an anti-oxidative. The molecule is a derivative of the para-chlorophenoxyacetic acid – which is a plant growth regulator.

***What about Henri Ey and Jacques Lacan?***

I knew Lacan well. He used to come to Sainte-Anne every Wednesday to give a lecture. I had met him before I met Ey. He was very friendly with me, but he dismissed me as a pharmacist. The psychoanalysts used to send me patients for a psychiatric consultation – I used to run a clinic every Monday. They would say to me "As a psychoanalyst, I cannot prescribe medication, but I can send them to you for you to prescribe them neuroleptics, antidepressants or tranquillisers and they then come to me more tranquil." I went along with this because we were friends and everybody was happy with the arrangement. Ey was the psychiatrist at Bonneval and he also came to Sainte-Anne every week to give a lecture. You know in the early days Ey did not try 4560. Nobody did. The older psychiatrists were reluctant to use it.

Actually, I should tell you this. I had a laboratory in Sainte-Anne that was close to the Rue d'Alesia. Each Saturday there was a market there – fish, meat and all sorts of things. I used to pop out to buy some food for my family, sometimes in my white coat. During the spring and summer the windows of the hospital would be open onto the street and you could hear the wailing and the screaming of the patients. But the first year of the neuroleptics, I remember one fishmonger who knew me well pulling me aside and asking me with wonder "Doctor, what are

you doing with the patients up there, we don't hear them anymore." I'm not killing them, I told him.

I should also tell you about my meeting with Cerletti, the inventor of electroshock, and Sakel at the Congress of Psychiatry in Paris in 1950. Sakel did not impress me. He offered all these theories about how he developed Insulin Shock, but I think he was just fishing for an explanation. Cerletti on the other hand did impress me. Delay told me "Thuillier could you attend to Cerletti who comes from Rome to the Gare de Lyon." So, I went there and met him. He was a big, very impressive man. Delay told me he had some money for the Congress and he told me to take Cerletti out to dinner. We had a dinner in the Luletia and he told me the story of the discovery of electroshock.

He had been very impressed by the activity of cardiazol injections and shock therapy done that way, but he was anxious to find another method because of the side effects of cardiazol. He had a brother-in-law who was a veterinary doctor at a big abattoir in Rome. His brother-in-law told him that when they killed the pig, they put an electrode on the head of the pig, which goes unconscious without stopping the circulation. It was necessary to do this because they had to cut the neck of the pig while it was alive so that they could collect the blood. But sometimes, even after the cut neck the pigs were not dead. Cerletti told me he had a good assistant who knew electricity very well – Bini. They made an apparatus and tried this out on animals. The first time they tried it on a man, he said they were very frightened, but it worked. Cerletti however was not very happy with this new method. He wondered whether there might be something that was released by electroshock, which brought about the therapeutic benefits. He looked for this in animals in the abattoir in Rome and reported on a substance called accro-agonin at the conference in Paris. It never replaced ECT though.

***You've mentioned artificial hibernation but what about sleep therapy because the first phenothiazine, promethazine, was used for sleep therapy as well?***

When I came from neurosurgery to psychiatry initially, I was only with Delay but elsewhere in the hospital, there was one of the most intelligent men in psychiatry at this time Dr Guiraud. He was also a specialist of histology of the brain. He looked at injection of meclofenoxate in the rat for me and made a special preparation of the hypothalamus. Anyway, he was interested in my work and he had lots of ideas. He was the first to use promethazine – Phenergan – to produce sleep. This was at a time when it was only used as an anti-histaminic. But I think he was the only psychiatrist in Sainte-Anne to inject Phenergan. Huguenard and Laborit preferred Diparcol to Phenergan because Phenergan was not so useful in their cocktails.

Ey on the other hand was a specialist in sleep therapy. He used Ektanol – an alcohol injected by the rectal route. But I think you are right many people first used neuroleptics as part of a sleep therapy approach. But after seeing its effects, they changed.

***When did people begin to think these drugs were antipsychotic rather than just a means for sleep therapy?***

Well in Delay and Deniker's service, sleep therapy was not used much, so this made a difference. I think sleep therapy was on people's minds, but this changed rapidly at least in Sainte Anne. At the time there was about 5,000 patients in Sainte Anne and 1,000 nurses. Now there are only 1,000 patients but there are 5,000 nurses. At the start though the doses were very strong – it was given by injection and this often caused a drop in blood pressure, so the patients were kept lying on their bed during the early phases of treatment but they were not put to sleep. It was clear that something else was happening. I used to visit the ward on Mondays and I vividly remember one woman who had a hallucinatory psychosis. She was tormented by voices saying to her she was a bad woman. She was one of the first people I gave chlorpromazine to and there was quite a change. She said that now she was well and she needed to go home to work. Everything was okay.

***When you saw responses like this, what did you think was happening?***

Well fairly soon when they raised the doses and got the extrapyramidal effects, which Deniker asked me to film, they became fairly certain that there was a biochemical action of these drugs. I may have had an influence here. I was interested to study biogenic amines and early in this period I gave a lecture on serotonin. I had met Erspamer who was the discoverer of serotonin and I lectured to the students on the actions of serotonin. At this time we had acetylcholine, serotonin and derivatives of adrenaline. I produced a review of what was known in this area in 1956, which will give you some idea (4). Delay's name is on this but actually I wrote the paper unaided. You could see the link with LSD in this paper. You know in the Sandoz laboratory, the chief of the department of pharmacology after Rothlin was Cerletti – a different Cerletti to the electoshock Cerletti. He was a close friend. He had found that LSD inhibited serotonin, but I found that very small doses of LSD had the possibility to increase serotonin.

But if you look at the people involved, Laborit, Huguenard, Deniker, none of them were pharmacologists. They were physicians. They did not know about the mechanism of biogenic amines or even about this type of term. At this time we knew nothing about dopamine of course. That came later. But when Deniker saw this crisis of rigidity and tongue protrusion, it was very spectacular, and he associated this with the effects of encephalitis lethargica.

***What was the reaction among nursing staff etc when you began to see these reactions first? Were you scared? Did you think you had done irreversible damage?***

No. We immediately gave antiparkinsonian treatments – Diparcol and drugs like that. I think we were the first to see these reactions with Deniker. Many people were scared to manipulate these drugs and so they gave very small doses, so maybe they didn't see these reactions initially. The appearance of these side-effects retrospectively doesn't seem to me to have been a problem. Maybe this was because we just had no other treatments that made any difference at all. When I had come to Sainte Anne, there were no drugs that made any difference. There were straitjackets, hot and cold baths and insulin comas. I remember one lady who was burned to death in a hot bath because the cold-water pipe was blocked. Lobotomy was also used.

***Can I ask you about Jean Delay? You describe in your book a man who gave the main address to the First World Congress of Psychiatry in Paris in 1950 and gave a marvellous***

***address but he also seems to have been a very shy and somewhat obsessional man and maybe very hierarchical.***

Delay was also interested in writing. He was a confidant of Montherland, Andre Gide and others. One day in his office Delay had a visit from Michaux – the poet who used mescaline. He called me and asked me "Thuillier could you come and meet me, I am with Monsieur Michaux, the poet. He has given me some psilocybin samples." Michaux had received this from Hofmann who synthesised it. Delay took psilocybin in a glass and asked me to describe his comportment during the period after he took this. It was a very low dose and there was almost nothing to record but because of this I met Michaux.

Delay was a very generous man. He had a wonderful memory. He was open to everything and had a tremendous grasp of the psychological sciences. He was the son of a well-known surgeon from Bayonne. His uncle was a cardinal in Marseille. Because of this he was the psychiatric expert for all the Catholic congregations, when psychiatric problems emerged. I saw many sisters and priests for him, who had mental problems of one sort or another. I used to talk a lot with him and he encouraged me later to write novels. In fact, I used to talk much more with him about literature than about science. He asked me to the marriage of both his daughters of whom one was a member of the jury for the Prix Femina.

We were very close friends, when I was in his service, but he became more distant when INH built for me my own department for research, fifty metres from his own building. I was also more interested in pharmacology than psychiatry and he had no real understanding of pharmacology. But I liked Delay very much. We had a common taste in literature. He knew that I kept a journal and that I was writing novels, which I hadn't completed. Delay was born in 1907 and so he was 14 years older than me.

***What was Delay's importance because after all he didn't discover the drug?***

He was important because at this time, the professor until he retired was the chief of everything. Pichot, Deniker and myself, whatever we did we had to add Delay's name to everything. Deniker asked Delay would he sign with him the first publication on chlorpromazine. Delay of course liked the popularity. At this time, you must remember, there was only one chair of psychiatry in Paris, so everything had to go through him. But I have to say he never stopped me from doing anything I wanted and I appreciated that very much. This left me free to establish my own independence when I got involved in pharmacology – this was a science which Delay, Deniker and Pichot knew little about.

But to give you an idea. Each morning Delay would enter his room. He would put on his Drap Bleu and sit behind his desk. At 12 he would ask his chief nurse if one of his assistants, Deniker or me or one of the others could be sent to him to bring him home. He was jealous of Lacan who came once a week to Sainte-Anne and who was able to draw much larger crowds along to his lectures and seminars. One day he told me that he was going to ask Lacan to give his lectures elsewhere, which he did. After that Lacan gave his lectures at the Ecole Normale Superieure in the Rue d'Ulm. Delay did not particularly like psychoanalysis, but he was interested in the

method. He thought that all psychoanalysts should be doctors. If Lacan had not been a doctor he would never have been able to make an entry into psychiatry.

As regards the Nobel Prize for chlorpromazine, Deniker and Laborit should have got one, as well as the Lasker Prize they got. But it was impossible for Delay to get a Nobel Prize for his contribution, he could not have accepted it.

***So, the American's snookered him by giving the Lasker Prize to Deniker and Laborit only?***

I don't think it was that exactly. Denber was probably the one to arrange that. He was a very close friend of Deniker and he contributed greatly to making Deniker known in the United States, bringing him to the attention of the Lasker Prize Committee. Delay at that time was a foreign member of the Nobel Prize committee. This perhaps led to a block on Laborit and Deniker getting a Nobel Prize. I know this because I knew many of the members of the committee. I also knew Bovet, Pauling and Axelrod all of whom got the prize, so I had many ways to know what was being thought. Bovet and Pauling used to visit me when they were in Paris.

***Did Delay accept that Laborit had an important part in the discovery?***

He never met Laborit at this time. I have to tell you also that the only time Laborit and Deniker met, as far as I know, was on the plane on the way over to the United States to talk about chlorpromazine in 1953 and then later to get the Lasker Prize in 1957. Deniker, as I mentioned, was a close friend of Denber and I think both of them together downgraded the contribution of Laborit. While Deniker was the first to publish the use of chlorpromazine used alone without artificial hibernation, Laborit also has his role. Chlorpromazine would never have left the shelf without Laborit.

***One of the things people say that Delay did was play Deniker and Pichot off against each other – that maybe he gave haloperidol to Pichot to investigate to compensate for Deniker having chlorpromazine. Pichot sometimes says that a great deal of what happened in Paris will go with him to the grave.***

Delay never gave a drug to one or other of them. Deniker and Pichot had the possibilities to get access to these drugs themselves. There is another point which is that haloperidol was never regarded in France as a major discovery even though it became very widely used. I don't think Pichot will be taking anything with him to the grave. All the "secrets" are in my book *Les Dix Ans qui ont Changé la Folie* or here. There were the secrets of Polichinel – because everyone knew that Deniker and Pichot were very dependent on Delay, who controlled their career. Pichot was more interested in psychometrics than in drugs, whereas Deniker was much more interested in drugs and after chlorpromazine it was clear that drugs were going to play a much more important part in psychiatry. As for Pichot developing haloperidol, he wouldn't have done much, except perhaps have had some input on rating scales. The work on haloperidol will have perhaps been done by Mme Lempérière. Pichot would not have been particularly interested in haloperidol.

***Portraying Jean Delay and Pierre Deniker and Pierre Pichot as you have done, risks to the modern ear creating the impression that these men were subservient to Delay or treated badly by him. But this is not the impression Deniker gives - everyone says that he was concerned that Delay should get due recognition and in my interview with Pichot, he praised Delay a lot. Has something in the mentality changed? Junior members of a department are now less deferential and perhaps less loyal than they were in the 1950s, where perhaps people were more happy to be under the wing of a great patron as it were.***

As I said, Deniker and Pichot owed their careers and their promotion to Delay, so it was quite right and proper that both of them should praise him very much. I was much more independent as a pharmacologist in the first instance and as a psychiatrist subsequently. I had patents on drugs, which I took out with the CNRS, my own INH and later INSERM institute. I also had my own pharmaceutical laboratory. Because of all this, the psychiatrists forgot me slightly. But I later went on to set up The European Journal of Medicinal Chemistry and to become the Chairman of the First World Congress of Medicinal Chemistry.

After Delay's departure, the Chair in psychiatry at Saint-Anne was divided in two, one for Deniker and one for Pichot. Each of them would have had the same attitude as Delay toward their assistants and their collaborators would have been subservient to them. I think now, however, that junior members of a department are less deferential, but they remain loyal although maybe happier. Being under the wing of a great patron, as used to happen, would be too suffocating for a young student now.

***Did Delay have a role in the classification of the drugs?***

Well, I drew up a classification in 1957, not the first one but it was my one (6). Delay's name was on it, as it was on everything, but I don't think there was an earlier classification drawn up in Paris. This included neuroleptics, psycholeptics, psychoanaleptics and psychodysleptics, which were all words Delay had coined. We also had psychotonic drugs, sedatives, hypnotics, euphoriants, hallucinogenic agents and depersonalisers. This classification was in a paper I gave at the Second World Congress of Psychiatry in Zurich in 1957 on Chemical Concepts of Psychosis, which was organised by Rinkel and Denber.

***In 1968, when the student revolution was happening here in Paris, Delay retired. Where the two events connected?***

In the student troubles, one of the things that happened was that they sacked his office. He was disgusted by this. He was also happy to retire to write his memoirs and go on with his literary work. He was also a member of the French Academy of Letters, you know. I continued to visit him at home as a friend.

***Lots of things happened in 1968, there was a change from more formal and deferential social structures to less formal ones. But also, and I would be fascinated in your views on this, there was a revolt against biological psychiatry. The drugs, and in particular chlorpromazine, which had so recently liberated people from their chains, were seen by many radicals as a***

***means of state control or something like that - at any rate something that student groups targeted? What was going on, do you suppose?***

This was partly a reaction triggered by some of the older psychological medicine practitioners who lost some of their patients who had been cured by these drugs. Antipsychiatry developed which was a movement that only lasted for 10 years. This was also caught up in a hostile philosophical current directed by Michel Foucault in his book *A History of Madness in Classical Times.* People did not know or did not remember what the real state of mad people had been before 1953 and because of this they were able to claim that people had been turned into vegetables by neuroleptics. I have tried to address some of these issues in my book *A History of Madness* published in 1997.

***Talking about Nobel Prizes, Kuhn feels that one of the reasons he didn't get the Nobel Prize was because you portrayed him as un petit psychiatre perdu dans la campagne – not the kind of man you would give a Nobel Prize to.***

Well, there are a number of things here. It wasn't me who referred to Kuhn in this way. I never met him. It was Domenjoz who came out with this phrase. But he also said that Kuhn was a very good clinician. Compared with chlorpromazine, however, at least in the early days, an antidepressant was not something that was very popular. It was initially only a me-too of chlorpromazine. And if they had not given a prize for chlorpromazine, how could they give one for imipramine. But I think one of these men, Laborit, Deniker or Kuhn should have got a Nobel Prize, given that Wagner-Jauregg got it for impaludation in 1927. And what about Charpentier, who synthesized chlorpromazine or Mme Courvoisier who did the early pharmacology studies? This was a time when physicians were given the first place and chemists or pharmacologists were an underclass to the physicians. At this time there was no biology or pharmacology in psychiatry – the psychiatrist was the only man when it came to madness. Now in France, the psychiatrists think that the discovery of the tranquillisers happened in the United States. I met Laborit last year, shortly before he died. For the rest of his life he tried to find another psychiatric drug. He used to say to me that I had made a good move marrying a chemist.

Another man you should consider is Lewin, who was a precursor of the psychopharmacologists. One of the secretaries to the Nobel Committee made a historical study him - he was really the first psychopharmacologist. The man who opened up the hallucinogenic drugs. He was a friend of Freud and the first to say to Freud that he was a very dangerous man to promote cocaine as an antidepressant drug because of its possibilities to induce toxic states. Lewin was a pharmacologist who was in Berlin when Freud was in Vienna. I have introduced the French edition of his book "Phantastika." The last reprint of this came out in 1996

***What role did Boissier have – he was also a pharmacologist?***

When I was in the pharmacology department, Boissier, Lechat and I were assistants. Boissier was sent to Kabul to teach pharmacology in Afghanistan. He was a pharmacologist, who knew no psychiatry. His pupil Pierre Simon did know some psychiatry and he came to Sainte-Anne to work with Deniker. But in the end Boissier did not contribute anything. He lectured a lot but did not do anything. Apart from me, though he was one of the only pharmacologists. When I

left my institute in 1967, Boissier was my successor. Simon was working at this time with Deniker before he left and went to work for Sanofi. Boissier, as I see it, took the psychopharmacology train, in the hope that there might be some possibilities. All the developments you see happened between 1953 and 1967. After that it is just me-too developments. This was part of the reason for me to change career at this time and also after that to write the history of what really had happened.

***What about your work in INSERM?***

Since 1960, I began to focus on two routes that promised something. One was clinical and chemical studies on derivatives of auxinic acid, in particular centrophenoxine, and meclofenoxate. The other was the effects of psychotropic drugs on biogenic amines and the energy of metabolism. With Nakajima, we were interested in a variety of animal models as screening tests for new psychotropic compounds. One of these was a turning mice model. I had found several years before that if you gave mice a dinitrile derivative IDPN, they began turning, like the genetic dancing mice. This was a way of screening for new compounds. We also looked at antagonism of LSD and mescaline and at the vegetative and humoral consequences of giving these drugs. Actually because of all this work, Linus Pauling who visited me, made my wife myself an offer to move to Pasadena to work with him.

We also did research on quaternary ammonium salts – the ganglioplegiques as they were called, and I also continued research on curare. It was because of this work that I later became the President of the European Committee on Medicinal Chemistry and president of the World Congress of Medicinal Chemistry in 1970, as I mentioned earlier. I was able to tease all these people that they had a psychiatrist as their president.

***What about your other careers?***

When I left Sainte-Anne, I helped create the Laboratoire Anphar to develop drugs I had patented with the CNRS. Meclofenoxate, Lucidril, sold all over the world – in Japan, England, Germany although not in the USA. As I mentioned it was used sometimes for coma cases. It was also used in anaesthesia for those who were slow to recover from the anaesthetic and as I've mentioned I've recently heard reports of some usefulness in Alzheimer's. I sold my laboratory to Lipha and Air Liquid and they sold to Merck Darmstad.

Anyway, during this time, I wrote a book, a novel, *BULANDE* under a pseudonym Jean Briance which came out in 1967. Roger Caillois who was a member of the French Academy praised it as a very good book. It did very well but my work in the laboratory make it difficult to continue writing. After I retired and sold the laboratory, I had more chance to write. There was a book of poems *Poemes de Sophie Tambour*, another work of fiction, *Campo Morto* in 1993 as well as a number of books on psychiatry or medicine. These included *Les Dix Ans qui on Change La Folie* in 1980 (7), a book on Semmelweis in 1984, a book on MESMER in 1988 another psychiatric book on Monsieur Charcot. Most recently I brought out *La Folie; Histoire et Dictionnaire*. A number of these have won literary prizes of various sorts.

After I retired, both my wife and myself also became interested in running an art gallery we had acquired – Galerie Jean Briance. So, psychopharmacology has been only one of my adventures. Perhaps my career has been too dispersed, but I have been interested in many things and I am now happy to be a witness to some of the events I lived through. My latest projects involve China and Chinese Art. With one of my daughters, I have developed a relationship with the Chinese, who are translating my psychiatric books and I now have an office in Shanghai.

**REFERENCES**

1) Delay J, Thuillier J. Curarisation by rectal suppository. Science 1953;117:57.

2) Delay J, Pichot P, Thuillier J. Les nouvelles chimiotherapies de l'alcoolisme. Ann Medico-Psych 1949;427-9.

3) Thuillier J. Naissance de la psychopharmacologie ou "une histoire de nez." Urgences 1994;1:2122.

4) Delay J, Thuillier J. Psychiatrie experimentale et psychopharmacologie. La Semaine de Hopitaux de Paris 1956;62:1-7.

5) Thuillier J, Thuillier G, Rumpf P. Evidence of a specific action on the central nervous system by the esters of some plant growth regulator acids. Nature 1960;188:152-3.

6) Thuillier J. Classification of psychotropic drugs. In: Psychopharmacology Frontiers, 2nd International Congress of Psychiatry, Zurich 1957, Little Brown & Co; 1957.

7) Thuillier J. Les Dix Ans qui ont Changé la Folie. Robert Laffont. Ten Years which Changed the Face of Mental Illness. Martin Dunitz, London; 1980. (This has been translated by Hickish G and Healy D; 1999).

8) Thuillier J. La Folie. Histoire et Dictionnaire. Robert Laffont; 1996.

*Adapted from The Psychopharmacologists, Volume I. Interviews by David Healy. London, Weinham, New York, Tokyo, Melbourne, Madrid: Altman. An Imprint of Chapman and Hall; 1996, pp. 543-563.

April 14, 2022