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The Birth of Psychopharmacotherapy: Explorations in a New World – 1952–1968

This interview was primarily with Paul Brouillot, Paul Broussolle, Jean Guyotat and Pierre Lambert, with extra time spent with Jean Guyotat and Pierre Lambert. Jacques Greffe and Patrick Lemoine from the CLRTP also contributed. Isabelle Soares-Bouchaud and David Healy asked the questions (in italic).

Can we start by quickly outlining how each of you ended up in this field – Dr Lambert?

Lambert: I am from Dijon. I will begin in 1940. My father obtained a post in a psychiatric hospital in Dijon called La Chartreuse and I started my medical studies at that point. At La Chartreuse I saw some terrible things. We always said that we needed something to do for these patients. There were things that I really do not want to describe. Toilets consisted of a bucket placed in the middle of the room – it was frightful. But at the same time, I do not regret having seen how things were in this period before 1950, because it was very gratifying later for the psychiatrist when you could see the difference treatment made. Now it is much less obvious, the difference it makes. So I do not regret anything and, if I had to do it over again, I would still become a psychiatrist.

There was a doctor there called Franz Adam, who was a shade hypomanic. When he saw me arrive on my bike, towing my luggage including my furniture, he whistled from the window – 'You're Pierre Lambert'. I said 'Yes'. He turned out to be very friendly, very sympathetic, and he explained a lot of things to me. For example, he showed me how to recognize the features of early Parkinson's disease. You had to take and hold the hand of the patient for 5 or 6 minutes and wait to feel the onset of a gentle trembling. At that time, there were a number of subjects who developed this syndrome after an encephalitis that might have

happened 10 or 20 years before. I spent time with him on his rounds, going from one patient to another. He had a notice-board in his office on which he wrote 'Think with your head and not with your feet'.

In 1945, I went up to Paris to complete my medical studies. Six years after I had met him first, I went to Rouffach Hospital in Alsace, where Doctor Adam was the director of the psychiatric hospital, a hospital which was taken over by General Leclerc at the end of the war, where he had his army billeted. At this point it was slowly returning to its original function. I arrived there as an intern in 1946 and I left in 1950, having received my psychiatric hospital training certificate in 1949. It was at that point a hospital of 2000 patients and I was the sole intern. I was there with two doctors, Franz Adam and Paul Frey, a doctor who had translated the works of Kraepelin into French. I stayed there for 4 years. So, if you ask me why I became a psychiatrist, it was partly by contamination.

How did you end up in Bassens?

Well, I finished my training in November–December 1950. After I qualified, on 1st January 1951, I took a post as a doctor at Pontorson in Normandy, near Mont-St-Michel. For more than 6 months there hadn't been any doctor there – for either the male or the female side of the service – except one generalist who basically treated any intercurrent infections. The place was a museum of schizophrenics and melancholics. We began doing electroshock, insulin shock, fever therapy, everything. There were good sisters there, it must be said, very good.

But then I came down with tuberculosis. I went to the sanatorium and when I left, cured, after a year, I went to the Department of Health where it was suggested to me that I might consider a place in Chambery. They were aware that the post at Pontorson was not suitable for me and, while I was in the sanatorium, they had kept a place for me at Chambery where the climate would be better for my health. One of the people in the department, Mlle Mammelet, who was very supportive of developments in psychiatry, had been keeping this option open for me. That is why I came here. I stayed because I liked it. The nursing staff were very good. Things were done there the way I liked. There was an orchestra there; we organized parties for the patients as well as theatrical events in which both patients and staff did the French cancan. It was a fun place, a very sympathetic place with a devoted staff. This is no longer the case now, even though the work is not so heavy. But that is another thing.

In addition, we began research with the CLRTP almost from the start in 1954.

Professor Guyotat, why did you become a psychiatrist?

Guyotat: I don't really know. Perhaps because I was the son of a country doctor who was working to the south of Lyon. I was very undecided about a career in medicine but I ended up by doing it. I did my studies at the Faculty of Medicine in Lyon and later did my internship in the Lyon hospitals. I was very undecided about what to do. I wanted at one point to do surgery and in fact I did 6 months of surgery. But I was not very adroit and I was too emotional. So this helped me decide. In France, one chooses the service to train in year on year, so I chose

neuropsychiatry, training with Jean Dechaume who was the Professor of Clinical Neuropsychiatry at the time.

I found this very interesting. I was already interested to some extent in the issues of madness because one side of me was interested in literature. I chose this service because, while I was interested in madness, the atmosphere in the clinic at this time was very different to what you found in the hospital at Vinatier. It was much less miserable, but conditions were also pretty hard. On one level there was a neurological service and on the second floor there was an acute psychiatric service. At this time, I was interested in acute psychiatry of this kind. I wrote my thesis on the effect of electroshock, which was producing such remarkable results in melancholia. In addition to melancholia, at that time there were gross conversion hysterias. This was a pathology that was quite different from what I was to get to know later on. It was an acute disturbance, which responded relatively well to interventions.

So I began to get interested in this orientation, to the surprise of my family. I had a father and older brother in medicine who found my interest in psychiatry bizarre. I continued, nevertheless, and ended up with the post of clinic chief just at a time that was to be of great interest to psychiatry. At the start I had been a neuropsychiatrist, which means that, in the course of training, I spent time in neurology, although it was psychiatry which interested me above all. So it was all very simple and by chance almost, starting off in one of the big Lyonnese hospitals, Edouard Herriot, and moving slowly, bit by bit, toward psychiatry, partly by choice, partly by accident. But mental illness interests me and I find that I can tune in to the patients, which may be a little bizarre, but there you are.

You were saying to me earlier that, before the drugs were introduced, psychiatrists were almost ostracized – poorly thought of, poorly paid, poorly regarded.

This was not so much the case for me because of my neuropsychiatric orientation. At that time, we worked part of the time in hospital, but I earned a living in private practice. This meant that I had a different status from my colleagues in the big psychiatric hospitals. Altogether different in fact, because I had a private practice. But it is true, for instance, that I would not be so inclined to say to my patients that I did some work in Vinatier. I would say it more later on, but initially, at least, I would only say it when it was absolutely necessary. If it came to the crunch, I could say that I worked as a neuropsychiatrist or that I was a neurologist and that I did some psychiatry to amuse myself. Now, of course, it's very different.

Monsieur Brouillot, what about you?

Brouillot: I am a pharmacist. After I did my thesis in 1947, I took up an appointment in the Timone Hospital in Marseilles in the central pharmacy for the Marseilles hospitals. I was interested in biology there – I had been initiated into this interest by my mentor, Professor Derrien. And that was how I had my first shocking contact with psychiatry. The thing that later interested me in psychiatry was my first contact with Vinatier, and, above all, what I heard about

the ostracism of psychiatric patients and those who looked after them. That struck me as an absurdity, but it was not very long since the time when the mentally ill were very badly treated and were looked on as diabolical or possessed. Even without being a doctor or a psychiatrist, that struck me as shameful. When I made contact with the doctors at Vinatier and with psychiatry, I personally became very, very interested. This was a whole new world. If I had done medicine, I think I would have chosen psychiatry rather than cardiology, for example, or another discipline. What interested me were the humanities, or the disciplines dealing with the question of meaning; this was altogether more passionate than cardiology. So this is how I came to be involved in psychiatry and have remained interested in it ever since.

Did you have contact with other people in Rhône-Poulenc such as Halpern?

Halpern was the allergy man. There was Delcours; I don't know if you know him. Daniel Bovet was another who was there at the start, and then there was Courvoisier, who you could say was the midwife to chlorpromazine. Julou and Courvoiser began to get interested in psychiatry.

L: Mme Courvoisier showed us catatonic rats, for instance. She showed how you could set them down with their four paws on four corks and, even though they were unstable, they would continue in the same posture, even when you moved your hand towards them. By this time, new neuroleptics were selected based on their ability to produce catalepsy like this, rather than because of any anti-emetic activity they had. In fact Mme Courvoisier and our group later produced an article on a compound which had pure anti-emetic properties but no antipsychotic activity – to demonstrate the point.

Br: It was interesting to see the ease with which they became interested in what was a new domain for them also. These were the golden years of psychiatry and it was interesting to see how the industrial environment responded. They recognized the interest and importance of this at a time when it was not obvious to everyone. And it was because of this recognition and these people that I got a good budget for research in this area. This was at a time when the senior figures in Rhône-Poulenc still said 'Psychiatry, what is that to us? What interest could it hold for us?'.

Le: I think you are being too modest. If you hadn't insisted with the hierarchy that Largactil was important, that entire budget for research would not have existed.

Br: Maybe. But I was remembering this with Lambert just now. When we had the first meeting of the hospital committee, which was to become the CLRTP, I mentioned this to the management in Spécia – I said that Courvoisier or one of her assistants should come along to the meeting to explain a little how the research issues looked from their point of view. These very gentle people in Spécia at that time said, 'You shouldn't think for one minute that the scientific department in Rhône-Poulenc is going to be interested in this'. I said they

should be and asked who should I make contact with. They told me and I went along and visited Koetschet.

I told Pierre Koetschet what was going on. He listened to me for quite a while – which was unusual, because Pellerat had warned me that he was very busy and he wouldn't be able to give me much time. The meeting lasted almost an hour. At a certain point he asked me, all of a sudden, where and when this meeting was due to take place. I said in Vinatier at the start of October, the first Thursday I remember. He took up the telephone, and as I understand it, called Julou at the Rhône-Poulenc research department. Julou said to him that he wasn't free that day at that time, but he said 'Look Julou, you should go on Thursday to Vinatier in Lyon and Mr. Brouillot will accompany you'. He was impressive, this Swiss man, an organizer, who from 1000 kilometres away understood the importance of what was going on in this place.

And you, Doctor Broussolle?

Broussolle My father was a military doctor, but he had the bad luck to die of typhus in Morocco, where he was living, at the age of 37. So I became, just as he had been, a doctor, initially in the Paris area. I was set back in my studies by an infectious disease and, when I did qualify, I later went to Dijon, where I had a mixed internship and at one point I took up otorhinolaryngology and then infectious diseases, just at the time the first great antibiotics arrived. In between these two stages, I discovered psychiatry, which was much more depressing. What gave me a taste for it was a doctor – Léculier – and the nurses working with him. Some of these nursing types were really remarkable – a little bit like Charnay who we used to have here. He used to work in the service of Requet and he was so remarkable that we ended up perpetuating his memory by naming one of the pavilions after him. These were people who took part in the movement to develop the profession, to establish training methods etc. It was this that gave me a taste.

After that, I went to Lorraine to the hospital at Nancy, where there was a tradition, following Morel, of a very classic psychiatry. This is where démence précoce came from – it was very organic. Then I came here to Lyon in 1953 – provisionally. There was not much competition. The place there was run down, but things weren't so bad in Vinatier. I had four large pavilions of patients, 350 altogether. One example of how bad things were in some ways was that there were no toilets for the women. They used to use small tubs, and you would see them coming down from the first floor in the morning with their pots. There was only one intern, no secretary and no social work input of any sort.

In these miserable surroundings, which I shared with my colleagues, I began to benefit by osmosis from the thinking of Balvet, Requet and Beaujard and Revol. There was also someone else, Dechaume, who had the heavy task of reconciling psychiatry with the neuropsychiatry service. I felt happy at that time to take this on because it seemed a friendly service in Vinatier. I put my energies into trying to humanize the service. The training of mental health personnel was beginning to take place at both local and national levels and I took part in

this. I took part with Professor Colin in developing a psychiatry service to the prisons in Lyon.

And then, after 3 years there, there was the CLRTP, this adventure, which gave me a training in biology. I saw the biological side of things develop step by step. I saw, for example, the term catatonia become an object of dispute between veterinarians, biologists and psychiatrists, with celebrated disputes between the various groups. I saw an era where really the biological input was developing and becoming useful to psychiatry. But during this time we were also interested in phenomenology, Pavlovian conditioning, psychoanalysis, antipsychiatry and ethnopsychiatry. A lot was owing to Pellerat, who generally did a lot for research of all kinds in Lyon. Brouillot played a big part, and Perrin, who was dynamic and very aware of what was possible.

I practised through to 1989. I have been retired now for 9 years. It seems at the moment as though there is a return of the biological to psychiatry, but let's hope that the neurosciences have really made sufficient progress to provide us with benefits. If I were to start again, maybe I would make fewer mistakes – who knows?

Gentlemen, can I take you back to the start? What was the difference in mentality among the doctors and among the public?

L: Well, first of all let me say chlorpromazine was not the only motor of change. At that time, interest was growing in psychiatry partly because of the sad circumstances of a large number of patients who died during the war because of famine. This inspired a number of psychiatrists, people like Daumezon, Le Guillant, Sivadon, Bonnafé, Balvet and others, even before the introduction of chlorpromazine, to create services, mainly in the Paris region, which after the war were models of research into the issue of how to rehabilitate patients. So, my own experience unfolded in favourable conditions which contributed to putting in place logical solutions and to the evolution of psychiatry.

When I came to Bassens, I took charge of a service spread over four pavilions, two for men and two for women, with about 400 patients. The way things were designed, it was possible to convert the service over to a mixed one. This novelty was something the nurses were prepared to go along with, though with some reservations, which were quickly laid to rest.

Later, when faced with an increasing number of patients entering and leaving the hospital – the revolving door model – it was decided that care must be brought out to the outside world and this led to the policy of sectorization. In 1957, I published the first experiences with operating a sectorized model. This meant that one part of the service received, treated and continued to treat after their discharge all the patients from a particular geographical area. Both doctors and nurses, therefore, had to follow up both sexes.

The clear antipsychotic effects of the neuroleptics led to a revitalization of the spirit in the hospital and especially to a fresh enthusiasm for involvement in care from the nursing staff. Some of them volunteered to be involved in domiciliary visits to the patients' homes, and cars were organized for them. Others

opted to get involved in occupational therapy activities or in either sports or games. It was about this time also that the first open service was started, that is, a pavilion which accepted patients at their own request or that of their families, patients who remained free to go also at their own request. Up till then the hospital had only taken in patients who were detained by administrative order or who had been certified by doctors outside the hospital.

The mentality of the generalist physicians was hard to change. There were only two neuropsychiatrists for this whole region of 350 000 ~~patients~~ inhabitants, whereas now, with the same population, there are over 30 psychiatrists and neurology has, of course, become a separate discipline. Psychiatric hospitals had a very bad reputation amongst both physicians and the public as places where nothing happened. Patients were often admitted and remained until they died. The hospital had its own cemetery.

Let me give you an example where things turned to outright hostility. Things were different for us in Savoy, compared to here in Vinatier, because we have many long valleys where life for the general practitioner is difficult, especially during the winter and when they have to try to get access to some of the small villages up in the mountains. The valley of Maurienne was one of these valleys and physicians there knew that sometimes they could count on no-one but themselves. They wanted to be kept in touch with things in all circumstances. Somewhere around 1960, they sought a meeting with the sector team that I represented. A meeting was organized at which almost all the doctors, including the occupational health doctor, were present. The main accusation was as follows: – that the psychiatrists were sending patients out to them with prescriptions mentioning the names of drugs they had never heard of. And, very often, one of the first things patients would do when they were free like this was go to their doctors and ask whether they needed to be on these pills. So why, they wanted to know, didn't we let them know about these patients coming out on leave and what their prescriptions were.

They were more than justified in their complaints. We were in the wrong. We only had our good faith to fall back on. What could we say? That we had more than 100 patients in the sector to follow up? That each week at least 12 patients went on leave and sometimes these leaves would be one weekend after another – did they expect us to inform them each time? We had no social work input. The secretarial support was limited – it was only enough to cover the discharge summaries when the patients finally did leave for good. In terms of aftercare, at least initially, hospital doctors were not allowed to practise outside and there didn't exist any dispensaries used to psychiatric practice. It took a decree from the ministry to set up aftercare surveillance properly. In time, things changed and communication got quite good. Both sides began to use the phone more.

These doctors were faced with the worries of families who had been through an episode of madness and this often led to anxious phone calls from the relatives or the doctors :'He's not going to relapse, is he?' Besides, some of the older psychiatrists didn't really believe in the power of chlorpromazine. They had known the limited results that had been obtained with insulin coma or

convulsive therapies and this new medication, for them, represented a fashion, which would pass.

Meanwhile, treatment with chlorpromazine spread and became something easy to prescribe and effective, a treatment for the masses, something that had never been seen before in psychiatry. Even the doubters began to use it eventually; those who, with a smile, would still call themselves alienists. Timidly, some families began to suggest to the doctor that he might try this new medication. I should add on this point that the press, both the medical and the lay press, played a part, sometimes by exaggeration, in the transformation of the psychiatric hospitals.

I can give you an example of one psychiatrist who, in response to the increasing demands from carers, grouped together in one dormitory 30 beds filled with patients with chronic schizophrenia, some of whom had been hospitalized continuously for more than 10 years. He had the curtains pulled so that the room was dark, just like for a sleep cure. Morning and evening the treatment was given by injection. Day and night a religious nurse was there. The results, which began to build up after a few weeks, were convincing. Usually, in the morning, one or another of the patients would get up and ask in appropriate terms whether they could either go and visit their families or go out. It was very moving to watch a patient who perhaps had been sunk in complete alienation for years come out of it and very often without asking what he was doing in that state. The return to reality could happen from one day to the next.

I remember one catatonic patient who spoke to no-one and who took up some strange postures, one of which was owl-like – he would not let his head rest on his ears at all. The morning of his recovery, a sudden and unexpected recovery, he was smiling and joking. I came to visit him and he greeted me normally and began to talk to the nurses, from whom, curiously, he asked for some billiard balls. In a manner totally unexpected, he used them to do some juggling tricks – something he used to do before he came into hospital with schizophrenia. The split between an unawareness of the troubles, which he had presented even the previous night, and his return to lucidity that morning was striking.

In some cases, worries centred on the medication. In the case of one patient, we learned that the pharmacist in his area had advised and given him 25 mg tablets of Largactil, where we had prescribed 100 mg. Sometimes, the anxieties affected the managers of the hospital, who realized that letting people out into the community would reduce the size of the hospital. I remember one of the presidents of the administrative commission of the hospital in Bassens addressing a meeting of the doctors and saying to them 'I beg you, don't let any more patients go'.

Even in the hospital there were worries. I remember signing an order to get some knives for the tables in one of the pavilions. This was the first time anyone had asked such a thing. It might be dangerous. The order went through all the echelons of the hierarchy of the hospital before finally we got some knives with shortened blades.

We had a visit on one occasion from a mayor and priest from one village. They came to implore us, to testify to the disquiet in the village after a family

had let people know that a patient who had had a delusional episode some years before, was going to come out. The village was in uproar. These ambassadors asked us to hold on to the patient. The solution was to propose a series of trial leaves of increasing duration and to review progress with the people from that village.

Br: Well, to convey the change in mentalities, I should tell you about my first contact with the old asylums in 1947 in the Timone Hospital in Marseilles, in their psychiatric quarter. I was a pharmacist there and in 1947 or 1948, there was a congress of the psychiatrists of France and the French-speaking countries. One of the psychiatrists, Baudry, who was quite a remarkable fellow, had the idea to visit the psychiatric wards. The programme envisaged a visit to the male wards of the hospital. At that time the sexes were rigidly segregated. Each section of the hospital had a number of different wards – one for the dependent or chronic patients, for instance, and another for the difficult psychotic patients. It was this latter group of patients the conference proposed to visit.

Well, this gave me a terrible shock. I don't think the ward staff could be called nurses, they had to be wardens, jailers. I remember having to stay in the ward office, – I don't know if it was for particularly psychiatric reasons, but there were very heavy chairs on the ward, leaden, which one patient had picked up and thrown at us, just like you would pick up a small piece of wood, probably because he had been aggravated by our presence. Another had torn apart one of the straw mattresses that they had in their cells. It was astonishing. When we left, I remember a chap from Berne saying to me that our sick patients really were being kept in pretty awful conditions. That was the least you could say, I said to him. The visit left a painful impression on me, especially of the tormented look of the patients, a mixture of aggression and doom. I continue to have a very clear memory of those patients, the state of desolation of their cells and also of the attitude of their attendants.

Despite this, it could be a place where therapy happened. At that stage, they had bromine, chloral draught, Gardenal and then later, towards 1950, Phenergan for agitation. They also had Sakel's insulin coma therapy, which had been known since 1936 but was not used in France before 1947. Above all, electroshock was there. This had come on stream in 1938. It was effective in major depressions, but also in other pathological states, especially when there was agitation. There were lots of different therapies used, but none gave very good results, except electroshock. I say this because recently, at a meeting, Dalery said the psychotropic drugs were discovered by chance. I had to interrupt and say this was not completely the case. They were not discovered by chance in the sense that they were exactly what we were looking for. We were looking for products that would calm the nervous system in the face of shocks and stress. So, in that sense, they weren't discovered by chance.

In 1949–1950, following work on postoperative states, notably the work of Reilly, but also the work of Selye on stress reactions, Henri Laborit, who was a naval surgeon, began studying the mechanism of surgical shock. As part of his research, he began to use, in the course of anaesthesia, a cocktail of medicines

aimed at producing effects on the neurovegetative system and he also began to use the new antihistamines. This anaesthesia potentiated by a mixture of compounds was shown to be of great interest because it did diminish the risks of shock. Laborit thought that the promethazine he was using in his cocktail had an important role because of its action to reduce metabolism.

It was then that Rhône-Poulenc, working with Laborit, turned their attention to making more centrally acting derivatives of promethazine and this led at the end of 1950 to the discovery of RP4560 – Largactil. In 1951, Largactil was given to Laborit, who used it in collaboration with Huguenard to produce a form of potentiated anaesthesia – artificial hibernation. So, it began its use for this purpose, but at the start of 1952, in an article entitled 'A new stabilizer of the neurovegetative system', among other effects, Laborit noted a curious state of psychic detachment among the patients. It was this effect that led him to suggest it might be useful in psychiatry.

I think it was Laborit who first understood the implications of RP4560 for psychiatry. It must be said that at the time there was very little contact between psychiatrists and anyone else. Psychiatry was the most marginal discipline in medicine. One talked about it as something completely different from the rest of medicine. In the university hospitals, there was a neuropsychiatry service, which was run by neurologists. The participation of psychiatry in university faculties was extremely limited. It was only after the discovery of the new molecules that things changed. And, in fact, it was only after 1968 that there was a proper separation between neurology and psychiatry and psychiatry began to become a proper medical discipline in its own right.

Now, to convey the change in mentalities, I need to tell you about my first meeting with Jean Perrin. It was in the context of reports of some accidents with Largactil in Vinatier. I was sent there. This was in 1953. I was working with Spécia as a pharmacist and was covering the Lyon hospitals. I was working with Dr Pellerat, who was on a committee for research on medical therapies, which was concerned above all with infectious disorders, dermatology and parasitology. Now, at this time, the management in Spécia were told by a medical visitor about some serious incidents at Vinatier Hospital with Largactil and they asked us to make enquiries of the doctors there. I contacted Pellerat and asked him whether there had been some deaths. He said no, that he had heard nothing and if there had been something like that he would have heard. Something like that wouldn't have gone unnoticed.

I remember it very well. I had little contact with psychiatry up till then. The hospital was vast, huge, with wards full of patients, often very distant from each other. At that time, the hospital actually extended over 130 hectares and filled a rectangle almost a kilometre wide by a kilometre and a half long.

Fortunately, when I had arrived, by chance I met a young doctor, slightly hypomanic maybe, very dynamic and very gentle, who was an intern at the time, Dr Jean Perrin. I told him why I'd come and asked about the difficulties, the accidents with Largactil. 'Accidents?' he said. 'We haven't had any of those. On the contrary, the results have been spectacular, at least in Dr Requet's

service.' (He was working for Requet.) 'Why don't you come with me and I'll take you around the wards.' And on this tour of the wards, I remember well one chap, a psychotic patient, who had already been hospitalized for 5 or 6 years. He was a farmer, who now, following treatment, was quite well and wanted to go home to see his wife and to his farm. This was almost a resurrection. Someone who all of a sudden almost wakes up and says 'What am I doing here?' How long have I been here and what has happened to my farm since I've been in here?' this was extraordinary; at least, it seemed that way to me.

Talking all the time, Perrin took me around the different pavilions, and it was clear that there were a great many extraordinary changes that explained his enthusiasm. This was the moment at which I became enthusiastic about what was going on. I was stunned. I said as much – this, at the end of the day, was really extraordinary. This visit brought back to my memory the early visit to the Timone Hospital and that stimulated me to revisit these doctors many times to get to know better their experience with using Largactil. Later on I heard from Balvet, Beaujard and Broussolle about all that was going on.

Then I said to Perrin, 'Look here, how many cases like this do you have here?' He said 'Lots'. So what happened after that was that I came back in the evenings to spend time with the interns at Vinatier, collecting observations on all these cases. So much so, that once I didn't get back until 3:00 in the morning. My wife became suspicious. She asked where I had been and when I said 'Vinatier', I don't think she believed me.

What I took from all these conversations with the doctors there was that their clinical experience was remarkable, and I felt I could play a part in underlining the interest in this by helping to assemble and analyse the observations. Now, at this point, I must mention the essential role of Professor Revol, the chief pharmacist at the hospital, both in facilitating my contact with the various doctors and also producing the first booklet on chlorpromazine. His role was the foundation stone of the later functioning of the committee and the successful development of its research.

Analysing all the observations was a great deal of work because there were over 700 in all, which came from different parts of the service. But we began, and got through the work in several weeks, thanks to the efforts of all the interns and especially the dynamism of Dr Perrin. The experience of the doctors in Vinatier was soon supplemented by Dr Lambert in Chambery, where Dr Perrin rotated on a training placement. Dr Perrin filled Dr Lambert in on what was happening at Vinatier. So this is how we put together the observations, which allowed us to put together the booklet on *Therapy with Chlorpromazine in the Practice of Psychiatry*. This work was also the subject of many communications in different congresses.

It was then that it seemed a good idea to me to organize the doctors together in a Committee for Research on Therapy in Psychiatry along the lines of the model which Dr Pellerat had already organized in the other hospitals in Lyon. And the management at Spécia accepted this project, in great part because of the efforts of Professor Revol.

Br: You haven't mentioned that, partly because of your influence with Rhône-Poulenc Spécia, we got to meet German and other colleagues. Denber in particular was very keen to set up a study involving New York, Erlangen in Germany, Brussels and our group here, with all the patients having the same treatment and all being rated the same way by a pair of German psychologists. The idea was to see if there was a transcultural factor. It was too complicated a study and it never happened in the end.

But let me get back to what we were asked about the ambiance of the service at this time. It was an atmosphere of misery and poverty. The services as such were not organized. Treatment was delivered *en masse*. There was no individualization to particular patients. The staff were not properly trained – this even applied to the doctors. The notion of medical ethics barely existed and only developed slowly. Research protocols in the early days were very thin documents. It was very much a case of just amplifying on the animal studies. Everything has become much more complicated now, in contrast. I am not regretful about the past though – I am not nostalgic.

So how did chlorpromazine actually come about?

B: These molecules, the phenothiazines, had been synthesized a good deal earlier by the Germans, but were just lying around the laboratory.

Gr: Yes, even in Spécia, when they were tested first, it was as possible anti-helminthic agents for use in Africa, antiparasitic agents. Then their anti-histaminic properties were looked at. Phenergan was the first of them and it had already been used for agitated states before chlorpromazine.

L: I remember being at a conference of alienists and neurologists working in the French language in Besançon in 1950, where I went with Dr Adam. I didn't have my diploma in psychiatry at that time, but I was giving a paper at this meeting on the subject of my thesis. An old psychiatrist was there at the meeting – Paul Guiraud. His talk caught the general attention because it seemed to be introducing something new; you could even say, with the benefit of hindsight, that it presaged the coming of Largactil two years later. The subject was the treatment of mania and agitated states with promethazine, Phenergan, in which he got good results. Now, if you look at the formula of that molecule, you can see that the side chain has two atoms of carbon in it, as does the side chain of chlorpromazine – except there are three carbon atoms. This chain, which is termed aliphatic, was a necessary condition for antipsychotic activity, as Janssen later showed, and it was incorporated in all Rhône-Poulenc neuroleptics.

So, we had medications before Largactil. And it was because of the feedback from the use of these that Mme Courvoisier created Largactil, working in conjunction with the chemists and pharmacologists.

Initially, were the antihistamines, including Phenergan and Largactil, used for sleep cures?

G: Well the very first time I used Largactil, it was with a barbiturate and it was for a case of sleep therapy.

How long was it before people realized that Largactil did something quite different to sleep therapy?

G: It took about 2 years.

L: Things developed in roughly the following way. We were quickly able to see that the sedative medications, particularly when given in the course of a sleep cure, did not do very much good for the patients. When we used sleep treatments at this time, it should be mentioned that we used them under the influence of Russian psychiatry – Pavlov – which emphasized the idea of treatment by conditioning sleep. But we fairly quickly saw that Largactil did something different, that it also had an antipsychotic effect. And it was then that the Comité Lyonnais learned of the work of Labhardt in Basel who was giving 500 mg per day to all his schizophrenics and getting good results. Beaujard, one of our colleagues in the CLRTP, brought us back reports of this.

I increased the dose and saw some of the chronic schizophrenic patients coming back to reality. This opened up our horizons. Even in Paris at this time, they were only using 200 mg per day. We used the higher dose and this led to a number of publications. In this sense the discovery of the specific antipsychotic action took some time, because chloral and the bromides were very effective sedatives. Our thinking at the time when faced with agitation or excitation was that sedation was the answer.

Another point, perhaps, is that, against the background of the time, there was a preference for more sedative compounds and this led to the creation of Nozinan – levomepromazine. We used Nozinan as a second-choice medication. As I remember, Beaujard used up to 500 mg of it. I used Nozinan also in melancholias and other depressions, with a response rate of up to 50%. An article by Deniker suggested that Nozinan was even more effective when accompanied by antidepressants. After Nozinan, however, we came to appreciate that it was necessary to treat at least some patients with something less sedative. We realized this because of the work of Broussolle with Stemetil/Tementil – prochlorpemazine.

Another point, too, was the influence of Laborit's ideas. He had included chlorpromazine in his cocktail because he wanted a ganglioplegic cocktail – he wanted ganglion-blocking drugs to block the effects of stress, and chlorpromazine was going to be the neuroplegic part of that, leading to a sedated central nervous system which was less sensitive to the effects of stress. But, as we got compounds with less sedative effects, we eventually realized that we didn't need this neuroplegic effect, that it came with too many undesirable side-effects which did not contribute to the restorative neuroleptic action, which was what we wanted.

B: Well, if we can back up a step, I can tell you another story, which illustrates how things developed. The team at Spécia was very proud of a new antibiotic they had in 1952 or 1953 – Aureomycin – that was to prove very successful. Their great success with it encouraged them to get a research team together. This was under Pellerat, as you've heard, who had people like Lebrun and

Schott participating. This meant that, right from the start, there was a multidisciplinary approach operating in Lyon. They had gastroenterologists, stomatologists, neurologists and others together.

I asked Pellerat if I could do some work with them. He decided he needed to test me out and he gave me a multivitamin product on which some studies had been done in the polytechnic college. The idea was in the refectory to give thirty people the new preparation and leave thirty without and then to change them over blind to see what happened. Now, it was just at this time that Stemetil/Tementil was made.

It was developed as an anti-emetic agent. But we learnt very quickly that there could be problems; there were dystonic crises and other problems, which led to something of an outcry against Spécia for putting this problem medication on the market. There were complaints from obstetricians when it was given to pregnant women for nausea and vomiting and they had problems. It was because of my earlier contact with them that I got involved in assessing this.

Br: One of the best-known episodes was when it was tried out on a group of marines to prevent seasickness and vomiting before landing manoeuvres. It was a very powerful anti-emetic, which didn't put soldiers to sleep or impair their capacity for vigilance, but some of them were left with dyskinetic movements, tetanized and catatonic on the beach. This is what drew the issue to our attention. I think it was a military doctor who said that it would be necessary to have a psychiatric opinion on what was going on.

L: Didn't he say that this was a medication that might perhaps have a psychotherapeutic effect?

Br: No, I think the view was that it might be useful in psychotic states. This was how Stemetil/Tementil came into psychiatry.

B: They came to me because of my connections with Pellerat and we tried it out. With a certain amount of astonishment, we gave it to a number of the inhibited patients, to patients who had not spoken for years – of course, in part this was an institutional pathology, that stemmed from the inhibiting aspects of the asylum system. But the nurses and myself watched astonished as we saw the inhibitions go and the patients come out of their mutism and lethargy and their interest increase to the point of psychomotor excitation. At this point it became clearer that there were similarities with states that had been seen after encephalitis lethargica.

Actually, also, I found out later that Laborit had recommended Largactil to the American army as an antistress agent. As a consequence, a number of American soldiers had ampoules of Largactil in their baggage. They were supposed to use it if they were injured. However, the sedative effect left some of the soldiers in the Korean War in 1953–54 inert, and as a result they didn't make efforts to get picked up by their rescuers and they died on the field of battle. This unfortunate military use of Largactil remained concealed for many years and even now is not very well known.

When these pregnant women had these problems with the drug, I've heard some talk that it was thought that they were being hysterical.

G: I think we thought then that there was some overlap between hysterical problems and the phenomena caused by neuroleptics. There were some publications to this effect at the time. These reactions, these dyskinesias, seemed open to suggestion, as you can easily see still. Kammerer wrote about this in 1964. This made them very interesting. In France at that time, we were using Babinski's definition of hysteria, which he called pithiatisme, which was that hysterical difficulties were those that were open to modification by suggestion and countersuggestion. It was clear that, while these drug-induced effects might not have been totally caused by suggestion, they were open to modification by suggestion.

L: Yes, these difficulties were called excitomotor difficulties at the time.

G: That's right. Now we call them dyskinesias. But it does seem that the more attention is paid to them, the more of them there are, and the less attention, the fewer there are. Some of the dramatic reactions seem to have completely disappeared now that less attention is paid to them. So, while they were not completely caused by suggestion, you can see why there seemed to be some overlap with hysteria. But it should be noted that this was a case of hysterical symptom. We didn't talk at the time of a hysterical personality.

B: There was some talk that some products might make people more prone to hysterical developments.

Le: Was it you who coined the term disinhibitor about Majeptil?

B: No, it was with Tementil. I showed this to Schott, who came once to see these patients who had been sunk in lethargic states and who, under the influence of Tementil, woke up. Some of them developed very odd movements and a festinating gait. We published a piece on this in 1957. This was at a time when we were still referring to these compounds as neuroplegics. According to my observations, the term disinhibitor seemed appropriate. I didn't, perhaps, exactly specify what I meant. I suppose I could write to the Académie Française to see if I can have the copyright for the term.

On the question of side-effects, we should add in here that we also noted other side effects such as amenorrhoea and galactorrhoea, for instance, as well as a gain in weight.

G: I was in private practice – in 1952 or 1953. You asked what there was available at the time. Clearly, there was electroshock and malaria therapy for general paralysis, but I was also using a lot of narcoanalysis. I don't know whether this was ever used in Britain or, if it was, whether it still is, but it is used here still to some extent and I used it a lot then.

What did you do it with – barbiturates?

G:Barbiturates and sodium amytal – Eunoctal.

B: There was at the time socially, and also in psychiatric mental states much more often than now, a great deal of inhibition, a great deal of silence. In France, we have seen a big difference in this since May 1968. People talk much more readily now. It really is the case that back then, in those years when Deniker introduced the procedure that he promoted as narcoanalysis, there were many more mutes, many more catatonic patients than now. This is a good example of a therapy that lost its place owing to the changing clinical picture.

G: That's right. I think it was Delay at the start who wrote that narcoanalysis was a chemical psychoanalysis. Something that could be done when psychoanalysis didn't work. This didn't please the analysts. This has all stopped now, but it was interesting all the same.

L: There were also amphetamine shocks. And at one stage people used to mix the two – amphetamines and barbiturates.

G: Behind all these techniques there was the issue of the importance of sleep and the emergence from sleepy states of unconscious material. This was the thinking.

L: There were also the psychodysleptics. Did any of you use LSD? You used to drink it. One of my patients called it the Devil's brew.

B: We could also mention that the military contemplated experiments using the psychodysleptics for military purposes.

From the point of view of people here, was the discovery of chlorpromazine in Paris owing to the great skill of the best clinicians in France or was it something that was inevitable – it would have happened anyway?

L: Well, it was the case that they had it first. They got it from Spécia laboratories. So, necessarily, Delay was involved first.

Br: This is really not a complicated story. Chlorpromazine was synthesized at the end of 1950. After the animal work and toxicity tests in 1951, the definitive clinical work was done in 1952 and it was commercialized at the end of 1952. So, for a year, it was not used in psychiatry at all. It was used first in surgery and anaesthesia solely. It was first given to Laborit and his military colleagues at Val-de-Grace. And in the end it was because of the observations of a military surgeon, Henri Laborit, who noted that something of potential importance to psychiatry was happening when you gave it and that he should get the opinions of his psychiatric colleagues. It was 2 or 3 months later that it was given to Delay. Because of Spécia's relationship with him, he was the first to get it in psychiatry. From that point onwards, in Spécia you can see the first orders for this compound in psychiatry over the next 5 or 6 months.

B: What about Hamon, the military psychiatrist who published before Delay?
Br: Yes, he published before Delay, and then there was also Mme Deschamps who published before Delay. It was unusual for a women to be a psychiatrist. She worked in Orléans, but her work did not have much public impact. I don't

know where Mme Deschamps fits in to this. I know how we got it here so quickly: I asked Spécia for it. But I don't know how she got it.

B: I knew Mme Deschamps well. She was extremely competent and ran her service in the psychiatric hospital of Fleury les Aubrais very well. She was, perhaps, too modest and not enough of a self-publicist. I also remember, when I was a young student in Nancy in 1952, being told of a publication by military psychiatrists at a congress in Luxembourg on a new compound.

G: These publications were all about its effects on acute agitations. The recognition of its effects on chronic states came later. It took at least a year for this to develop. I remember a publication by Henri Bonnet on this. It wasn't obvious that there necessarily would be good effects on chronic states. It was used for acute states initially, but some of these were in chronic patients.

Broussolle, you used it right from the start, but that was for acute agitations. What about the effects on chronic states?

B: The action on manic agitation and anxiety states was what was reported by Hamon, Paraire and others in 1952. This treatment of excited states derived from the principles of hibernotherapy.

I published a paper in 1953 in the *Lyon Medical Journal* with Hamoneau on thirteen cases of prolonged treatment with chlorpromazine in serious psychoses. I was devastated later on, although I have a high regard for the German Swiss, when in 1954 they published in the *Swiss Psychiatric Review* similar observations on psychotic states. My problem was that I had published in a small, local journal that did not have much of a medical circulation.

When the various side-effects began happening first, did you at any point think that something serious might be happening, that you might be doing some permanent damage?

L: When we met the first troubles of a Parkinsonian kind, we did not recognize them as such. These difficulties seemed bizarre for the most part. Sometimes they posed a real problem at the start – for example, cases of trismus or general hypertonicity. I don't remember asking myself if these might have long-term implications; the immediate question was what to do right then and there. Some psychiatrists went so far as to recommend an intravenous injection of caffeine before we settled on the use of antiParkinsonian treatments.

The first time this was drawn to our attention properly was by Hans Steck, a Swiss psychiatrist from Lausanne. He liaised particularly with Deniker. He described very clearly phenomena following neuroleptics, which were entirely characteristic of the problems seen after encephalitis described by von Economo. This made it simple to identify the source of the phenomena, but we spent some time after that working out what was the best thing to do to manage the situation.

G: I have to add here that these secondary effects did not particularly worry us because the overall results were so good.

B: We made enquiries of the neurologists, though. Do you remember Alexandre Garde? He was an excellent neurologist colleague, to whom I sent a patient. For him also this was something new – these Parkinsonian syndromes. We also had enquiries from Professor Schott and many other neurologists. There was an increasing interest from neurologists and increasing disquiet on our part, because we didn't want to produce a chemical encephalitis. And after that there was, of course, tardive dyskinesia.

G: Yes, above all there were the tardive dyskinesias, but they weren't seen in the early days. I think the development of this problem depends on a number of things.

B: Yes, there were big differences in doses as a function of the atmosphere between hospitals and between hospital and outpatient settings. One of our colleagues, who is now dead, Dr Requet, made a journey through the USA from the west coast to the east coast and he found that the doses dropped as you moved from the east to the west of the country. The maximum dose was in Texas. This was the case here also – you could see the same variations.

Dr Fouks used high doses, didn't he?

Br: Well, this was not an example of good practice. He was very provocative. If you leave this case out, dosing regimes across France were fairly comparable, except for one or two cases.

Gr: At congresses most people put some distance between themselves and him.

Br: We never used particularly high doses – 200–300 mg in psychotic states mostly. It depended on the neuroleptic. As I remember, we were appalled by some of the doses being used by the Americans. You heard about 2 g being used.

L: Two grams and people developing violet skin.

Br: That's another thing; there was a difference in the thermic sensibility in anglophone and francophone zones in Canada. Maybe this had something to do with alimentary practices or habits. I'm sure there must have been some reason for this, something to do with customs, environment or diet. They continued with the butyrophenones, for instance, with haloperidol at extraordinary doses. It wasn't harmless.

G: There was also the problem of eczema and dermatoses among the clinical staff, especially among the nurses. It was very important at the time but it seems to have disappeared.

B: Did they change the covering of the pills?

Br: They did, but that was afterwards, and after that these allergic manifestations disappeared. They made it so that the powder was less likely to disperse.

G: There were protests from nursing staff unions. In contrast, psychiatrists weren't very much affected – they didn't touch the pills.

B: The other point to mention is that there was a compliance problem among the patients, particularly in the big hospitals. They used to get rid of their pills.

Why was there a compliance problem with neuroleptics but not with Valpromide later?

B: On neuroleptics, the patients complained of lack of motivation and sedation.

G: We held a meeting here on the notion of passivity. The question was whether this passivity was part and parcel of the illness or whether it was caused by the neuroleptics. I had initially thought that this passivity was due in great part to the situation of hospitalization. I thought this because I had followed for a number of years some patients who had been put on relatively low doses of medication, who had escaped without hospitalization and who showed no passivity. So, I thought the hospital situation played a role. But it is true that, with Depamide later, it was very different.

L: Well, to add a little bit to what you say: I used to find that if I was treating people at home, I would use half the dose that I used in hospital.

G: Yes, the context of the prescription is important, especially at the start.

L: In our idiosyncratic language here, we used to see this in terms of transference issues.

Here, in Rhône-Alpes, you produced one of the first classifications of neuroleptic drugs – into sedative and incisive. How did the phenomenon of akathisia relate, if at all, to these distinctions?

L: The start of the issue of akathisia with neuroleptics is not something I remember terribly well. In fact, initially, I thought the sedative neuroleptics were more likely to cause akathisia than the incisive ones. To the extent that one moved towards the more antipsychotic agents, you had less sedation and less akathisia.

G: Are you sure the more sedative ones were more likely to cause akathisia?

L: Well, it seemed to me that when you gave Tercian or Nozinan, people were more likely to be like that, and when you gave Majeptil, they had shaking and trembling.

G: Restless legs, this was akathisia wasn't it?

B: And impatience. The first comments of Steck on this issue of akathisia were in connection with reserpine.

L: Reserpine wasn't a bad drug. It has a bad reputation now because of the depressions it was supposed to cause. But I have often observed, particularly in chronic manias, that it was better tolerated than Largactil or other phenothiazines.

On the other hand, it could cause a severe depression. I have a typical example. A lady came to see me for 3 years in a row. The mayor of Bassens brought her. She said she was very depressed. She used to come to Bassens for

3 months of the year to exercise. She was taking reserpine for hypertension, which she only took when she came to Bassens. It was only after she took this for the third time and became depressed for the third time that she made the connection between the reserpine and her depressions.

Br: This was indeed a major development, this depression. Reserpine also suffered because of the fuss that was made about the phenothiazines. There was also the enthusiasm from people for the results they were getting with chlorpromazine.

L: They then took reserpine and made a simpler version of it – tetrabenazine. When we used it, we immediately saw problems with liver function tests, for instance – gamma GT levels and transaminases and other tests. I remember calling Deniker to find out if he had been seeing anything similar. This drug slipped out of use. But it had been made by breaking down the formula for reserpine, which was extremely complicated. They ended up with a very simple compound chemically, but when it didn't work, it spelt the end for the whole series.

B: The mystery of Hindu botany reduced to modern chemistry.

People were obviously very enthusiastic – up collecting observations until 3:00 in the morning. But what observations were actually being collected?

Br: We collected 600 observations on chronic psychoses, schizophrenias, delusional psychoses, and hallucinatory psychoses. Anything that could be considered a psychotic condition – manias, delirious states and others. Do you remember the hairdresser? This was another resurrection of sorts. This was a man, who was a hairdresser, who had already been hospitalized for 2 to 3 years. Anyway, he recovered. Then, all of a sudden, one day he got involved in a discussion with Perrin and he said to him that he was a hairdresser. Perrin, who wanted to find out if he really was better, said to him 'Fine then, shave me'. So he shaved him. This was shaving with an open blade. This was a time when they didn't give out Legion of Honour medals as easily as they do now. I always thought this was a considerable act of courage that deserved some kind of decoration. The man was discharged home a few months later.

B: Yes, this was the time that we began to think about getting together a research group of five or six clinicians. We also began to interest the Americans. I had just written my first paper, when I was approached by someone who said 'Ah you did this, you published all these observations, how much do you want for them?'. This was the first and last time in my life that anyone offered to pay me for my work. After that we had become a collective.

Where did you report the observations?

L: There were three congresses we presented at – these were at Vercelli in 1956, at Milan in 1957 and at Rome in 1958.

B: We also published observations on 530 cases in Philadelphia in June of 1955. After that we had lots of contacts from abroad. The biggest number of cases

reported on was in the *American Quarterly Journal of Clinical Psychiatry*, where we reported on 4000 cures collected over 7 years. Everything moved very quickly at this stage. In 1959, there was the first meeting with the West Germans and then in 1960 we went to Berlin.

Br: Yes, in a sense these observations were so clear and so important that they overcame even deep antagonisms such as those between the provinces and Paris or between us and the Germans. I remember it as being something like the impact of penicillin. I had been at the Centre National de la Recherche Scientifique when penicillin became available and I remember the impact of that.

G: It's important to remember that it all seemed so extraordinary then, because, in fact, this has all been forgotten now.

Le: One of the main differences to appreciate between here and Paris is that all of us here were psychoanalysts. Psychopharmacology research was almost a side show to the main activity – the therapy which was being done. The state of mind here is psychoanalytic. This meant that we were interested in Balint groups based on neuroleptics, for instance. The psychoanalytic view about drugs is not interested in the same specificities that psychopharmacologists are interested in. The view here then was that the drugs were a means to make people more open to psychotherapy.

L: Exactly. One of the things the drugs did was to bring the patients back to reality and we were then able to work with them. This was the point about the story of the hairdresser – he was back to reality in some sense. This is what you saw: patients who one morning, all of a sudden, came up and shook your hand and said 'I want to go home'.

I remember a petrol merchant. Before the war, petrol sold in 5-litre flagons. I don't know if you remember the kinds of petrol pumps we had at that time. But, anyway, I can't remember exactly what the figures were, but one day I said to him 'petrol, do you know what price it is now? – It's 5.80F'. He responded that this couldn't be true, it was only worth 3.40F. He thought about that, but he found it impossible to accept. This was one of the first cases I treated with Largactil and at that time we were not convinced that we needed to continue the treatment indefinitely. We let him out and he relapsed 15 days later.

B: Yes, there were very many examples. There was also the point of view of the nursing staff, who now were able to think about doing other things. There had been a great lowering of anxiety, as well as a lowering of the noise levels. This was a global phenomenon, which took place very rapidly, which you saw reproduced in every hospital. The work conditions normalized and this was very important. A therapeutic atmosphere was able to develop.

L: What you are saying was also important because, just at the time that these miracle cures with Largactil began to come onstream, there were big changes in nurse education. The new nurse training courses, at least with us, I don't know about Vinatier, dated from 1950 or 1951. From then on, the nurses who had

played the role of wardens before really began to play an increasingly valuable part as they often came from just the same settings as the patients.

G: Yes, there was a transformation of the institutions. I want to support the point made by Dr Lambert about the patients' return to reality. I did some work at the time on the awareness of time of these patients. When asked their age, many of them gave the age they had been when they came into hospital. Time had stopped when they came into hospital and they re-entered time when they went on neuroleptics.

L: I remember that the first congress on psychotropic drugs in Paris in 1955 had the title International Colloquium on Chlorpromazine and Neuroleptic Medications in Psychiatric Therapy. The term neuroleptic was created for this occasion by Delay and Deniker. This meeting of psychiatrists from the various industrialized countries was a great success – a revelation for some. The proceedings of the meeting came to more than 1000 pages of communications attesting to the complete sea change in psychiatric practice and thinking which had taken place in less than 3 years. In 1956, the CLRTP, under the initiative of Revol, published its book on *Therapy with Chlorpromazine*. And then, in 1957, at the World Congress in Zurich, the first presentations on the antidepressants took place.

Why did we have so much to say? Because the evidence of a pharmacological effect was so clear, the numbers treated were so great and the new style of work that was needed required a great deal of communication and exchange among psychiatrists. The fabric of the hospitals themselves needed to be changed to suit new purposes.

Nevertheless, despite the pooling together of energies, it was necessary to keep our feet on the ground because we had a great number of daily difficulties – there were the great number of relapses and patients returning to hospital. At the 1957 World Congress, I presented a CLRTP paper on this subject – that 50% of patients who left hospital relapsed within a year. Accordingly, we had to redouble our efforts towards aftercare. Initially, we gave neuroleptics to anyone who might benefit, schizophrenics, chronic delusional states, whether or not they were hallucinating, maniacs. Among the patients, some got well with very small doses, others we came to recognize as resistant cases and, later, for these we would go up to 500 mg of chlorpromazine. These patients, when they responded and left hospital, were the ones who finally led to the drop in the in-patient numbers that took place around this time. The very numbers of people being treated as out-patients made it difficult to monitor all of them properly and a percentage of them relapsed. It is worth remarking that our experience in collecting these cases was that many patients seemed to have up to two relapses but then to be protected for a long period from a third relapse.

So, if you were psychoanalysts here and they were psychopharmacologists up in Paris, how did this actually affect clinical practice? Was clinical practice here superior to what was happening in Paris?

G: Things really were different between Lyon and Paris. In Lyon we always had an interest in psychotherapy, even after 1955. We were interested in psycho-

analysis without being psychoanalysts. We were interested in the analytic approach. Was our practice better? Absolutely.

Br: From my point of view, things were different, but this was an idea I picked up here. Here, the clinical domain was first and foremost. When I went to Paris, I often went to Sainte-Anne, the Salpétrière occasionally, but mostly Sainte-Anne. And I was disappointed there. It was much less clinically oriented than I was used to here. I'm trying to find the best way to put this, but they seemed to put much more emphasis on the medication without being as concerned to add in the psychotherapeutic component. And I think that psychotherapeutic input was very important for the full restoration of the patient to normality.

L: It was very important when it came to the patient accepting the medication in the first place and continuing to take it after that.

Br: The issues of follow-up and relapse were important. We haven't talked much about relapse, but this was an important issue. It is important to know what leads to relapse.

L: I think what psychoanalysis gave us was some empathy, some rapport, an ability to use our intuition and notice changes in the comportment of the patient. It was something of that nature. It also gave us a conviction about the primary importance of contact, listening and relationships. Our interest in using treatments to improve therapeutic relationships was made very clear in 1964 when we organized a meeting, that united in Lyon psychoanalysts, mainly from the Paris region, and psychiatrists from this region. We published the proceedings under the title *The Relationship between the Doctor and the Patient in the Course of Psychiatry Chemotherapy.*

G: For example, the question of depression in the course of treatment is often raised. Sometimes there is an idea that depression fills the gap left by the delusional system. When a patient had the delusional system, he had a system in which he could believe. What will happen when you remove this belief system? You can see why there might be a certain sort of depression. There has been a tendency to give this kind of explanation anyway.

The patients would sometimes say 'doctor, you have deprived me of everything'. These were things we were interested in here more than they were in Paris. But, on the other hand, the work of Delay in Paris had a great impact on doctors in other specialties. This was much less the case in Lyon. Delay was very clear in his thinking. Other doctors could understand much more easily what he was saying than they could appreciate what we said. And he appeared much less mad for a psychiatrist than the Lyonnese psychiatrists did.

From your point of view down here, who was the important person? Was it Jean Delay or Pierre Deniker? Delay was the boss, but did he actually see any patients?

G: Yes, he had done at one point, but over the years he saw less and less. Except perhaps his private clientele. It was something of an advantage to have a private clientele at that time. That was when you were on your own with the patient

and the medications and I think it was important at the time for the rest of my practice that I spent some time in private practice. It gave me important possibilities to follow up patients and to make relations with specialists from the rest of medicine or general practitioners who would refer patients. They were not up to date with the new medications because they had had no training in psychiatry. But they could see the effects, and I think they were interested.

Br: Yes, its important to remember that at this time generalists did not have a training in psychiatry. I didn't realise it at the time. I was very surprised. I expected that psychiatry was taught in the medical faculties, but not at all. I met many doctors who had absolutely no psychiatric training or, if they had, they might have spent at the most 6 months in psychiatry.

G: The general practitioners began to get interested in the effects of these medications, but it took a long time. At first, they used anxiolytics in depressions. It took time repeating the message before they began to understand that they should be using antidepressants. I think in this regard private practice was important because, by this means, you were able to educate them as to what they should be doing.

But would generalists and general practitioners have not preferred psychopharmacology to psychoanalysis – this would be closer to something that they would understand?

G: Yes, indeed, for the generalist the psychopharmacology model corresponded to their practice – one illness, one drug.

Before Largactil, what was being used in either in-patient or out-patient settings?

L: Before Largactil, chloral was used, morphine, scopolamine and Gardenal. We didn't have much. There was electroshock and there was sleep therapy. I really don't know much about what was used in community settings before that. I began medical practice in 1953 and, when I arrived here in Bassens, one of the doctors already had Largactil, which had been made available commercially at the end of 1952. I don't think anything other than advice would have been given to people being seen at home.

The private practice physicians would see neurotic or depressive conditions. They refused to see anyone with schizophrenia. Part of the reason for this was that patients could only be detained in hospital. They could not be admitted informally. They had to have a medical certificate, which justified their placement in hospital. This meant that at that time the cases were usually pretty serious ones. Individuals usually ended up in treatment because they had done something pretty serious – they had been violent or had made an attempt at suicide. They were already seriously disturbed cases. In 1956 or so, it became possible to open up an informal service where people could come for help, just as you might to any other hospital, and from that point onwards, private practice in psychiatry developed. Before that, neurologists, who advised on character difficulties, neurotic complaints and insomnia, for instance, saw many of the milder cases. From about 1957 onwards, all physicians began to get

some training in psychiatry. Before that there was nothing. The options were either they had a mild problem, which meant they could be kept and looked after at home by their doctor, or they had to be sent to the psychiatric hospital.

Were there any major areas of controversy between you and Paris?

L: It was not a controversy, more rivalry, an incentive to work, to criticise etc. When I had my retirement party from Chambery, the people from Paris came and Deniker was the chairman of one of the sessions. But it was necessary to reach a *modus vivendi* between Paris and us. For example, when we started to publish on Majeptil, our observations came out second and theirs came first, even though we had many more cases than they had. On the other hand, as hospital doctors, we had more time than they did in the university, where, in Sainte-Anne in particular, there were many more demands.

There was a compound called Mopazine, which they were using for a time in Paris, and they were saying it was the equivalent of Largactil. This became an issue between us because we said it was inferior. In fact, Mopazine was withdrawn several years later.

Was there any serious argument at any point?

L: There was one serious problem. At the CINP meeting in Rome in 1958, I presented for the first time, after having discussed it with my colleagues here, the classification of Lambert and Revol. Why Lambert and Revol? Well, I had written to each of the members of the committee to find out what they thought of my classification. None of them answered except Revol, who pointed out some changes here and there – he was very attentive to pharmacological issues. So I submitted it under the names of Lambert and Revol and presented it in Rome. Delay was there in the hall and when I was finished my presentation he was furious. He was purple with rage. He accosted Revol, who was pale, and he began to argue with him. When he returned to Paris, Delay tried to influence the ministry to have me put back in my place. Why? Because I was not showing enough respect to him, the discoverer of the neuroleptics. I was maladroit in effect in not citing his name. I had cited the name of Revol instead.

Gr: But this was your work, so why was he jealous?

L: I think they had got stuck on the question of the classification of the neuroleptics. They never came up with a good classification and now they had been beaten to it. Their problem was trying to reconcile animal and human data. What was remarkable was the attitude of Revol, who took the full brunt of the attack. He didn't say much, but we did talk about it nevertheless. I was in agreement that we could change my text a little. Because of this, I waited 2 years and republished the classification in the *Presse Médicale*.

What was the importance of Jean Delay? He didn't see patients.

L: No, but it was his position. It is certain that he was an excellent representative of French psychiatry during this period. He created the category of

neuroleptics, giving them certain characteristics that are still a matter of discussion to this day. With Deniker, he created a society for psychopharmacology in Paris and I went along to several of their meetings. He was very encouraging and very approachable, but it was necessary to make sure you didn't impinge on his domain.

Actually, when I was placed outside Paris for my training in 1946, I asked the Sainte-Anne Hospital whether it would be possible for them to take my name for a placement there as soon as one became available. He was actually the president for my thesis. He chaired the session well, in fact. You could see that he had read it and there was a good discussion.

At that time, it was said that Professor Delay wanted to achieve a certain standing. His talents as a writer led to him being nominated for a place in the Académie Francaise. Later, it was said that one of his goals was to get the Nobel Prize for chlorpromazine. It was never said, but everyone knew that he was waiting for it and that it wouldn't happen, because he had not been the sole discoverer and, indeed, he wasn't the first discoverer of chlorpromazine. If the prize should have gone to anyone, it should have been Laborit. For Delay to have any chance it was necessary that everything to do with the neuroleptics should be seen to come from him and he put something of an embargo on any other work. Let me give you an example. In 1956, Broussolle discovered the disinhibiting effect of prochlorpemazine – Tementil – in severe schizophrenia – the first of a new series of compounds. His article on this was immediately followed by an article signed by Delay and Deniker which gave a magisterial overview, not of the therapeutic effect of this drug but of its side-effects, especially the Parkinsonian ones, which were very like those that had been observed during the encephalitis epidemic by von Economo. They used it as evidence for their concept of a neuroleptic.

Gr: So, if he didn't see patients, how could he make a classification? Your classification was based on clinical contacts.

L: Well, there was Deniker. Delay wrote a book on all this with Deniker. He wasn't a bad psychiatrist. When he left in 1968, Deniker replaced him without any obvious loss. Deniker doubled up as both a good clinician and as the leader of a school.

I've heard that, towards the end, Delay was very phobic, very obsessional. Is this true?

Gr: Its curious that sometimes, when someone is excited, they can be better than otherwise – this was the case with him wasn't it?

L: He was most concerned with his own honour and standing. It was for this reason that the students ransacked his office. He was very removed and distant from them. He had no feeling for the needs of others. He was completely confused by the events of May 1968. They emptied his drawers in front of him, threw his papers up in the air – at least as far as I know. After that he never worked again.

Your work was very clinical – how did this fit in with the emerging science of receptors etc.?

Br: There is something I would like to add here, touching on areas that Patrick Lemoine is more up with than I am. But there was a considerable hope and enthusiasm following the work of Mr Carlsson showing that dopamine was involved in the action of these drugs. The discoveries of receptors, neurotransmitters and all that have been very important, they did explain the extrapyramidal effects of the drugs, but, as it seems to me now, it was a false hope. Don't get me wrong; the discovery of dopamine and serotonergic receptors was a formidable achievement, but it has been much more important for our knowledge of how the brain works. From a therapeutic point of view, it has been something of a let down. I feel let down, anyway, that these advances have not contributed to progress in anything like the sensational way that the earlier discoveries did. I agree with Professor Simon who later wrote 'Only relative progress has been made in the area of manipulating side effects of the newer neuroleptics. In actual fact, though, they do not offer much more than the original chlorpromazine'.

In part, I wonder if the slowing of progress was because of the evolution of an excessively bureaucratic attitude in the Department of Health as regards clinical studies. They produced ever-longer lists of rules, which were not well adapted to research in psychiatry at least.

When the action of neuroleptics on dopamine receptors was discovered, everybody settled on the idea that this was their common mechanism of action – that this was all that counted, that all the neuroleptics were essentially the same. They act on dopamine and everything else is just side-effects. Now here, in particular from very early on, before dopamine and its receptors were discovered, you had the idea that they are not all just the same. That they do different things; that some are more sedative and others more incisive.

Br: Yes, this exclusive dopamine focus was unfortunate, but on the other hand, when it came out first, the dopamine story aroused considerable hope and expectations and it was important in its own right.

B: I'd like to give you a personal view. For many years, I think what we were doing was pragmatic work without any great theoretical support, like in some ways the prospectors for gold in America. We would find a thread, a seam, and chase this up, and bit by bit people built up theories. Then the mathematical types appeared who wanted very precise sequences, ending up finally with some Parisians, for instance, who wanted to be able to predict the clinical effects from the molecular structures. None of this ever produced anything of any practical importance. One of the foremost of these Parisians was Simon, who worked at the Salpétrière, who edited a psychopharmacology journal. So we saw the appearance of these prophets, who, based on molecular design and animal work, thought they could predict functional effects before these drugs were ever tried out in humans. Fortunately, some of the rest of us thought otherwise and kept on doing the coalface work.

G: I think this is so important. Our work was essentially clinical, involving descriptions in detail and recording numbers of observations. It's important, also, to keep track of the impact of treatment on the relations between the doctor and the patient. This is where I think the Lyon experience is so important. We tried to keep the psychotherapeutic and chemotherapeutic aspects of treatment linked together here from the start. Our work was clinical in the best sense.

L: Well, I would like to add here the fact that there was some theoretical input from the start. The chemical formulae were there from the start. It was because of manipulating differences between them that Mme Courvoisier came up with chlorpromazine from promethazine and Kuhn, for example, came upon imipramine. And based on the stereochemical formulae, Janssen was able to define the common spectrum of all the neuroleptics. We also saw how prochlorpemazine had psychiatric effects and that these stemmed from a piperazine node in its structure, and using this node formed the basis for the synthesis of another series of neuroleptics.

Br: Well, Kuhn's position in all this was interesting. He was known as a phenomenologist with little interest in medicines or molecules. Then you have a St Paul on the Road to Damascus conversion and he appears at the first international psychopharmacology congress at Rome with his psychopharmacology standard. But before that he was known as an abiological phenomenologist, maybe not anti-medicine though. It was a strange experience to see someone with a background of 20 to 30 years' work in phenomenology turn up out of the blue making claims for a rough drug, which was, of course, very effective.

L: Brouillot should remember this because both of them had been together at the Second World Congress of Psychiatry in Zurich in 1957.

Br: What I remember, actually, is the meeting in Milan in 1957 when Jean Delay came down from the mountain top bearing the definition of a neuroleptic. It was a tour de force. At the meeting, every speaker put forward his or her own definition, which was more or less clear. They were all wrong, according to Delay. At one point, I heard him muttering 'No, no no'. Then it was his turn to take the podium; he took the microphone and he said 'This is what the neuroleptics are – A, B, C'. It was an impressive performance. There was a thunder of applause and that was the end of it. There had been 3 hours of discussion and bickering before that.

What was the impact of the new treatments on the public? What effect did they have on the way people saw mental illness? – There could have been de-stigmatization or maybe increased concern that there were more mad people out in the community.

Br: It completely changed the image of both madness and psychiatry. Insanity was no longer something diabolical. It was an illness just like any other illness. From that point of view, I am sure all this had a very positive impact on the public.

B: Yes, but there also was, nevertheless, a very real strain of antipsychiatry, which picked up on the bad side-effects of the neuroleptics, which had led, for instance, to the bad reputation of electroshock. A certain amount of paranoia came into play, which raised the issue of the abuse of medication. I can speak about this because I featured in a full page in the periodical *Libération*, which featured me as 'Monsieur Placard' for medication, solely on the basis of us doing the studies we were doing. And there was one patient who destroyed all the furniture with posters saying 'Long live Albania, Long live China' as well as doing a lot of other things. He was detained in hospital, but he was someone who was a benefactor of a number of antipsychiatric associations. In the course of his stay, he had regular visits from these antipsychiatrists and they used to advise him to make a careful note of all the side-effects. And, on top of all that ,I was repudiated by a mad psychiatrist in Bassens, who was involved in testifying against me in a legal case.

There was something of a revolution against therapy and associations, which may not in themselves have had a huge impact, but which fed publications like 'Libération' and 'Le Canard Enchainé'. At the end of the day, it was not too important, but it was a persistent strain of hostility.

G: The term that was used by the opponents of treatment was *camisole chimique* – a chemical straitjacket.

Well, on just this point, can I ask how could a treatment which was so liberating in 1952 become by 1968, only 16 years later, such a symbol of state oppression that when the students revolted, one of the key things they did was to sack the office of Jean Delay, who was forced to retire? In Tokyo they occupied the department of psychiatry for 10 years. Herman van Praag, in Holland, had to have a police escort because biological psychiatry was seen, for some reason, by the public as being very dangerous and an instrument of oppression.

Br: You have to look at the context of May 1968. In the USA and England, it was a movement for liberation from all kinds of repression and interdiction – it had become forbidden to forbid. But, to come back to psychiatry, people like Racamier and Lacan said, broadly speaking, 'Ah yes, before the discovery of chlorpromazine, the patients maybe spoke a bit louder, they made noise, but now in the psychiatric hospitals there is silence, absolute silence, the silence of the cemetery'. That was the contention, that these drugs were another kind of straitjacket into which we were putting the patients. But this was entirely wrong, although it is true that certain colleagues went along with this idea to some extent.

Le: You must remember that, in Lyon, Gerard Hoff published on the neuroleptic medications in his book.

B: Ah yes, this is an important detail. He was one of the interns in our hospital. He was a bit crazy but very intelligent and he was an antipsychiatrist within the hospital. He almost had an antipsychiatric delusion. He wanted to turn the doctors' residence into a centre for social therapy, a Danzig corridor. It is an over-simplification to say that he was a little bit crazy, but in 1968 he wrote a

book, *I am not a Psychiatrist*. But the same doctor had patients coming to the pharmacy to demand a supply of cocaine. This is an example of some of the reactions there were.

G: In 1968 there was a transformation of the hospital at Vinatier. There was a whole series of meetings, at which the director of the hospital was present and the doctors, as well as the nurses, the gardener and the carpenter and lots of other people. They all got together in meetings to talk about psychiatry. All of this took place over the course of a few weeks. Now, at this time, one of the things that I was involved in at a national level was the issue of certifying psychiatric training. Partly because I was seen at the time as somewhat progressive, and given that I was also from the university, I had said that we needed to think about whether it was necessary for certain things to be known and that the subject of the experiment should be tested.

One of the interns attacked me, saying, ' We know how this starts and we know how it ends. How does it end? It ends in the concentration camps'. This gives you a flavour of the madness of the period. In France at the time there was a return of repressed memories to do with the occupation. I was marked by the occupation because I was 20 years old when it happened. It seemed natural then to see everything pharmacological as less dignified and, in contrast, the psychoanalytic movement profited from the moment to seize power. This was idiotic really because, from a scientific point of view, psychoanalysis is interesting but psychopharmacology is also. This was one of the major consequences of 1968. On the national level, there was a strong opposition between Jean Delay and Henri Ey.

It's very unusual to have a group of people like this who have worked together so consistently, over almost half a century now.

Br: There hasn't been another group like this, at least in France. It can be very difficult to make this work, given the interaction of different personalities.

L: There was a group in Marseilles, which didn't function for long. There was also a Paris group.

Br: The Paris group didn't work as well. It was not formed mainly of clinicians. They were mostly psychopharmacologists – Simon was one of them.

L: They did work with Neuleptil on personality difficulties. It was sent to us afterwards to have a look at and to see if we could confirm what they had found.

Br: But what impressed me when I came here was that there was a clear research group and it had an authentic clinical focus. This was not a group of researchers who were occasional clinicians, but a group of clinical researchers, which is not the same thing. They had a good clinical feel for the medications. They talked about both the dynamics and the medication aspect of things, which was lost on a lot of others. So what was this all due to?

How did the group actually get started?

B: There are two factors. First, there was an enthusiasm for treatment where there had been nothing before. Second, we also had a discipline of frequent meetings. And I should mention that we were assisted by a number of people from Spécia, I should mention Dr Pellerat and Dr Rives. They attended our meetings and they took notes and this added a certain discipline to the proceedings. It reduced the workload and gave us the incentive to do something.

Br: There was something else because, at least initially, in the service people were not working in concert to the same extent. It was this working as a team which was so special. Perrin was the first to suggest a meeting. He said to me when I called out to Vinatier that we should work together on this, but that people were not in the habit of doing so. I said, well, maybe it was about time that we started – that it was time to boogie.

Le: What's interesting is that, in Vinatier, there was a facility to work together with the university, the pharmacy, the industry, the psychopharmacologists of the hospital, but also with the antipsychiatrists, including Balvet. We should mention Paul Balvet here. He is 94 or so now. He was maybe 2 years younger than Requet. He was not a psychopharmacologist strictly speaking, but he observed the psychopharmacology that was going on in Vinatier. He came here in 1943 or 1944. He was the first to describe and the first to publish on the passivity syndrome of neuroleptics. He was an antipsychiatrist in the meaning of Laing or Szasz. The term passivity syndrome comes from him. They all accepted that it was necessary to work and think together. This working together of people with different orientations is what was original about here.

B: Professor Revol was almost the senior person. He was the Professor of pharmacology, who had a considerable research reputation.

Gr: He was an exceptional personality. He was a pharmacist who was at the same time a professor in the Faculty of Medicine and Pharmacy. He specialized in materia medica – pharmacology. He also worked with galenical preparations. Outside of his work in pharmacology he had lots of ideas. I think it was he who came up with the idea of introducing different colours into the compounds we use and researching the effects of presenting the drug in different colours. Maybe he wasn't the only person to have this idea, but he had it very early on and did a lot of work on it. Now, because of him, you can often know what a pill is by the combination of shape and colour.

Br: It seems silly, but it's true that in many hospitals at the time there could be grave mistakes. In the faculty of medicine, there was a man called General Manceau, who had a favourite among the students. Revol found out and made an issue of it. Manceau took a walk one day with Leulier, who had lost an eye, and who said to him 'My dear Manceau, you are putting a foot in the grave'. Manceau replied 'I would prefer to have a foot in the grave than a foot in the *merde*'.

Gr: In order to have favours from this student, Manceau was letting her change her answers after the exam papers had been collected. Revol, who was not particularly high up in the hierarchy at this time, photographed this and complained to the University Board. Manceau was fired.

Revol was a pharmacologist, but at this time pharmacologists were generalists. Sometimes they were doctors and sometimes just pharmacologists. He was only a pharmacologist. But he also had a good scientific background.

Le: I heard that he was at one point the youngest assistant or associate professor in France.

Gr: When he came to Vinatier, his father-in-law was also on the faculty of medicine. He was a pharmacist and a doctor. He wore two hats because he also had a pharmacy – Bretin. The mischievous chatter around the place was that, when Revol married Bretin's daughter, he got at one and the same time a chair in the faculty and a pharmacy. This was in 1929.

B: He was very experienced in research on animals, an expert on nutrition; he was also very close to the patients and he had taken part in the drama of the war. He was very interested in clinical work.

Gr: He used to come to see the patients. He would scrutinize the treatments. He has not signed his name on many of the CLRTP articles because he wouldn't, on principle, sign his name to something that he had not actively participated in. At this point, working as a pharmacist meant looking at the materia medica, the medications, but also at the food and the wine in the hospital. One of the things that used to be done then, which is still continued now, although it is something of a heresy, was the daily preparation of a potion for the patients. They used to make the preparation for each individual patient. Now, often these things were all the same, but they had the patients' names on them and I think they must have had a considerable impact. Nowadays, the heresy is that these are labour intensive and costly.

Revol used to make them for the staff, also. He was a counsellor for many of them. In fact, he used to do a lot of other things. He participated in designing the programme of training for psychiatric nursing staff for the ministry. He was also interested in the training of any clinical personnel.

He represented pharmacists on the Faculty of Medicine in Lyon. He was involved in many different things. This is because, at the time, there were few people to occupy the various different posts. Partly, he got involved in so many things because there were very few people who wanted to have anything to do with the work. At that time, doctors wanted to earn lots of money, so people would go into private practice. Between one thing and the other, he was often travelling to Paris. When he got back, sometimes he would work till 2.00 or 3.00 in the morning. He would sleep over in the hospital when he worked very late and he would then get up very early. His wife cannot have seen him very often. He was someone who was very active during the war. Some of his interns were involved in channelling money and arms.

G: Is it true that he used to make up special potions rich in protein?

Gr: Yes, he used to go the abattoir to get ingredients and he invented a special blood potion, which was supposed to have special amino acids that were more rapidly absorbed.

Le: He made out that it was for medicinal purposes, but the idea was to nourish the patients. There were people here in Vinatier who worked as pharmacists but who, in actual fact, were trying to escape deportation. I think he was one of those people who managed to save a great number of people from deportation.

Gr: He also set up an association of pharmacists. This stemmed from his relations with his old students. So, he had a very wide network of relations with all sorts of people. This was how he got an invitation to Prague shortly after the war.

Le: I also know he went on many occasions during the German occupation to the prefecture to plead the case of the patients. At one point he was so insistent that the Prefect, Angeli, who was later imprisoned for collaboration, said 'Who is this man possessed?'. He was very insistent. He was a man of the very greatest courage.

Among the other names of the founders of the group was Dr Achaintre. What can you tell me about him?

B: He was an excellent colleague for whom we all had a high regard. He was a good clinician who had training in psychoanalysis, which didn't do him any harm. Different members of the committee brought different things to the group. Requet brought novel ideas. Balvet had a phenomenological approach. Achaintre produced observations – he had a good clinical nose. Along with the rest of us, he gathered data on something that seems out of date now – whether this compound was more anti-this or anti-that. These were always debatable, approximate descriptions that we came up with, but by this means we were able to get a grip of the issues. It was a matter of trying to decide if this compound scored one cross, two crosses or three crosses etc. for antihallucinatory effects, or whatever.

Le: He was interested in occupational therapy – this was one of his big things. Also, during the war, when he was a medical student, he was caught transporting publications for the Resistance and he was arrested. He only just escaped being transported, in fact. He was carrying 'Christian Witness material'.

G: He was full of interesting ideas. His thesis was on schizophrenic crystallization. This is an interesting point of view clinically. He compared what happens clinically with what Stendhal said happens in love – there is a moment of crystallization. This is a line of thinking that is very French. Balvet's teacher, whose name was Pascal, had an interest in this question of the history of crystallization quite independently of the issues of Freudian structures.

There was an interest in this issue in Switzerland, also, on the part of Luc Ciompi. He was interested in the notion of disturbance followed by chaos or the disturbance, which leads to order, such as that which makes the pearl in the oyster. At the bottom of this idea, there was the notion that some small detail might be the occasion for much larger psychotic disturbances.

Le: This is catastrophe theory. At one moment the lake is at zero degrees and it is liquid and then a leaf falls and the whole thing freezes over.

G: Just as can happen in love.

Requet is another of the names that has come up

B: Requet was someone of great learning, like Balvet, who had philosophical tendencies. He began his career in Sarreguemines, at a psychiatric hospital in Lorraine. So, he was exposed to the full force of the German occupation. He worked with Herman Simon, who was the creator of occupational therapy.

What was interesting was that he came here and married a Savoise some time in the early 1930s. He continued to develop his competence in and knowledge of psychiatry here. He had a knowledge of German psychiatry and phenomenology and he had an acute ear. He contributed significantly to the critical mass of this service. He was interested, with a good deal of passion, moreover, in lobotomy, insulin comas and, later, in all biological treatments. As a younger practitioner, I benefited immensely from his erudition.

Le: He was particularly interested in alcoholism. He published one of the first studies of Disulfiram in France. It was not available in France at the time and, with Revol, he went to see it in Copenhagen. They tried to make the molecule when they came back, but it was something of a catastrophe. They made something which was like Antabuse but which had some serious side-effects.

After that, you could say that he more or less invented the concept of self-help groups for former alcoholics. He also played a part in inventing art therapy with Sylvain Fusco, a patient you could say he was almost in love with, in a philosophical sense. Requet would often say that he hated Vinatier, which was a horrible asylum – this was before the war – and the asylum in Lorraine had been much better. He only stayed, he said, because of this patient. He said it to me several times.

You could say there were two great personalities from this generation – Balvet, who was an Italianist, and Requet, who was a Germanist. He was a romantic and flamboyant Germanist. He was Wagnerian.

He wrote an article about the end of the neuroleptics in 1958. He ended up more antipsychiatric than the antipsychiatrists did. For him, in the end, the schizophrenic was the man of the twenty-first century, the superman of Nietzsche. To cure the schizophrenic, then, was to give them poison. It was almost a mortal sin, like suppressing Mozart. Killing Mozart was the same as killing the genius that is at the heart of any schizophrenia.

B: My wife, who used to live here, was quite struck, when she saw him talking with unwashed, abandoned patients in the midst of a full psychotic breakdown, by the courtesy and attention he showed to them.

L: He used to spend a great deal of time in the service. He almost slept there, he used to stay so late at night.

B: He had a feel for what was likely to be a fertile time. Engaging this kind of patient is not something that you can do from 9 to 5. Sometimes, the right time is in the evening, the time when things can get said.

It was a special time. There was one patient, an alcoholic, who was the director of an orchestra, so they put on a play called Night of Love. One of the dancers was a patient of mine who was having insulin coma in the mornings and would rehearse in the afternoon. I was the flutist. Someone from administration was the violinist. Mme Requet was the chief of the ballet and responsible for the decor. The surroundings were fairly poor because we didn't have a hall at that time. But there were moments like that, moments of fusion between staff and patients, which were very powerful experiences.

One of my chums, a colleague who had been catatonic for 7 years, had spent some time with Professor Baruk but had not had shock therapy. He was a friend that I had lost contact with until he came here. We used to wake him up with narcoanalysis. Just as in certain novels, he used to say when he woke up 'What am I doing here?'. Anyway, this friend, catatonic, prostrate on his couch, took part in this spectacle and when he was woken up the next morning he said, 'This spectacle was a naïve piece of silliness'. It was an extraordinary mix – this was in 1956. Everyone took part.

Le: Requet was a man of fortune. Things happened by chance, on the spur of the moment. Art therapy started by chance. I can give you another example. On the first of these musical evenings, a nurse from the women's service had secretly arranged for a man to come who sang very well – he had a nice voice, the voice of a tenor. Requet knew him and, instead of punishing the nurse, he congratulated her and asked the man to continue. To the great scandal of the other nurses, he danced with her that evening.

Can I ask about this conflict between university and asylum psychiatrists, which you seem to have solved here?

Br: For the CLRTP project to succeed, it seemed necessary to me to get the support of the university clinic. Now, you must remember the situation in 1955 as regards psychiatry and, above all, the opinion university people had of psychiatrists. Bearing this in mind, you'll realize that getting their support was not an easy thing. I had many discussions, some epic discussions in fact, with Professor Dechaume to get a psychiatric member of his staff – not a neurologist mind you – to participate in the committee. He had difficulties with this, even though he immediately grasped perfectly the importance of the exercise. So it was then, finally, that Professor Guyotat became part of the committee.

One of Professor Dechaume's questions was 'Yes, but who will chair this committee?'. I said 'No-one'. He said, 'What do you mean no-one?'. I said, 'Well if you want this kind of committee to work, you don't want someone who tells people to keep quiet or who cuts you off. It is necessary to have mutual confidence'. He thought he was going to be the chair. I suggested a meeting with the people in Vinatier and, in fact, I invited him to a dinner because I knew he liked dinners. But he said no, that that would not be possible. He did finally come along to one of our meetings when Denber came to visit.

The functioning of the committee was put under the guidance of Dr Pellerat, who had links with the research departments in Spécia and who, moreover, was chief of a clinic in the general hospitals in Lyon. The work of the committee had a big impact very quickly and many people came to Lyon to see what we were doing, Germans especially, but also Americans and Japanese.

What seemed to me particularly important in this work was the way it maintained clinical relevance. That, along with the diversity of psychiatric orientations that the committee members had, all contributed to the work. Along with the work done at Sainte-Anne and the foundation of the Collegium Internationale Neuropsychopharmacologium (CINP), I think the work of this committee played a significant part in helping psychopharmacology develop.

G: There was, indeed, a certain tension, not too marked, between the university clinic, where Jean Dechaume was in charge at the time, and the hospital service. I am not absolutely sure at the end of the day why there was this tension. Dechaume wanted to control everything. He also had a general hospital attitude, which affected me also, that I talked about earlier, which involved a certain mistrust of psychiatry and psychiatrists. People did not accept that psychiatrists could be neuropsychiatrists. I felt there was an unfortunate tension between the general hospitals in Lyon and, in particular, the clinic of Jean Dechaume and my colleagues in Vinatier, whom I had got to know bit by bit. When I heard about this group, the CLRTP, I was interested. I made some overtures about joining the group and I think the group made things easy. I was an emissary from Dechaume at the time. I asked him to let me get involved because I thought it would be interesting, and it was.

Le: But why did this formula not work elsewhere?

Br: Well, this is why I said earlier that when I talked it over with Dechaume he was understanding, because we never developed the hostility that there was in Paris, for example, between Pichot and Delay and then with the other psychiatrists. It was terrible. In fact, I never heard Dechaume say anything disagreeable about the asylum clinicians. Where he himself was concerned, I think he was afraid of losing some of this authority – that was all. Elsewhere, the splits were more profound. At Marseilles things weren't too bad because the personalities were less entrenched – Paris was the most marked.

G: I travelled a bit and what I noticed was that everywhere there was a certain tension between the general hospitals and the psychiatric hospitals. The

psychiatry that was practised in the general hospitals was easier, it involved acute cases. Compared to Vinatier, they skimmed off the easier cases. They treated the easier cases, but if they became more complicated or refractory, they were shipped off to Vinatier. This was something peculiar to the hospitals in the larger cities.

B: One of the things that lowered the tension, I think, was the advent of sector psychiatry. This eased the tendency to skim things off. I remember, in one brief trip to the USA, there were services so specialized that, for instance, they took obsessional neuroses only. In a sectorized service everyone had his or her share of responsive and refractory patients.

The other thing was, of course, rather than wait for the patients to get so bad that there was nothing for it but to take them into hospital, intervening *in situ* often made it possible to defuse, to dedramatize, the situation, to get therapies going which actively involved elements of the patient's own social network.

G: This skimming off of the cream by the clinics, which could choose their patients, also let them produce important publications, besides which it was, of course, less difficult to get responses from acute patients than from chronic cases. The clinic situation also helped in that it came with a certain amount of status, which was helpful.

Br: In addition, of course, the cases there were not considered as mad.

G: This is true, but it was not all bad. There was a good side to general hospital psychiatry, which is that you saw a certain type of psychiatric patient for whom you could do something effective. So much so that I was not entirely happy when I came up against a very pure and rigid form of geographical sectorization.

B: When I arrived here, I knew no one; I was faced with 300 pharmacists, 2000 doctors and I was overwhelmed with the senile dementias of the hospital. When sectorization came, I had to get to know rapidly 17 pharmacists. I became a country doctor once again. And there was something else: it reversed a certain convenient tendency to consign people to the asylum and abandon them there. I remember there was a debate in the Municipal Council, where the mayor of Lyon, Edouard Herriot, said 'It costs a lot to help the handicapped – it is cheaper to send them to Vinatier'. This created a tremendous pressure and a certain sense of persecution.

G: Yes, it was scandalous. It is amusing to remember these things now. I remember when I was in private practice being furious to have patients dumped on me. I recall a patient turning up one day, a madman who drank a lot. I had a little waiting room at this time and my children, who were still little, would be playing in the corridor outside. Apparently, this man was not accepted in Vinatier and you sent him to me – I had only been working in these rooms for a few months. I came home that evening to find this man terrorizing my family. I swore at the rogues in Vinatier who would do something like this. I figured you were doing it to amuse yourselves.

Another time, I was called urgently to the general hospital where there was a senile lady who I couldn't place anywhere in the general service. So I sent her on a detention order to Vinatier; I had no other choice. She went in under Broussolle, who put her on a 24-hour detention order and called the certification unjustified. This led to the police arriving to ask me about this unwarranted detention. I explained the situation and we were able to sort it out. I think, at the time, you were submerged with all sorts of referrals and there was a tendency to dump cases on you.

B: Another aspect of all this was the rejects, who were the psychiatric patients in prison. This is where I found myself in your situation in a sense, in that the hospital did not want to take them if they were thieves or rapists.

L: There was a film about the impact of Largactil which looked at how things were before it and then 3 or 4 years afterwards.

Le: Yes, this was an important film. It was made in 1960. It was about the glory of the neuroleptics. Eric Duvivier made it, the nephew of Julien Duvivier. It is a paean in praise of the success of the neuroleptics. It's like an advert for washing powder almost, where you see the linen before and after – you see the neuroleptics before and after. Before you see the cells, the hefty nursing staff, the little judas flap through which the nurses could inspect the patients in their cells, and then Paul Brouillot arrives and, with him, Largactil. Then the patients get better; you see them going out in a coach for a walk and you see them at occupational therapy. It's marvellous. A very important historical document. You really do see the interior of the asylum as it was before the neuroleptics.

La: In the film you see a patient who was a village mayor who was persecuted, I think he was paranoid. He makes a critique of his own persecution to Beaujard, I think it was; he says, 'Yes, I don't know why I was the way I was but now and the change is due to Largactil'.

I'm better
L.

Le: The film was very successsful. It was shown widely. You see occupational therapy as well as therapeutic outings.

L: There was another film made with Dubois on the classification of neuroleptics. Revol is in it, showing some of his work. He had some fish from Siam, some fighting fish, in a vessel, and when he added Largactil, they lost all their red colour and they became dull.

Le: I have some photographs from the period, the end of the 1950s, after the neuroleptics have arrived. You see the doctors and the nurses and the patients together, symbolically knocking down one of the old walls of Vinatier with pickaxes.

La: When we are talking about communication, we should also mention that it was Monsieur Brouillot who, 30 years ago, created the committee which established the review that is now called *Confrontations Psychiatriques*. This has become one of the best psychiatric reviews in France. About 10 000 copies are

published, I understand, and it is disseminated throughout France and the French-speaking countries. The thirtieth anniversary is due soon and I understand there is going to be a celebration in Paris.

We should also mention that altogether we studied over 80 compounds, of which 13 were later commercialized.

What about your work on depot neuroleptics

LA: The depot neuroleptics, if I remember correctly, were conceived around 1963 by Squibb. Squibb were actually the second laboratory that approached us with support. Our contact there was Pierre Ardoint. Then, in 1963, the depot neuroleptics, appeared with Moditen Retard being the first. We had them clinically in 1965, if I remember right. We got to look at them before people in Paris did. What was not perhaps said earlier was that the companies were anxious to get involvement with Paris; they put great store on the expertize of Delay, although it was Deniker who signed on for the studies and it was the interns who did the work.

So, initially, there was Moditen, which Squibb followed up with Modecate. There was little difference between them, except that Moditen lasted for 2 weeks in the system and Modecate for 3 to 4 weeks. Then Spécia produced depot neuroleptics, seeing that they were behind the Americans, and their compound was Piportil. Then, after that, Lundbeck came out with Fluanxol, and this was later followed by fluspirilene, but this wasn't so interesting. In France these depot neuroleptics were used a lot and continue to be used a lot. Spécia at one point had a compound, whose effect would have lasted for 2 months, but there were skin side-effects, plaques, and its development had to be stopped. This was of considerable interest because, in the case of psychopaths, you could give an injection and give them their liberty for 2 months, during which time they remained calm.

Another aspect of the history of the depot neuroleptics is the fact that you could use them in very low doses in ambulatory patients. I remember a concierge who was worried, who took badly to people in her house, and with a small dose every fortnight she could be helped with generally good results. These really did allow the community treatment of patients who would not have been happy to take regular oral medication.

But, I should also add that with these depots there were suicides. The first person to mention this was Alarcon. We also had attempted or completed suicides among patients who were put on depot neuroleptics but who were not sufficiently monitored. It is all too easy to give a depot neuroleptic to patients and then to forget about them for a fortnight or 3 weeks. The instructions for the nurses who visited them at home were to check if they were watching television. The families were often very happy that their relative was sitting in a chair and not moving. But one could sometimes see that they were not watching the television, but that a depression had set in. We wrote this up in 1969/1970, but Alarcon was the first to flag up the fact that he had six suicides following the utilization of Moditen in the USA. We paid attention because of this.

Gr: Was there a problem with low doses? I have seen in an article on depot neuroleptics that sometimes mini-doses were used – 5 mg rather than 100 mg.

L: Well, the issue of low doses is very important in psychiatry. A number of patients can be cured without noticeable side-effects at these low doses. But the pharmaceutical companies in general don't like to support debates on this issue. I haven't ever heard of a symposium aimed at pinpointing what it is about those patients who respond to low doses that makes them respond.

You can find a certain number of studies in which 1 or 2 mg of a neuroleptic was used, and this was fashionable with Majeptil at one point. I had a patient who I followed up until I retired, altogether 28 years, who even had a child during this period, who took 1 mg per day. On this dose, she could, nevertheless, be depressed and I also had to give her some imipramine. But doses this low can be used for some patients. The neuroleptic effect can be variable, depending on the paranoid node in the patient. When the patient becomes actively deluded, you need a higher dose. For paranoid schizophrenia, you need higher again. But there are a great number of patients who can get by on much lower doses and in these cases 5 mg of a depot might be okay.

One of the really big discoveries from this group, Jean Guyotat in particular, was the discovery of the effect of antidepressants on obsessional neuroses. Can we discuss how that came about?

G: You must excuse me for speaking about my private practice again, but in private practice this was a very important issue, because general physicians did not understand what depression was or that it affected many patients and could cause functional problems or somatic problems which masked the depression. As I said earlier, they were inclined to treat these problems with anxiolytics. When faced with these problems, I was more likely to use Tofranil. I was one of the first to use it here.

Let me explain. At that time I was primarily known as a psychoanalyst and, because psychoanalysts were thought to be interested in obsessional neuroses, I was referred many cases of obsessional neuroses. At the time, I was going to Geneva for psychoanalytic supervision and I was able to get a supply of Tofranil there and bring it back, even before it became available in France. After coming back from Geneva with Tofranil in my pocket, I gave it to my patients and, in particular, to my obsessional patients. This was somewhat illegal maybe now but it was possible at the time. Out of this I got the first publications on the successful use of a drug for obsessional neurosis.

Let me tell you what my thinking was. I thought at the time, in fact I always thought, that certain forms of obsessionality in a sense are masked depressions, in just the same way that certain somatic presentations may be masked depressions. I wrote a paper on this in 1960. Anyway, this worked quite well. I also tried Neuleptil at one point, but this didn't work as well. I think the antidepressants are now recognized as having a place in the management of the obsessional disorders and that they give reasonably good results.

But my approach to all this was in the context of psycotherapy. I looked at the issue of what the antidepressants were doing from this point of view. It should also be said that these patients did not have depressions of the melancholic type; definitely not. At that time, we had a meeting here on the treatment of melancholia and I remember a debate argument with Perrin on the chemotherapy of melancholia. We agreed that this was no problem, but other depressions might be different. I don't remember if this was before or after Surmontil, but the chemotherapy of melancholia was acceptable at that time, in the sense that drug therapy was recognized as being effective.

Anyway, partly because of the clientele that I was seeing, I was developing an interest in this area. I tried to provide a psychodynamic explanation for what was happening. At that time, there was an interest in marrying psychodynamic and drug therapy approaches; an interest in translating the effects of medication into something understandable within the terms of psychoanalysis. Lambert has done a lot of work in this area and there was a movement in France to see things this way, although there were very few French names associated with it. A number of others, some English and some Canadians – Azima and Sarwer-Foner – were also linked to this kind of approach. Apart from Lambert and myself here, however, there were no French figureheads for this approach. So, this is how it was; the rest developed as a matter of circumstances. Also, we had, at the time, infusions of Anafranil, which we used for severe depressions.

Le: We should add in the fact that you were the first to use imipramine-like drugs for obsessional disorders

G: I also used monoamine oxidase inhibitors. Others were taking this approach and in Marseilles they were using Neuleptil. It was seen as anti-temper and anti-aggressive. I was very interested in a recent book, *Listening to Prozac,* which was almost a *succes de scandale*. I was interested because Kramer, who wrote it, was describing the conditions in private practice, that were similar to what I was faced with. He described marital problems and family problems and he attempted to describe the impact of antidepressants on these domestic relationships. He showed that certain conflicts went hand in hand with certain authentic forms of depression. I found this very interesting because it was very much a psychological approach taken to the action of the antidepressants. Lilly wasn't terribly pleased with this approach; it seemed to be a the 'happy pill'. They were worried that they would be accused of flashy propaganda. I thought Kramer's clinical insights were good.

The book was extensively debated here, in the media and the press. The philosophers said it was a disgrace, improper, to ask for a medication, a chemical to give happiness. Happiness was something that could not be delivered by a pill. It was a big scandal and, I suppose, for those who have no knowledge of psychopharmacology, this could be a scandal.

Can you give me some vignettes of the first few people who had obsessive–compulsive disorder (OCD) who responded to either imipramine or Anafranil? What did you think was happening when they responded?

Well, there were 15 patients whose symptoms were largely obsessional or phobic. If they were depressed, they were only mildly so. Seven were in hospital, three in psychoanalytic therapy and eight were being seen for a psychiatric opinion. They had all been treated before, with either chlorpromazine or levomepromazine; four had had electroshock and one had had insulin coma. None was restored absolutely to normal by imipramine, but five were practically symptom free at the end of a 3-month treatment period. Four were much better and four either had no response or relapsed after an initial response.

One of the first cases was a young woman who was living with a friend she did not love and who was infatuated with another student, already married, whose mistress she became. After the relationship broke down, she became obsessional. Repeated images of her friend were imposing themselves on her, which got in the way of her getting on and doing anything else. Neither neuroleptics nor tranquilizers made any difference to her but after a few days of imipramine she was transformed. This was one of a series of cases where the obsession seemed to be playing the part of maintaining contact with an object which had been a source of frustration – where the obsession involved maintaining contact with the environment.

The second case was a woman who had had obsessional ideas of 7 years' standing – the typical banal parasitic kind of ideas you can get, and it was this that exasperated her. In order to relieve herself, she would sometimes have to speak things out loud, 'with her lips', as she put it. This state had been there for 7 years, but it had cleared up briefly when she was in hospital, only to relapse when she was discharged. It had also cleared when she had fallen in love and had had extramarital affairs. This method of treating herself had to stop when her husband found out. Imipramine made a spectacular difference to her and she was still well when I reviewed her 5 months later.

Another case involved a young college teacher who had an obsessional preoccupation with detail. He was unable to decide between entering the priesthood and getting married. Marriage was blocked by a very close, but ambivalent, attachment to his mother. This resulted in an obsession about noise. It began with one of his colleagues who used to play Wagner on his record player, perhaps a bit too loud. The young man ended up unable to think about anything but noise, to the point where the whole college became aware of his obsessional rituals aimed at defending himself against noises. Here again, imipramine transformed the picture where nothing else had made any difference.

There was another group of people who were, if anything, made worse by imipramine. These were individuals with a lot of rationalization, with hypochondriacal preoccupations. My impression was that these were almost psychotic subjects who were protecting themselves by extensive ritualizations, in whom anxiety and depersonalization were always likely to appear at any moment.

My impression was that the patients who responded were those who held certain obsessional ideas, but who didn't attach too much importance to them. Imipramine didn't make any difference to fundamental obsessional traits. It helped where obsessional symptoms or problems developed following a period of depression or anxiety.

Were they responding because a depressive element in the picture was clearing up?

Yes, in part, but not only this, because these patients were not melancholic at the time of treatment. The psychoanalytic group here in Lyon did a great deal of work on this question. I put forward the idea that there could be an action on the narcissistic relations between doctor and patient. Psychotherapy, for instance, acts on the narcissism of the patient. I had the impression that something could be happening in this area. But I also had the impression that their obsessions were not so important for the patients any more and they were able to live without them. They were less supported by their rituals; the new mechanism seemed to take their place.

B: The opinion in Paris later was that this was solely an action on mood and only secondarily on the obsessions.

G: Well, this is something else. My understanding was that there were certain forms of psychosis which in fact were depressions of a certain kind, manifesting in this way. At the time I was not thinking of anything other than depressions and antidepressants. I wrote about forms of psychosis, which I called Type II; this was before Crow used this term in a different way. These were psychoses responsive to antidepressants. I now think this was an error; it would have been better to talk about conditions responsive to thymoregulators. I think the dysthymic schizophrenias fit in here.

B: Kuhn, in fact, used Tofranil in the psychoses and it was clear that it made certain psychoses worse.

G: Well, in Kuhn's case he began giving Tofranil to psychotics and there is no doubt that it can make psychosis worse. I wrote a paper on this showing how, if you gave antidepressants, Tofranil, to certain psychoses, in some cases you got an increase in the delusions and excitation, while in other cases there could be an improvement. In Marseilles there was a professor of psychiatry, Sutter, who also described the effects of antidepressants in different psychoses. I also discussed this with Deniker, who agreed that, even in certain cases of paranoia, you could see an effect of antidepressants, particularly in the sensitive paranoias of Kretschmer.

In Paris, of course, they think they might have even been the first to describe the anti-obsessive effects of Anafranil

Le: Well, this is entirely wrong. I was in the National Institute for Mental Health (NIMH) in the 1980s and when they heard I came from Lyon they said to me, 'Isn't that the place where Jean Guyotat, the man who described the effects on Anafranil on OCD, comes from?'.

Many people seem to think that Lopez-Ibor Senior or Junior was the first to describe this effect. Lopez-Ibor published around 1966–7.

G: Ah well, you see, one of our problems has been that we often published our key papers, very important papers, in obscure journals without much circulation.

It now seems clomipramine is useful for OCD because of its action on the 5HT system. This leads on to a Rhône-Poulenc drug which, as I understand it, was the first selective serotonian reuptake inhibitor (SSRI) to be released clinically – Upstene, Indalpine. Can you tell me anything about it?

Br: Well, it wasn't made in Rhône-Poulenc. It was Fournier Frères, who were part of Pharmuka, who in turn became part of Rhône-Poulenc. Indalpine was launched in 1983.

Gr: It was withdrawn because of side-effects, neutropenia supposedly, but that was not all. This drug had been launched before all the carcinogenicity results were in and, when they were all available, the drug had to be withdrawn.

The CLRTP had a letter written by the husband and children of a woman who committed suicide saying that she wished that, instead of flowers, a headstone or anything else at her funeral, a collection should be made for medical research. This was a lady who had been depressed for 20 years, who got better with indalpine and was able to return to normal life, but who relapsed when it was withdrawn, and after that nothing that was available could stop her becoming depressed again or committing suicide. Before committing suicide she had indicated to her family what her last wishes were.

Br: I put together a dossier on Upstene, made up of letters like that from many psychiatrists about the consequences removing this drug had had on their patients. This dossier was presented to the Ministry of Health and was discussed in the course of meetings, but without success because of the agranulocytosis and other problems it could cause. Of 500 000 patients treated in 1984, the Pharmacovigilance Committee had reports of 30 cases of neutropenia. Upstene won the Prix Galien for pharmaceutical innovation in 1983. I think that, if it hadn't been used so widely by general physicians, it would not have been necessary to withdraw it completely, and it could have been maintained for use in psychiatry, the way clozapine eventually was.

Indalpine was only launched in France. Can you tell me, therefore, whether it was essentially the same as the other SSRIs, or was it something different?

Le: I personally had no experience because I was in the USA at the time, but I heard Deniker later say that it was a very good treatment for melancholia, that it was as quick as electroshock.

La: When there were responses, they were clear-cut and quick. You either had them or you didn't.

G: Deniker told me that indalpine had first been synthesized in a German laboratory, the director of which had a son who had an ~~antivalent~~ ambivalent relationship with his father. The son was a very active ecologist, which meant he was anti-psychotropic drugs also, because these are all *camisoles chimiques*, and he began a campaign against Indalpine. Indalpine's withdrawal coincided with the start of a campaign against psychotropic drugs in general. Whether this story can be believed or not, I don't know. Deniker was not in the habit of telling stories, but this would still need to be verified. It seems plausible enough though – the German ecologists are a very active group. Ecology in this sense, of course, means a concern about artificial substances etc.

There was another Rhône-Poulenc antidepressant which came out of Lyon. One of you, as I understand it, had the idea of combining the nucleus of imipramine with the side-chain of levomepromazine, which gave rise to trimipramine – Surmontil. Is this what happened?

L: That is right. I wrote to Rhône-Poulenc in 1959 to ask if the laboratory would be interested in a medication which combined some of the properties of imipramine and levomepromazine. The idea was to take the nucleus of imipramine with the side-chain of levomepromazine. It seemed that you should be able to get a compound that was both antidepressant like imipramine, but with the sedative properties of Nozinan. Nozinan is the most anti-histaminic of the neuroleptics. It also seemed that you should be able to make two isomers of this, just as they had with levomepromazine.

They replied favourably and they made it. What they made was a racemate – a mixture of the levo isomer and dextro isomer of the molecule. Guyotat and I tried it out clinically and it looked very good – it had just the properties we expected and this is what was launched on the market. We then asked them to separate out the isomers and we tried both of them. The dextro isomer caused agitation and epileptiform episodes at high doses – 400–500 mg – but was otherwise antidepressant like imipramine. But the levo isomer was a sedative antidepressant with a very gentle profile of side-effects. It was useful in melancholias, but had a somewhat slower onset of action. The problem was, they told me that it would not be possible to make the levo isomer only for commercial use because it would be too expensive. Nozinan uniquely came in only the levo form. In the case of Surmontil, the racemate is used. There were some problems with Geigy about the licence for this, but they were relatively minor.

When it was made and used, were you clear that it was a very different kind of antidepressant? In one of the early publications at a CINP meeting you described an antihallucinatory effect.

L: Well, it was not completely different. It was imipramine-like but more sedative. We thought that, because of its close relationship to Nozinan, there was a possibility that it might be useful in certain forms of psychosis. What we ended up with was a sedative agent that was useful for depression and could also be useful in certain forms of psychosis, but more in affective psychoses, probably not in schizophrenic states.

Well, interestingly, in the 1990s, with the discovery of the D3 receptor, there was also the discovery that trimipramine (Surmontil) acts on the D3 receptor and, all of a sudden, at international meetings there were reports of its usefulness in certain forms of psychosis.

B: Nevertheless, it should be said that this was one of the few cases where a specific proposition regarding a molecular manipulation resulted in a clinical outcome in line with the prediction. So often these predictions were wrong. We should mention Hippius here. He was a very sympathetic German who was in Berlin, but who later was in Munich. He did a great deal of work on molecular structures and predictions.

Now, can I finish up with one of the other major discoveries, the discovery of the effect of Valpromide on mood disorders, which Pierre Lambert was closely involved with. How did that happen?

L: Depamide has a history which demonstrates very clearly how chance can work to the service of science.

It began in the Laboratoires Berthier, a small pharmaceutical laboratory in the provinces who asked Professor Carraz, a professor in the Faculty of Medicine and Pharmacology in Grenoble, to study a substance for them which appeared to have some antiepileptic activity. He used to work in a small laboratory, which he insisted was important – great discoveries, he said, were made in small laboratories rather than in big institutions. The first difficulty for Carraz was finding something to dissolve the product in – it didn't dissolve in water. After some searching, he finally discovered that the acid dipropylacetic dissolved it satisfactorily. But then he found that the product, at whatever concentration it was dissolved in dipropylacetic acid, had the same anticonvulsant activity. He was forced to conclude that it was the valproic acid which was blocking the electrically induced convulsions in animals. He followed this discovery up by showing that valproic acid itself was very well tolerated. This led to its use in humans, and the demonstration of its therapeutic effects led to the introduction of Depakine as a pharmaceutical agent.

Why, then, did anyone get interested in another compound which was chemically its close neighbour – dimethylacetamide? Carraz became interested and hopeful because at the time the conventional wisdom was that all the known psychotropic compounds had an azote moiety in their structure. It was relatively easy for him to replace the acid moiety with an azote, leading to dimethylacetamide. There was a certain justification for thinking that the newborn compound would have some advantages. That it would be antiepileptic seemed clear from its chemical formula, but it was not much more so than its predecessor. Did it have other properties, either in the laboratory or in people?

The answer was vague, because by then this provincial laboratory was concentrating on Depakine and they never set out to explore the properties of Depamide in any great detail. They knew that Depamide had some differences from Depakine. For example, they knew it protected animals against epileptic

convulsions triggered by strychnine or tetanus toxin, which was not the case with Depakine. Depamide also crossed the blood-brain barrier more readily, leading to a higher concentration in the cerebrospinal fluid, for instance. Later, a significant incompatibility was discovered for Depamide that did not exist with Depakine – it interacted with carbamazepine.

How did this molecule end up in Bassens being looked at in humans?

L: The original study of Depamide had its origin in a friendship between Serge Borselli and the pharmacists of Berthier in Grenoble, especially Pierre Eymard. It was Borselli who introduced it to the hospital. He had to undertake a study for his thesis under the supervision of an expert who figured on the list established by the Department of Health, so he asked me to supervise his studies. In fact, the work was shared. He treated the epileptic patients, of whom there were about 40 hospitalized patients at this time and I busied myself with looking at the primary and secondary effects of Depamide in other patients. The antiepileptic activity was adjudged to be much the same as, or slightly superior to, Depakine, but it should be noted that we had no strict comparator group. Depakine was not directly compared to Depamide.

The most important problem that had to be overcome by Borselli was how to give Depamide to patients who had been receiving a number of other anticonvulsants for a long time. It was necessary to proceed in steps, bit by bit, to replace the Gardenal and other anticonvulsants. At times the sedative synergy between Depamide and these other agents was so strong that the patient's state of consciousness was altered to the point of confusion. But when we got to the stage of being able to use Depamide on its own, it was clear that it worked as an anticonvulsant and that there were benefits to the mental state of the patient over and above the previous medication. It seemed that it was not just a neurotropic agent, but that it was also psychotropic. Patients felt more themselves; the mental stickiness, viscosity, that had sometimes been there with earlier agents was less; we saw the disappearance of tendencies to depression, sometimes even a mild euphoria, it seemed.

Was this due to the Depamide? It was difficult to say at first because the Gardenal which they had been on before was sometimes accused of provoking some of these problems – a psychic slowing, a viscous character to relationships with others, etc. It was using it in a large number of patients that gave us a different view of Depamide. The patients seemed to develop a different life. Initially, they had been hospitalized and often detained because they caused social disturbances. For example, among the 40 or so epileptic patients, some were authorized to go out from their pavilion, but had to remain within the grounds of the hospital. I remember well how they would follow the medical team, going from one pavilion to the other, beseeching them with demands to be let out, either stamping or pulling at the sleeves of the doctors. This all stopped.

Depamide worked a miracle. At the time, we had a number of religious nurses who, in particular, were very quick to acclaim enthusiastically the ability

of this medicine to restore humanity to people. One of them even swore to us that one patient had his former hair colour restored, that it was no longer grey. Was this medication making people more responsible for themselves? One man, of no fixed abode, who had been hospitalized on innumerable occasions, was treated with Depamide. He responded with an attitude of engagement we hadn't seen before and, in a very surprising fashion, began to spend longer and longer out of hospital when he was discharged.

This was in 1966. Borselli made his thesis on this, while he was an intern working for me. Unfortunately, he had a heart attack a few years later, at the age of 45. He had left our hospital at this stage and begun working in private practice at Chambery. He was very enthusiastic for new products, especially anything for epilepsy, and his enthusiasm spread throughout the hospital.

There was another aspect to the psychological effects of this drug, which played a part in generating our interest in researching it further, and it appeared in the following way. Some of the patients, especially the women, showed a reduction in the compulsion repeatedly to end up in conflicts, repeatedly to provoke those around them, leading us to pose the question: did Depamide in some way reduce self-harm tendencies? Did it reduce masochism?

So, Depamide, thanks to the fact that it was supplied by the laboratory, began to be used generally in hospital services, resulting in something which, in general, the psychiatric literature has not remarked on very much – namely, the disappearance of the epileptic patient from psychiatric hospitals. I think it is necessary to conclude that, because of the medication, they were able to get about the business of resocializing.

Now, to come back to the psychotropic effects. As Borselli had shown, Depamide potentiated other sedatives, so much so that one of my memories of the early days of using it was of sleeping patients, sometimes confused, even those who might not be having anything other than imipramine, which is not very sedative. I have always insisted that this risk of potentiation should have been clearly stated before it was commercialized, and I am astonished to learn that Depamide is sold very widely in certain countries, especially the USA. I would worry about incidents.

On the other hand, this action to reinforce sedative effects could be put to good use. It was clear to us that we might try it in combination with chlorpromazine or levomepromazine for agitated, especially manic, patients. The results were good. These were mood-disorder patients, and when they recovered we were able to look at the effects Depamide was having on the quality of their mood. In some cases, we stopped the treatment when the patient went home, but in others the medication was sent by courier to the patient – you see, at this time it was not available in pharmacies. I remember, during one long postal strike, some patients had to come by car to the hospital to get their supplies. This pointed to a certain fidelity with treatment which was quite new for us – it was not what we were used to seeing with Largactil or other neuroleptics.

The number of patients we treated is important but must be seen in context. We were a sectorized service covering 100 000 inhabitants with 100 beds. Altogether, we made observations on 250 patients. These, however, were not entered into a comparative study. What we could say, at the very least, was that, taken over the long term, these patients showed an excellent tolerance of the medication.

There are two more detailed studies. The first was completed around 1980 with 32 patients. In these patients we looked at the number of manic attacks and the duration of hospitalization prior to Depamide over the period of one year and, using the same criteria, we again looked at this in the year following Depamide. On both of these criteria we saw change. There was a fall in the number of attacks by 50% and in the duration of hospitalization of 60%. A Polish psychiatrist, Puzynski, published a study similar to ours using the same criteria but looking prospectively. He published in 1984, with results that were almost exactly the same as ours.

Other psychiatrists became interested in Depamide and some came to Chambery to find out more about it. The one who sticks in my memory was Dr Semadeni. He came and took me in his plane to spend the day at Metairie, a prominent Swiss clinic, where he showed me a number of patients. He gave me a summary of the patients they had treated with Depamide, which gave 110 cures altogether. He had published his results in a Belgian review in 1976.

Among those who were interested in this normoregulator were both university and hospital psychiatrists. In the first group was Guyotat, but also Leger, Mlle Lempérière and Dufour and in the second group were Wilkin, Richou, Bornstein, Pouget and others. All attested to the positive effect of Depamide leading, among other things, to progressively longer good spells between attacks.

So, Depamide didn't remain unknown, but the laboratory did nothing to spread the word about it. Depakine sold well both in France and abroad, where its use has expanded to include usage as a mood regulator. Emrich, for example, who was one of the first to use Depakine for this purpose, knew nothing about Depamide.

You're absolutely right that we don't see epileptic patients anymore and don't hear about the character difficulties that supposedly went with the condition. Can you tell me more about them?

Impulsivity was the most important issue. Because of this, patients couldn't adapt to normal daily life outside. For the most part, within the hospital setting they had little problem and they were allowed to leave their pavilions and circulate around the hospital. On the one hand, these were patients who were much better behaved when you gave them their liberty, but on the other hand, they were too ill to live outside the hospital completely.

In addition to changes in personality, there was something else that could be seen between attacks. It was well known that there were difficulties between attacks. The psychoanalyst Abraham had written about the obsessional troubles

or other neurotic difficulties a long time ago. So, these kind of difficulties were well known and what we were seeing was that these difficulties were also improved by the medication.

I can remember the first patient I put on Valproate. She had a chronic low mood that might have been termed a dysthymia. We had tried many things, but everything had made her worse, until we tried Valproate, which made a big difference. I can remember her clearly and the fact that this drug seemed to be doing something different from the kinds of things other drugs do in the acute stage of an illness. But the idea of an action on the personality, that a pill could in some way be personality strengthening, would seem to the English a very French view – one that they cannot really understand. A view they like to dismiss in terms of the French impressionistic approach to psychiatry.

L: But you described a lady whose personality was transformed by this drug?

Indeed, I did, but I'm Irish not English. Working in England, I'm very aware that, for the English, these drugs treat diseases, they don't modify constitutions or temperaments – at least at the moment. Perhaps this was why Valpromide was so slow to get into the English-speaking world, because they couldn't understand the thinking.

L: I am very surprised by this. There was an English author, a psychoanalyst, Fairbairn, who wrote a thick book, which was published in France and had a big influence.

Ah, but psychoanalytic authors have never had a very great influence in England, at least not on the practice of psychiatry. Psychiatry and psychoanalysis are completely separate universes.

L: This is unfortunate because, for us, the English psychoanalytic school is of considerable importance. The people who succeeded Melanie Klein – Winnicott Meltzer, Rosenfeld – have been very important. The Tavistock Institute was a very influential centre for us. I am very surprised to hear you say this. A prophet is without honour in his own country they say. I could give you many examples of how our practice fits in with some of their concepts.

How long did it take them in Paris to recognize a discovery from the provinces?

L: Well, there was always a rivalry between Paris and the Lyon region, but you must understand that there was also a rivalry between someone like me who worked in clinical practice and the university establishment. One of the few exceptions to this in France was Jean Guyotat, who was the professor here in Lyon. But you are right, Paris would not accept a discovery made in the provinces, it had to be reinvented there. Despite this, there were a number of publications on Depamide, in particular one by Therese Lempérière, from Paris, which said that this was a good compound. But Deniker and most of the rest of them wouldn't believe it, so the story stopped there.

The pharmaceutical company was more interested in Depakine than in Depamide and it is only recently that they have begun to get more interested in Depamide. But slowly the product began to get prescribed throughout France,

so this product spread itself by practice and clinical word of mouth rather than by pharmaceutical company marketing or endorsements from senior figures. Only recently – 2 or 3 years ago – I was at a meeting in Paris where Hagop Akiskal was talking about the psychotropic effects of valpromide.

A number of other university departments in France did some studies with Depamide which were relatively positive. Volmat did a study at Besançon. But the pharmaceutical company did not get involved in disseminating the results of these studies. I suppose, from their point of view, things were going along satisfactorily without them having to do anything. They were earning a living with Depakine and as far as they were concerned most people were telling them that the two products were the same.

There was great surprise outside France at my publications on Depamide, because it was being used almost nowhere else. The only person who was using it was Harrison Pope. He asked me to write an article on Depamide, which he translated into English. This was supposed to appear in a book, but it has never appeared because, as I understand it, Depamide has not been licensed in the USA. That was 11 years ago -I wrote that article the year before I retired.

Depakote has been very big business in the USA since the 1990s – much more than in the UK. Not only that, but the Americans have become very enthusiastic about bipolarity. This seems to be one of the manias they get from time to time. At the moment, they seem inclined to diagnose many personality disorders as due to some variant of bipolarity, and they are prescribing Depakote accordingly. But the Americans are a little bit like the Parisians, it seems – something has to be rediscovered there before they believe it.

L: I can tell you about an episode like this. Twenty years ago, a group of French psychiatrists went to Harvard to attend some lectures and they heard about haloperidol, which had just been 'discovered' in the USA. They were told it was marvellous by some psychopharmacologist. They were not impressed because they had had it since 1958 and they hadn't gone to the USA to hear about haloperidol.

One of the interesting things about valpromide is that it seems to be very hard to do the kind of clinical trial that would show that it works, because of the length of time the trial has to go on. This poses a problem for people who only believe things that have been endorsed by randomized trials. They have problems with all of these agents – valpromide, carbamazepine, lamotrigine, gabapentin. Were we misled by the ease with which it was possible to show in short-term studies that agents like chlorpromazine or imipramine worked? Is this group of mood stabilizers a group of drugs that can only be shown to work in clinical practice?

It is true that it takes time to show the mood-regulating effect of valpromide. It is also true that sufficient doses need to be given and, on some occasions, people cannot tolerate doses of 900 mg or even 600 mg. In a number of cases it seems to work even better when combined with lithium. I have never had a problem with side-effects or anything else when I have combined the two, even going up to lithium levels of 0.8 or 0.9 mmols.

These days, all the anticonvulsants are being tested for mood-stabilizing properties. The interesting question to ask people, though, is whether they have any feeling for what these things do in order to help stabilize mood – are they anxiolytic or anti-impulsive, or what? In the Anglo-Saxon world, they won't be able to understand anti-impulsiveness, but they do understand anxiolytic or maybe anti-irritability actions. Have you any thoughts on what valpromide or any of these other agents might be doing in order to get patients well?

L: This is difficult to answer because I have not used many of these other agents. I have also treated very few epileptics. What I have observed is an improvement in personality. You get this impression from the reports that come from the homes of these patients – reports about the rapport with their spouses or their children. You could say there is an anti-irritability effect, but in the early publications there was also talk about an anti-masochistic effect. People seem to self-harm much less.

Have you been surprised that the history of this has not been written in English?

L: I'm surprised that it hasn't even been written in French. The younger people here don't know the story of what happened. In the case of Largactil, even, the two books that have been written were both by Americans. No-one has written the history of Valpromide. This is not, in my opinion, because the discovery was made in Rhône-Alpes or because I was working clinically and am not very well known, but because everyone is always looking to the future. Now they have brain receptors and this is what they are excited about. The past doesn't hold any interest for them.

I don't know of anyone in France who is interested in the history, unfortunately. I have been aware of a need in this area for a long time. The people who made all this history are now dying. It's a pity. These histories need to be written.

Do you know Mogens Schou?

L: We have never met, but recently I received a letter from him asking me to write a piece on the action of Depamide. I think he is in the process of writing or editing a book on products with the same functional effects as Depamide. Both the laboratory and I sent him some details. I am actually very surprised by what you have told me today about the popularity of Depamide in the USA.

Do Depamide and lithium do the same things?

L: I'm not sure; I have not had a sufficient number of cases to tell. It may be that one can make the other more tolerable. I think this is the case for Depamide, which makes lithium better tolerated. Otherwise, the combination is of most interest for bipolar episodes. At the moment, here, lithium seems to be used quite a lot, even in treatment-resistant depressions, even in some cases where there is no manic-depressive or periodic element. This is not the case for Depamide. At one point we wondered whether Depamide has the same effects in a depressive episode as it has in manic episodes. I still don't know the answer to that.

So, what happened to Professor Carraz?

L: Well, he was an original man who had a wonderful grasp of pharmacology, who initially didn't hesitate to own up to his mistakes. For example, he used to say he was able to cure mice with cancers but he was keeping secret the formula he was using. Nothing came of this experience, therefore. After he retired, he wrote to me that he had in his possession three molecules which he was sure had a future, one was a hypophyseal stabilizer which could be taken orally, the second was an anti-epileptic a bit like Depamide, and the third was an antisenescent agent which also had tranquillizing properties. At his request, I visited him with the director of a pharmaceutical laboratory who was interested. But it wasn't possible to come to an understanding with him. After a heated discussion, it was clear that we had to accept his description of the products without contradicting anything and without knowing anything about the toxicology, the pharmacological properties or even the chemical structure. So, I suppose there's no need to say that I never got to know what happened to these other molecules of Professor Carraz.

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