TWENTY-FIRST CENTURY DRUG DEVELOPMENT
PIERRE SIMON

So how did you come to get into the field of psychopharmacology?
I have to go back a long time. My father and two of my brothers were medical doctors. The three of them were radiologists. I was a very poor student. I wanted to be a medical doctor but I didn't want to be compared with other members of the family, so I decided to do pharmacy first. I began pharmacy and after that I decided to get a medical degree. Given my training in pharmacy I knew something about drugs at this time, when I went into medicine.

This was when?
I began in pharmacy in 51. In 56 I qualified as a pharmacist and then I began my medical degree. In order to support myself, I found a position as an assistant in pharmacology in the Faculty of Medicine. My boss was Boissier. He was young at this time and he had just begun to be interested in psychopharmacology. So very early, in the early 50s, I began research in psychopharmacology. I decided, however, to continue my medical training and I trained in psychiatry because I was interested in psychiatry but also I thought it would be very useful for my studies in psychopharmacology. I joined, at a low level of course, the team of Delay and Deniker. In general, I continued there, and I became in 1965, what's called in France Professor Agrégé de Pharmacologie, working in the team of Boissier. Soon after 68, the Faculty of Medicine was cut in 10 different parts. I was then put in charge of the pharmacology in Pitié-Salpêtrière. This was a quite large hospital, mainly neurological but with some psychiatry also.

Altogether for 25 years, I worked as a teacher in pharmacology for undergraduates but also teaching psychopharmacology for postgraduates. I began to specialise more in two fields - clinical psychopharmacology and the methodology of clinical trials and I also began working closely with the Minister of Health on different drug regulatory commissions and pharmacovigilance committees. Then having been deeply involved in research during 25 years or something like that, suddenly when I was a little more than 50, I decided to change my life completely. I decided to abandon the faculties and the hospitals. I had the opportunity to be the Head of R&D for Sanofi, which was for France quite important company. At that time it meant, I had more than 2500 people working with me. I did that for 10 years.

Can I go back and ask you about Boissier, who was he, what was his background?
He was born in Caen in Normandy and that's one of the reasons why I became one of his pupils because I also was born in Caen. He also began in pharmacy and then went on to medicine. He began as a professor agrégé of pharmacology in the Faculty of Medicine in Paris and he became interested in psychopharmacology, I would say, just after the discovery of chlorpromazine in 1952. He told me one day we have to specialise in one field and I guess this is a good field. You should train in psychiatry also. I also trained in psychophysiology and different things like that. He was quite a charming and extraordinary man. Certainly one of the best pharmacologists in France at this time. But he was more interested in animal studies than human studies. Although he had a medical degree, he had never the opportunity to see patients and he never saw any psychiatric

patient by himself. In France, the system of experts is very important and he was really after a few years a big expert in psychopharmacology, for the Ministry of Health. He had a central role in the assessment of new drugs especially in the psychopharmacology area. Later on he had an INSERM unit for psychopharmacology and I worked there with him during nearly 10 years.

What was the relationship between your department and Jean Thuillier? He was also interested in pharmacology, worked in the Department with Jean Delay and later went on INSERM.
I don't know exactly what the background of Thuillier was in the beginning. He was not from the academy at the beginning, he was a doctor. In the beginning, he had a small lab in Delay's ward with Nakajima who later was the Director of WHO. He was able to have this created into a unit of pharmacology but after a few years he decided, for personal reasons, to leave. He disappeared totally from the field in the late 60s, which was quite strange in ways.

When it came to looking at what the neuroleptics did, how did Boissier, Jean Delay and Pierre Deniker actually relate to each other?
I was the link between Delay, Deniker and their team and Boissier's group because I was trained in both fields. I usually worked in the morning in Delay's group with patients and with drugs. We were doing clinical trials. At this time most of the clinical trials were done at the same time as the experimental work. So in the morning I would look at one group of drugs in the patient and in the afternoon the same drugs in rats or mice or whatever with Boissier. Delay was Professor of Psychiatry in Faculty of Medicine in Paris. He was a big boss. But he didn't accept the outcome of 68 and he retired very early and never came to the department again after 68.

I wanted to bring up 68 but you've jumped there quicker than I expected. The way I've heard the story is one of the things the students wanted as part of the 68 demands was for Jean Delay to retire.
Maybe but I don't think so. I think that he retired because of a particularly stupid thing. He had a nice office in the hospital with all his certificates and citations and the students took that as a kind of joke. They messed his office up, as a mockery. Delay was unable to accept that it could be joke, that one could joke with things like that. But also to tell you the truth, Delay was a sick man. He had a kind of obsessional neurosis and some agoraphobia and I think it probably got worse at this time. Even before these events, I remember very well because I have been with him in large international meetings, when sometimes he was alone in a room and you know he couldn't move. He needed someone to take him by the hand in order to go out. That was very disturbing to see.

Before 1968, there was a big theatrical thing between students and professors. He was professor and was respected and the students were deferential. After 68, this attitude disappeared very quickly. The students became more informal. They would even say to professors "How are you today". So, he retired then and went on with his literary work. His ward was separated into 2, one for Pichot and the other for Deniker.

Let me give you an example of the kind of relations that existed at this time. When I decided to try to obtain a place in Delay's department, Boissier phoned to Delay and wrote a letter. I then went one day to the office of Delay and he said “cher ami, you sit there”. Then he said you seem an extremely interesting young man, would you mind if I call my 2 assistants, who were Pichot and Deniker. At this time, they were 40 or 45 or something like that. The 2 assistants arrived and stood at each side of Delay. I was in the chair in front of Delay, who was sitting comfortably and we chatted for maybe an hour. During this time, the assistants didn't say a word. This is really incredible, remember at this time I was 27 or something like that. So, you can imagine if he treated his 2 right arms like this, how his relationships with students must have been. He was born in a different era and he couldn't accept the changes that were happening.

To some degree, Boissier had the same type of reaction. Boissier became the big chief of Pharmacology in Paris. In 68, he had a large team. Then suddenly it was decided that there would no longer be one faculty of medicine but 10 faculties of medicine and he would be in one of these faculties. Some of his assistants became heads of pharmacology in other faculties and were now his equals therefore. He really never accepted that. He considered that the rules were changed in a stupid way, in a completely unfair way.

The other thing you hear is that Pierre Deniker and Pierre Pichot were competing with each other in order to the one who was going to get Delay’s job when he retired.
That is certainly true. But the retirement of Delay was unexpected. The decision which was taken then was because the department was so large to keep them both but in different parts. Of course they were in some kind of competition but they were in different fields. They did not have the same kind of interests. Pichot was never really interested in drugs. He was much more interested in psychology and things like that while Deniker was mainly interested in drugs.

Looking back at the Chlorpromazine story, the first name in the paper is Jean Delay but I can easily imagine that he wouldn't have seen any of the patients. Would this be the case?
To tell the truth, at this time he saw one patient a week, in front of a very large audience at the case conferences. He never went alone to the wards, so your thinking is probably right. Maybe he saw one or two presented by Deniker.

The other names on the paper then are Pierre Deniker and Jean Marie Harl. Who would have made the actual discovery - have you any knowledge about this?
I would say that Deniker was very close to the patients. I was not there at this time, of course, but I am quite convinced that Deniker had a very important role. Jean Marie Harl, who was the chef de clinique at this time, was in charge of the patients and so he was the one prescribing the drug and seeing the patients every day. When I arrived in Sainte Anne there were also the older nursing staff, who remembered the events very well and it was a pleasure to speak with them. They said that really when they saw the first patients treated by chlorpromazine it was so evident.

So it was the nurses who made the first observations?
Yes. It was so evident that for the first time some drug did some thing. Maybe I am too critical but I think that the main merit of Delay and Deniker were to be there at the right time. I am sure that a lot of discoveries could not have been done by different people but in this case it was really quite impossible to miss the discovery.

Yes, I accept that. But on the other hand discovery is something but its also necessary to persuade the world that this is important. From that point of view was it not important that this all happened in Paris and not in Lyon or even in Ireland.
Maybe even in Ireland it would have worked. But even to let people know all over the world the kind of compound chlorpromazine was, Delay was not very good. He did not have any English. He sent Deniker, especially to the US but Deniker had very basic English at the beginning at least. Afterwards he was more fluent but at this time like most of the people in France he had to learn his English papers by heart and he couldn't answer most of the questions. He went through the United States with the name of Delay, which was well known. He went as the representative of Delay.

What about the role of Henri Laborit?
Well it is difficult to say because so many things have been written about all this. I knew Laborit well. He was a little bit persecuted by this. Deniker didn't accept any participation from Laborit. The truth is that Laborit did introduce the drug to people for anaesthetic purposes and although they were not psychiatric patients he did observe a special kind of sedation and he said this to Rhône Poulenc. So, I think this role was certainly important at this time. He was consultant for Rhône Poulenc. The drug was originally studied as a kind of promethazine, another sedative but he understood very quickly that it was something else. I am not sure but you know that at this time, the anaesthesiologists used quite huge doses of the drug so you can imagine if you give 300 mg of Chlorpromazine, its not very difficult to notice something.

The drug was also studied at the same time as Delay and Deniker by a team in Val de Grace, which is a military hospital in Paris. So I think that probably they knew at the same time or even earlier than Deniker but they had not the skill to get the message over and also they were military men and they respected any kind of authority and they didn't want to publish too early. Delay and Deniker were very quick and they knew that they had to publish.

Within the Delay team, there were one or two other people. There was Therese Lempérière. When it came to Haloperidol, Paul Janssen said that if he ever really wanted to know what was happening with the patients, he used to call her. What kind of role did she play in the whole thing?
At this time she was not yet a professor agrégé. She was what we call chef de clinique, which is a little bit lower. So she had a ward of patients and she was responsible for them and she is a very good psychiatrist. This doesn't answer really your question probably because I don't know exactly the answer, but my feeling is that after the discovery of chlorpromazine, when we looked at the new drugs other phenothiazines or haloperidol, it

was very easy in animals to say it's quite the same thing. You know we could try to find some differences in certain kinds of side effects or activities but I think the study of the other neuroleptics after chlorpromazine was extremely easy.

At that point pharmaceutical companies went to Delay and Deniker and said they had a new one. They said okay. They didn't look too much except at the toxicity and they gave huge doses, which they decreased when the patients were too sedated. The doses used by some French psychiatrists at the beginning with different drugs were incredibly high and it was fortunate that these were not toxic for patients because if they had the same strategy with other kinds of drugs, they would have killed a lot of patients. But, Lempérière was more interested in patients than in drugs. Deniker was more interested in drugs than in patients. Probably not a large difference between them but I would say Lempérière wanted to cure patients and Deniker wanted to find new drugs and to work on new papers and things like that. That may be a little unfair on Deniker.

When I was working with Deniker, around 1964, I participated in the first study with clozapine. We treated 10 patients. One died from a malignant tumour, one had an agranulocytosis and one had a strange hyperthermia, so the drug was returned to the company with, saying that it was too dangerous to develop. Finally they continued with it but it took 30 years to reach the market. I don't remember the dosage we used, perhaps higher than the present one but it was really very toxic. We were surprised by the toxicity at this point because we were used to the idea that the neuroleptics were not toxic drugs. Of course we knew that sometimes you could have a malignant syndrome or things like that but this was very unusual.

I am intrigued by the image that you paint about Jean Delay.
He was a charming man. He was shy. In fact, extremely shy. He was extremely cultivated, knew everything in literature. Very aristocratic. But I didn't like too much the big presentations of patients in front of 200 students asking questions. It was a bit difficult to accept.

Did he have much part to play in the neuroleptic story other than to add his name and his weight to it?
In the neuroleptic story itself, maybe not. But he had a role in the first tentative classification of psychotropic drugs. He also had a role clarifying things - maybe too much. His view about the difference between psycho-analeptics, thymoanaleptics and neuroleptics was at this time really very useful. You can imagine the fog, which existed at this time in the mind of most of the people working in the field. He really wrote some useful papers with Deniker. Probably Deniker wrote the paper but Delay was doing the thinking. I think that was probably his main contribution to the field. As a teacher it was extremely useful for the students to have something clear and logical in the classification, even if its not completely true.

There was one more person called Jean Francois Buisson who had been working with isoniazid in people who were depressed around 52/53 and he showed it was an antidepresant long before Kline or Kuhn but this never got heard of.

He was also a chef de clinique, a very good man but in fact he was interested in psychoanalysis. And he always took the research on drugs as a kind of joke. At this time, you have to remember that there was quite a separation between psychopharmacology and psychoanalysis. He was a very charming man. There were 2 other guys in the group of Deniker – Daniel Ginestet and Pierre Peron-Magnan who were also useful to see the patients and in my opinion these two were the best psychopharmacologists at this time in the group. It was quite a good team because there was also Zarifian, Loo, and Colouna. These all became important in psychopharmacology.

But I was quite surprised when I arrived at Salpêtrière and worked with Widlocher, who was at that point purely a psychoanalyst but one who understood that the drugs were interesting. I learnt a lot of things through discussions with him - like trying to look a little bit further than the symptoms and to understand what was happening in the mental economy of patients with this kind of drugs.

In fact at this time the change in the early 60s, the drug had to be studied by Delay and Deniker, but the pharmaceutical companies also gave the drugs to two guys, Lambert in Lyon and Fouks in Poitiers. These guys had absolutely no inhibition to increase the level of the dosage and I have seen patients treated by Fouks, on 2 grams daily of fluphenazine, which is a huge dose. This was really bad but using that he saw different things of course. Lambert was more careful.

You had people like Michel Foucault here saying that psychiatry is an instrument of state oppression and its easy to see how the neuroleptics used in this kind of dose could be seen as a means by which the state does this. How much did this kind of thinking play any part behind the 1968 story.
Well there may have been some talk of this among the intellectuals in the movement but it was not a widespread perception. I think a more important factor was the use of neuroleptics by the Russians, which was certainly not well accepted. They understood very early the potential benefits of these compounds and this was known by the students. This is really an old story. But also what was said and it was true is that neuroleptics were used in elderly patients. This was criticised but nobody cared about that. This is true in some places with not enough nurses but its true all over the world.

My perceptions of 1968 are shaped by a visit I made in 1967 Cambodia. I went to teach at the Faculty of Medicine for 4 months. At this time some French professors used to go there for some months. So I went just before the events. I visited 3 psychiatric hospitals, so called. People were lying in large cages, outside, with one part with a roof to keep the sun off. They lived on the ground. There was no door only holes where the nurses would shove some food through - big plates of rice and in the rice they would drop 10 or 20 tablets of Largactil. This was the treatment.

I had to teach to the students about psychotropic drugs in such an environment. It was a real experience. But I never had such students. I had 63 students and at the end of the course, in the exam all the students knew word by word everything I said. Everything! I was really surprised. I went to see the Dean of the Faculty and told him I had never seen

anything like it. There must be some trick. He said not to worry but if I wanted to be sure, I should have an oral examination. We had one and they knew absolutely everything I said. He said that's normal. They were interested to have a young professor and they can memorise the presentation if they are interested. Six years later I saw in my lab one day a young man with a large smile. He said he had been one of my students. I asked him how he was doing. And he said things were difficult. I said why. And he said "well all my family was killed", smiling. "And the rest of your class?" I asked. "I am the only survivor", he said.

In France, I get the impression that everybody expected something like the neuroleptics at some point but nobody expected that there would ever be an antidepressant. Any thoughts?
Retrospectively I think that the neuroleptic story is less interesting probably than the antidepressant story. I haven't seen too much progress with the antipsychotics after chlorpromazine. There was haloperidol of course and some drugs were more or less sedative or induced more or less extrapyramidal symptoms but really most of them are me-too drugs except perhaps for some of the really new ones like risperidone or olanzapine. But the antidepressants were a much more complicated story. I don't know what is your opinion about the discovery of the antidepressants but as I understand it imipramine was synthesised by Geigy even before chlorpromazine. But it was not very interesting and so they put it back on the shelf and only thought about it again when the chlorpromazine story broke. The chemists looked at the structure and said it's similar. So they gave the drug to their psychopharmacologist who tried to find some equivalences but there were no equivalences with chlorpromazine. But they insisted and finally gave it to Kuhn and said this is a new neuroleptic try it. Kuhn was not very imaginative and he gave the drug to all the patients on the wards, whatever their symptoms. He went back after sometime to the company and said your drug is not interesting.

It seems that it was one anonymous doctor in the company, looking at the notes from the nurses, who found that the drug was certainly not a neuroleptic but that it had some effects in depressed patients. So they said in the beginning that it was a neuroleptic for depressed patients which was very stupid. And even the name, which was given to it - a thymoleptic. This is one of the merits of Delay and Deniker to classify it as a thymoanaleptic - the contrary! The discovery was in fact, therefore, written up by nurses, unseen by Kuhn and then picked out by a company man. Even today when we have to study a new drug, possibly acting in depression or schizophrenia, it's relatively easy to work out the answer for schizophrenia but extremely difficult, and more and more difficult for a lot of ethical reasons, to work out the answer with antidepressants.

Okay when you were working pharmacologically on these things, what was the situation in the late 50s and early 60s, in terms of what tests you did etc?
My first work in psychopharmacology was to try to understand the first paper of Courvoisier and Julou. I think Julou recognised that the phenothiazine drugs as a new depressant anti-histaminic were probably interesting in anaesthesiology. If you look at the first publications, you notice they are all about the potentiation of other drugs. I am sure that in the beginning Courvoisier and Julou were not thinking about schizophrenia, they

couldn't do it. The methods did not exist. It's much easier to find methods when you have active drugs. You can validate the methods and it was even easier when we had more than one neuroleptic to help the validation. So the main work was to find methods useful for screening first of all and then also for the evaluation of side effects. We were trying to find methods for what we called predictive psychopharmacology, trying to predict the dosage and trying to understand the relationship between the side effects and the main activity. The discussion about extra pyramidal side effects was quite interesting for a long time.

Personally I was more involved in trying to design and to validate new methods because people from industry were not doing this. It was a strange because the people who discovered these drugs had not the least idea of psychophysiology or things like that. The pharmaceutical industry in the States understood that it in order to make progress, they needed to hire specialists but the specialists didn't exist. The only guys they could find were guys who knew something about conditioning and behaviourism and so they went and looked for people like Leonard Cook, and others who in many cases didn't know a word about drugs, even 10 years later. There was a strange gap between different types of people.

Sure, but what was there to know about drugs. No-one knew how they worked. No one knew that they worked on amines of the brain.
Are you sure we know now?

No, but no one thought they knew then. There was no idea about what the drugs might be working on. You could show physiologically in the animals that things were happening but not biochemically. In a recent piece you wrote that there was a big divide between Europe and the United States. Over in the United States there was very much conditioning and in Europe there was no conditioning.
Yes we worked much more with observation of behaviour. We also worked quite a lot with interactions between drugs - morphine, oxotremorine, amphetamine, pentetrazol - all types of interactions. At the meetings, we didn't speak the same language. It was not just the difference between English and French, it was scientifically completely different between the US and Europe.

Do you think the US approach yielded anything?
No.

This is surprising really because chlorpromazine does have some very marked effects on conditioned behaviour. So in a sense what they were doing was theoretically very good.
Well I don't think that the conditioned behaviour approach led in anyway to the discovery of new drugs, except maybe in the field of the anti-anxiety drugs. They had no input at the start with the anxiolytics but later the studies of Geller and Seifter were really a new approach even if probably most of these drugs were found by serendipity. There is one definition of serendipity, I like, which is that a young man looking for a pin in a haystack,

finds the farmer's daughter. Which is quite interesting because if the guy is not interested by the farmer's daughter, he has no chance of doing anything.

When you look at the story of chlorpromazine you see the evolution of the dopamine receptor idea. But if you look today at the pharmacology of the new drugs you have to wonder if this is a side effect, is it the really useful thing. Maybe it works through sigma receptors. This is especially possible for Haloperidol. I think that the real interest of Haloperidol is through the sigma receptors. And there may be other things. The field of pharmacology is where the story about the drunken man looking for his keys is most true. We keep looking where the light is and not where we dropped the keys.

With all these drugs, you get the story that antidepressants act on monoamine receptors and the neuroleptics act on D2 receptors etc. The D2 receptor becomes almost a common meeting place for the basic scientists, the pharmacologists and for the clinicians. Each of them think that they understand what's going on with this story and they each in their own way have an interest to keep any other angles of the story out of the picture because it will get too complicated. Chlorpromazine as I understand it is a good Cox-2 inhibitor and most psychotropic drugs have effects on prostraglandin systems. Things like this about all these drugs are known but don't come in to any kind of discussion usually.

Chlorpromazine is such a dirty drug. It's difficult to be sure what it's doing. Arvid Carlsson did a lot to put the dopamine story on the map. He's a strange guy. At the same time both very serious but also open-minded. I never understood exactly how he works. A mixture of old and young. Another point which I find strange is that when you look at trials for new psychotropic drugs, when you look at what the drug is doing to animals, everyone looks for the effects on the receptor but they ignore whether the animal's behaviour or memory is depressed or stimulated. I don't know if it's useful but it's strange because the psychiatrists are even more fascinated by the biochemical detail than by the animal's behaviour which is difficult to believe because they don't understand a word about biochemistry but they are supposed to be fascinated by behaviour.

Can I ask you about another French neuroleptic discovery - the discovery of Sulpiride. How did that happen?

It was done inside Delagrange, a small pharmaceutical company. My guess is that they found that this drug induced in animals some extra pyramidal effects. They were looking for something in the gastrointestinal field and in doing the toxicology they found the symptoms of catalepsy and things like that in animals. But it was never written like that because the pharmaceutical company always denied that the drug could induce any kind of extrapyramidal effects. Their promotion was that it was the neuroleptic, which didn't induce this type of effect, which in fact is not really true, it's a matter of dosage. The man who was in charge of medical affairs was a big professor in internal medicine working for the pharmaceutical industry, he absolutely forbid people from his lab to publish things, which were off message. There was a censorship. I am not sure if these drugs are real neuroleptics. They had some success because they were used in low doses and people were interested to use drugs, which didn't induce too much side effects. But I think it would be probably extremely difficult to find the real story there because of the censorship.

When did you join Sanofi and how did the pharmaceutical industry look to you at that point?
That was in 85. When I joined Sanofi, I knew that there was a place because a friend of mine working there told me that the Director of Research and Development was fired and that there was a place free. You would do a splendid job and so forth. But I was not really interested. Then I happened to learn that to get the job two qualifications were absolutely necessary. First, you couldn't be French and second, it couldn't be someone from University. So, I found this challenge was quite interesting and I went by myself to see the President of Sanofi.

He knew me because I was known in the field of pharmacology and I was working in the Ministry of Health. I was also involved in training the medical doctors entering the pharmaceutical industry in these days. I was certainly considered as non-typical. But the true story was that when I saw Monsieur Soutier, who was the CEO of the Company, he felt that it was a good idea to hire me because I was known, because I had a good relations with the Minister of Health and clearly there was some kind of good human relationship between us. A few days after this, he called me, when I had not made any decisions about joining Sanofi and had not talked to anyone. He said "Dear Professor, I am very puzzled because one young chap from the pharmaceutical industry called me and told me that he learned from a common friend that you will join Sanofi. He had said he would like you to join Sanofi because it would be fun to work with Simon". He told me the name of the guy, who I knew - he was working for Rhône Poulenc at this time. And he asked me should they hire him and I said yes okay do it.

When I left Sanofi, I wrote my memoires for my children, my family and friends and I also gave them to Gerard Le Fur, who was this guy. He was my right arm and he was indeed my successor in Sanofi. Anyway, he said this is not the truth. Monsieur Soutier called me, he said, and said I have a Professor Simon, I guess you know him, he has no experience in the pharmaceutical industry, would you accept to work with him. So recently I met Monsieur Soutier and told him this. He said yes you are right but I would have thought that you would discovered that earlier. I said we had more interesting things to do than to discuss this kind of thing with Gerard Le Fur.

When you joined them, what CNS drugs did they have?
They had Tranxene, which is a just a benzodiazepine. They had Depakine, which is an anti-convulsant but at this time it was not known that it could have some mood-stabilising properties and they had Cantor, which was a strange drug, discovered by Laborit, which was sold as a psychostimulant, antidepressant or something like that. It was thought that it had some kind of aphrodisiac properties. But we removed it from the market quite rapidly because we didn't find any effect. In fact the CNS team was extremely poor. I came with one of my co-workers from Salpêtrière, Philippe Soubrié, a very bright man, and between us we completely changed everything.

What were you aiming to do by changing everything?

The main decision we had to take was whether to research seriously which was quite a different story to what had been happening. Secondly we had to decide that we were no more interested in me-too drugs. What we did at that point, and this was mainly Gerard le Fur, was we decided to try to find new targets. We were not going to be interested in dopamine, serotonin and things like that because too many people were working there. We would aim at new targets in the CNS such as neuropeptides. So we decided to work with neurotensin and the neurokinins and cannabinoid receptors and these kind of things. We would systematically screen all our compounds to try to find leads and then try to optimise through the new methods to find selective drugs. We had some successes. We developed a neurotensin inhibitor, a neurokinin-2 inhibitor and things like that. Some of them I hope will be one day or another innovative psychotropic drugs. From the start, I said to my bosses, I wouldn't be interested to try to find a new neuroleptic, a classical neuroleptic or an SSRI or a benzodiazepine. Certainly our approach is more difficult but it is more fun.

Sure. But haven't you got a problem the way the market place works these days - you could discover a new drug but the problem then is to find indications. But even if you find the indications, either it has to be a very big indication or else you have got to make the market, you have got to go to out and educate people and it's only one company doing it then it's awfully difficult. With the SSRI's there were 5 different companies all helping to make the market.

Yes it's certainly a more difficult approach but its more fun and I live for fun. Secondly, I am sure, and I was sure of this in 85, that the future life of the pharmaceutical industry wouldn't be in me-too drugs. Some people would have some money with me-too drugs but if you want to have a drug with a good price, you need real innovation. Now it's difficult. In 5 years it will be quite impossible to obtain a good price with me-too drugs. Only innovation will be reimbursed in the future, so it takes more risk.

Well that's okay for you but the industry is fairly conservative isn't it.

Extraordinarily but I am sure they are wrong. Maybe my predictions were too precocious too early but I am sure that this is the way it's going. When you have seen the quantity of money spent by the pharmaceutical industry for the research of me-too drugs, which sometimes have some minor benefits, it's in between 70 and even 90% of the research money. It's not for innovation. This is a terrible waste of money.

But is it going to change. When you can produce a minor variation of cimetidine and get ranitidine, which makes you more money than any other drug in history, its going to be hard to persuade the shareholders of the company that they need to innovate.

Yes, you are right but there is some basis for improvement by me-too developments in the first 2 or 3 years of the life of a new group of drugs. The major companies are working very early with drugs from each group. If you wait to make a me-too drug, when the drug is already a clinical success you are 10 years too late. You will have no chance at all. For instance in the field of the Angiotensin-2 inhibitors, from the first communication, even before any human studies, the concept was very interesting, so we decided to try for a me-too and then we found Ibersatan. At that point, we had a chance to find a drug, which

had some advantage against losartan and so now we have a large marketing share. Most companies began to try to have Angiotensin-2 inhibitors after the first publication of the anti-hypertensive effect of the drug, and this means lots of these drugs were in development. When you know the cost of development of this kind of drug, there is no chance they will make a profit. But, as you say, there is a problem of shareholders and financial analysts. A lot of my time was involved with financial analysts. Most of these guys, at least in the US and UK are very good and when they understand what you are saying, and when they understand that you are not lying, because lots of people are lying, then the strategy was accepted by the financial analysts.

I was talking recently to Adriana Dubini who was behind the development of reboxetine for Farmitalia. She was saying back in the mid-80s when she was trying to develop it there were 3 approaches you could take. There was a US approach for people like Tom Ban who was saying that it is very important to get the clinical diagnosis right. If you had that right, you would be able to work out what the usefulness of a drug was. Then there were people like Herman Van Praag who had a functional psychophysiology approach. Then there was a third group which was yourself and Yves Lecrubier, who said the important thing is to look at the systems on which the drug acts. Can you tell me about how this relates to what you have just said?

I am pessimistic in science. My feeling is that we don't know many things in the CNS field. Of course everybody tries to relate drug effects to some biochemistry or psychophysiology and this works with known drugs. When you know the effect of a drug in humans, you can put things into place. If you have something really new, my feeling is that it is impossible. In the field of neurotensin antagonists, we decided with a good rationale to try to develop this drug as an anti-schizophrenic drug. But with another rationale, people from Pfizer developed quite a similar drug in the field of depression. I think we are right but I am not sure. We will only know later on through clinical studies. So, the only way in my opinion to make progress is to avoid dirty drugs because it's too complicated, to try to have specific tools for one thing and to look very carefully to what happens in patients. Looking at the animal behaviour and things like that, we can predict that a drug would probably be more active in some conditions but even that I am not sure about. When you want to try to write papers, you can think and you can run an experiment but when you have to find drugs it's a different game.

I was speaking of serendipity. When you have a drug really active on one receptor, one part of the system, but we don't know exactly how it is regulated, the problem comes when you present it to the financial analyst. You say I have a new drug, a very interesting antagonist of neurotensin-3. Good they say, what is the market. So you have to write the net present value of the drug. That is to say, you have to decide for what indication it will be developed, at what dosage, what will be the price of the drug and so on. This is totally stupid but its what you have to do. And most of the people think that once they have produced that they must continue in this way. So I knew that I had to do something like that but I remained completely free in my thinking and try to change course everytime I have any idea.

That's fine but just on that point, if you are the only company doing this, then you can decide that a neurotensin-3 antagonist is going to be good for Simon's disease but the net value of this market is nil because no one knows what it is. But if there's 4 companies who have an interest in this, between you you can create Simon's disease and you can persuade the world that it exists - at least you can in psychiatry, I don't know about the rest of medicine.
I do agree that the story of panic attacks and things like that supports what you are saying. It makes sense but this kind of relationship does not exist between the companies. One maybe could exist between 2 guys in different companies but most of the big companies wouldn't play the game.

In a sense do the market analysts not force you to play the game? Because if you go along to the market analysts and say that we have got this drug which does this, they'll say you can't develop it. But if you go along and say we have this drug that does this, and 2 or 3 more companies have the same kind of drug, then they'll say yes that will run. The companies don't have to formally agree between each other but it still works out that way.
That's a matter of relationships inside the company. I think that with Gerard Le Fur, we really obtained quite early the full confidence of our boss. It was not easy. When we arrived we had to kill a lot of drugs which were without any interest but which were in development and on which the company had spent a lot of money. When I arrived there were 25 drugs in development but I only considered that 2 of them should be continued.

What kind of drugs did you kill?
Not specifically in the CNS but in cancer, neurology, cardio-vascular and in the anti-bacterial areas. The company had been totally stupid. The main advertisement was that Sanofi is present in all areas of research. I explained to the boss that it was very stupid – you cannot these days be good in all areas of pharmacology. You must specialise in 2 or 3 or maybe 4 areas but no more. I know a lot of friends in different pharmaceutical companies and most of them, when they are at high levels, are really discouraged by the relationship they have with their boss, who understands nothing but who takes decisions. Or decisions are taken by the financial advisor who understands nothing about drugs.

Many people say that during the 80s that there was a change in quite a few of the large companies from being run by medically trained people or pharmacology people to being run by people who were MBAs, business types, is this your experience?
In the beginning, the pharmaceutical industry was run by chemists. This was not so bad by the way. Now most of them are run by people with MBAs or things like that. People who could be the CEO of Renault, Volvo or anything. They don't know anything about drugs. Maybe after some time they begin to understand something but not in research. I think the problem is to try to speak to them in relatively simple terms. They must have the feeling that they understand. But they don't really.

Could I bring you back to your links with Yves Lecrubier. People outside France recognise a certain Simon - Lecrubier line of thinking. How did all this begin?

Lecrubier began very early in my team as an assistant. Exactly the same role as I had with Boissier. He specialised in psychiatry but he was assistant in pharmacology in my team for 10 or 15 years. He had a good background in pharmacology and he is unusually inventive man. He likes to play with the ideas. He didn't like too much to do experiments. He was more interested to elaborate theories and he presented these very well. We have a very good relationship. He was also very influenced by Widlocher, whom I mentioned earlier. He loves to understand things, which I am not interested in. I am interested to find new drugs. I think that we will only make progress in our understanding of the human brain through new tools. When you look at the progress, which has already been done, most of it has come about by drugs like chlorpromazine, imipramine, fluoxetine, benzodiazepines and so on. The theory has come secondary to the development of the drugs. He would prefer the reverse order. I understand that but I don't think this is the best way. It's better to find good tools and look at what you learn from that. He considers that I am a little bit old fashioned in this way of thinking, that now we know enough things to begin to put them together and so on. I partly disagree.

Can you tell me about Gerard Le Fur? What's his background?
He is a pharmacist. He's 47. He is now Head of R&D in Sanofi and No 2 in the company. He is General Director. When he finished his pharmacy, he decided he was interested to find drugs. So, he went to meet the Professor of Pharmacology in the Faculte of Pharmacy in Paris. He said he would like to find drugs. He spent 15 days in the lab before saying this is not a good place. So, he joined Rhône Poulenc directly. He made the first part of his career there. He entered the CNS group, which found indalpine. When he joined Sanofi, he was 35 but already he was head of biology at Rhône Poulenc, which was quite an achievement. He was an extraordinary but very bright young man. He understands everything in biotechnology, everything about any part of the pharmaceutical industry. His main interest is the CNS but he can also discuss immunology, serology, oncology and antibiotics. He was absolutely convinced when he arrived in Sanofi about this strategy of innovation. I remember vividly our discussions about the situation. We said what we need are screening tests but when we look at the history of drugs the only field where screening was extraordinarily effective was with the antibiotics. This is because you have a living target, which you can test anything against and this gives a clear answer. He said we have to develop the same thing, only replacing bacteria by ion channels, by enzymes, and to try to automatise this. He had strengths and the position to put this into action.

He was a little bit disappointed at this point by the death of indalpine. The drug was retired officially because of some hepatic problems. I remember very clearly the appearance of indalpine on the French market. It was really a revolution for psychiatrists. I guess that it was much more efficient than Prozac is and we never understood why. It was theoretically a pure SSRI. But in fact because it was so good, I'm not sure that the antidepressant effect of these drugs is related to their action on serotonin. There is something else there. We tried to understand what was going on behind the SSRI story.

Indalpine then must have been one of the first SSRI's, was it?

It was the first. It was marketed in France in 78. I will tell you a story, which has nothing to do with this but I like it. There is a French paper, which is called Prescrire. It is a medical journal for pharmacists speaking mainly about drugs without any kind of publicity. It is totally free from pharmaceutical industry influence. A little bit like Andrew Herxheimers Drugs and Therapeutics Bulletin but with more fun. I used to work when I was in the faculty with this journal. Each month they had an evaluation of new drugs. In France on the first of April, there is a tradition that we have jokes. So in this edition, I wrote a paper about a new drug, which was called Panaceum. The DCI was psychotropin. I said that it was a drug recently discovered, which was extremely interesting, and had just been put on to the market. It came on the market in boxes of one tablet, which was 1 mg of psychotropin. Nobody knew exactly how it worked, even if we had some ideas about such and such receptors. I said that it was very interesting especially for general practitioners because with one tablet of this drug you could cure all the psychiatric disease, regardless of the diagnosis. So there would be no more need to specialise in psychiatric disorders, you could just look at your patient, prescribe Panaceum - that's enough. We had a lot of problems with the association of pharmacists because a lot of doctors prescribed this and patients went to the pharmacist for 1 mg of this. It was a bad joke but it demonstrated that we can say anything even something completely stupid.

That's fascinating. Just on that score though, you have also worked as you have said for the Ministry of Health and you've looked at pharmaco-vigilance issues. The French have a curious attitude towards pills and towards the pharmaceutical industry. As regards the benzodiazepines, they have up until recently, taken huge amounts of them, more than most countries it seems.
Yes it's true for most of the psychotropic drugs. The story is probably different for the antidepressants than for the anti-anxiety drugs. Personally, I think the anti-anxiety drugs are extremely efficient and that most of the people who take them benefit. When you try to suppress anxiolytics, you replace them by alcohol or by Prozac and I am not sure whether this is better. I think that the toxicity of benzodiazepines is quite low. It does exist. There are some problems. There is some abuse. But I think that French doctors are less afraid of side effects and things like that than in other countries and also the people like this type of drug. It may be more true in the hypnotic field than in the anxiolytic one. You take them and they can become difficult to stop. So when you have a patient taking something like that, they take it for years if you don't suppress it. Most French doctors didn't care too much about the issue, so when patients came to their doctor and said could you write me a prescription for these sleeping pills, they had no problem.

The antidepressant story is more complex. When you take the studies, which look at the antidepressants prescribed to the depressive patients, the answer is only in 65%. This means that 35% are not clearly depressed. The problem is that in France, most of the patients are treated for years because the doctors are not worried about the long term effects. When a patient has a severe depression, he is treated with any kind of antidepressant. The doctor doesn’t stop treatment. This means that the number of patients is not very high but the consumption is very high. That’s one issue but then when you take different studies, taking the real depressed patients, you can find that up to 60% are not on treatment at all, which means that detection is too low. It’s a matter of

equilibrium between the two things. We recently debated this vigorously in the Ministry of Health. The Minister wanted decrease consumption. Personally I am sure that if I was severely depressed with one or two recurrences, I would take drugs for years and I would treat my wife for years without any doubt. This it seems is not considered as good practice but I would do it. So I am not convinced that the practice of medical doctors is not good. But I was much more impressed by the fact that 60% of the depressed patients are untreated by real drugs. They are treated by plants or homeopathy or whatever.

Well that leads me on to a further point. One of the things about 1968 was a certain hostility to industry. 1968 was linked to the Green movement etc in Europe much more than it was in the US. How was the pharmaceutical industry perceived? You would have thought the French pharmaceutical industry should be national heroes, with Rhône Poulenc producing chlorpromazine which changed the face of psychiatry, but are they?
They were recognised for that. I would say that the Green movement was not evident at all in the field of drugs in France. It did not touch at all the way doctors prescribed drugs. Maybe the number of alternative health agents - medicins douces - increased a little bit but not very importantly and especially not in the field of psychiatry.

How would the industry be viewed – as good guys or bad guys?
Probably a little bit bad guys like any kind of industry. But generally speaking I would say as good guys. I never saw any real reaction against the pharmaceutical industry. Maybe I didn't want to see it. But I think another point in this thing is that GPs are very poorly trained in psychiatry.

Well, can I ask you about that? In France, there is a real sense that the discovery of the antidepressants was much more of a shock than the discovery of the neuroleptics. It was always understood that schizophrenia was something biological. Depression seems to have been seen as not so biological, more psychological and maybe the right treatment is to talk to people.
Well I agree. But even outside the medical world, when normal people meet a psychotic patient, they don't know he is psychotic but they know that he needs some kind of drug. When they meet depressive patients they say, oh you have to be stronger. You have to motivate yourself. It's not a disease you know. There is a negation of the depressive disorder. Anxiety is accepted. Psychosis is not understood but they know that you have to do something. But this is not so for depression. It's complicated because in France, in the popular language, all psychiatric diseases are depressive states. For lay people, schizophrenia is a depression, and depression is a depression, OCD is depression. Everything is depression.

You mean in the sense that the brain is somehow depressed and not working as well as it should. Psychasthenia.
Yes. So the word depression is not understood. For most GPs, psychiatry is what mathematics are for me. A neurotic blockage. I don't understand a word about mathematics and I don't want to understand a word about mathematics. I am not interested in it. It’s the same for GPs as regards psychiatry.

Has this anything to do with the fact that here in France there was a very strong psychoanalytic school, which never really got overthrown the way it did in the US. In the UK of course there was almost no psychoanalytic school. But here Jacques Lacan was very influential. If I meet French psychiatrists to this day, they seem much more analytically oriented than their English counterparts. Does this play a part?

Well it's true. It's less true than it was. I understand the reason. People like Jacques Lacan were really bright and interesting for young psychiatrists. They had a way of thinking which was maybe not productive for the treatment of patients but intellectually stimulating for the psychiatrists. When I was young, I was extremely interested by all this and I thought about entering into psychoanalysis. But fortunately I had good friends and my wife is also a psychiatrist and they didn't tell me frankly but I understood clearly from them that I was too weak to enter into psychoanalysis. I would have risked wrecking everything inside myself. But psychoanalysis was really more stimulating than biochemistry or things like that. The problem is that I am convinced that unfortunately for 95% of patients, the results are useless and the side effects are probably as serious as the side-effects of drugs.

I have a good friend, a real psychoanalyst, who spent his life working in psychotherapy with schizophrenic patients. With some successes in some patients. Many times the results were not great and there were a number of suicides but he was doing something.

French pharmacology never seemed to develop quite the way German pharmacology did. Is there any reason for this?

Pharmacology was always seen as a poor field in medicine. If you were bright you went into cardiology, into psychiatry, into internal medicine or possibly into physiology but not into pharmacology. It was, it used to be said, for people who were not able to do better. Even now, the calibre of personnel in pharmacology is not great. Maybe there are 10 good pharmacologists. Maybe one or two are excellent. The rest can teach.

When I was a student this was how it was. It's less true now but it's not completely changed. When you are a student in hospital, what is most interesting is the diagnosis. Therapeutics are less interesting. Most of them are interested in the nice diagnoses you find in neurology. And generally in hospital you don't see people off the wards. So most of the young bright students are attracted to the diagnostic end of things. Thirty years ago I looked carefully at the syllabus of the medical students. Less than 10% was devoted to therapeutics and ninety percent went on diagnostics. Now in the faculty of medicine in France, you might have 80 hours of pharmacology. It's less than it was when I was a student. We had 120 hours then and if you look at a number of things we have to know now, 80 hours is ridiculous.

Within the wider international field of psychopharmacology, who have been the important people or what have been the important events.

I was really impressed by Paul Janssen and James Black. I was also impressed by Daniel Bovet.

You have focussed very heavily on the people who have actually discovered drugs. Not the thinkers.
I was also impressed by Boissier. I knew Lou Lasagna from the US. I like his views. In the UK, I was a good friend with Paul Turner. There were some good Czech people in the old days. I am not really easily impressed, as you can see.

But to judge by the piece that you wrote for the CINP book you seemed to think that people in the field can get very impressed with each other and what they think they are doing very easily.
Yes. But I don't know some of the people in the pharmaceutical industry, those who didn't go to the meetings. The conference world is very artificial. You meet people who are not interested by drugs or psychiatry or patients but by publications and to be invited to other meetings. That seems the main goal of most of the players there. Some are more intelligent, more polite or more friendly. I am probably very critical but I don't know many pharmacologists who know what is a drug. By this I mean the whole drug, from the chemistry to the patient. I have some good friends who are working in cardiovascular pharmacology who know perfectly their field but they have no idea about patients and the reactions of the doctor in front of the patients or their reaction of the patient in front of the drug and so on. They are in a kind of aseptic world. It's not real life. They can do useful things. There are some very bright guys in metabolism or pharmacokinetics, which is certainly important but its only one piece of the jigsaw.

This is why the progress in the antidepressant field is not as good as it could be. It's that depression is not simple and I don't think that it's possible to find a drug for all types of depression. So the program should be to try and find responders to a drug and the methods exist to define the profile of responders to this drug or to that drug. You need to treat a lot of patients and try to find by multivariate analysis, what these profiles are. But these methods have never been really adapted to this. And the pharmaceutical industry will never support such a study.

It breaks down the whole market you mean.
Yes. They want to have the whole market, even if this means treating patients who are not good responders. They don't care about it.

There are some clues to do with different personality types. Some temperaments seem to respond to antidepressants, which are active on catecholamine systems and others to drugs more active on the 5HT system. But as you say, that's not the kind thing that the pharmaceutical industry will want anyone to know about.
They will never accept this kind of report. And you cannot do a clinical study now without the support of the pharmaceutical industry. It's too expensive.

Well is this because the profession of psychiatry in a sense has almost ceased to exist. Psychiatrists could do it. They could co-ordinate. They could run these studies if they could only act as a group. The way the Danish University Antidepressant Group did. But we just don't seem to do it any more.

Well because they prefer to do studies paid by the pharmaceutical industry because it brings money to the lab and things like that. That's a thing I learnt from the pharmaceutical industry – how to run a large clinical study. We had a drug, which reduces platelet aggregation, and we had to run a study with 20,000 patients treated for 3 years. It was a real nightmare. We had 500 people working with the study. It cost around $250 million. The team for the study was really a company by itself. If you want to run large studies like this, you need so many quality controls and things like that to work correctly as well as comprehensive statistical support. You will never produce that without a grant from the pharmaceutical industry. The budget of Sanofi for research is larger than the budget of the whole French INSERM. That's not acceptable but that's the way it is. That's why I am critical of the me-too approach. I think this is a waste of money. We have the money in the pharmaceutical industry and I think we have a responsibility to innovate and not only to make money. That's why, I think that pressure from the economy that results only in the reimbursement of innovative drugs is ethically a good thing. But it will take10-20 years for this to feed through.