

## **DRUG HUNTING VAGN PEDERSEN & KLAUS BØGESØ**

### **How did you each come into the industry?**

VP My basic training is in pharmacy. After I had completed it and had been in the army for a few years, I did pharmacology and it seemed quite natural that I should go into the industry rather than into pharmacy. There was also a question of money. So my idea was to go into the industry which I did. I was in pharmacology here for eleven years when I was asked would I move into development, which I did.

KB I'm a chemical engineer from 1969. I was due to go into national service but chose to go into the civil defence. After ten months because I was a chemical engineer I got a position at the Royal Danish School of Pharmacy with the Civil Defence. I was in a laboratory analysing mustard gas taken up from the North Sea and so on. But also I was involved in a number of research projects on anticholinergics one of which involved derivatives of the phenothiazines. I was very happy with this because I loved organic chemistry and organic synthesis and that was what I wanted to do. One day a person came with an advertisement, a clip out of a newspaper, that Lundbeck was looking for an organic chemist. I applied for the job, not knowing anything about what Lundbeck was. At the job interview with PVP it turned out to be an advantage to have worked with phenothiazines because these compounds and the thioxanthenes were a speciality at Lundbeck - which I didn't know of then. I had never been very much aware of the pharmaceutical industry but I got the job.

### **Where did the Lundbeck Company come from?**

VP. Well its a 100% Danish company. It was founded by Hans Lundbeck in August 1915. It was purely a trading company in the beginning - they did not sell drugs. In the 1920s he started to collaborate with a Mr Eduard Goldschmidt, who was involved in the distribution of medicines in Denmark. He had a licensing arrangement with some German companies and he was allowed to bring some products with him to his new company. But there was no production facility then. That began in the 1930s.

The Lundbeck company today is owned 100% by the Lundbeck Foundation. In late 1967 Mrs Lundbeck, the widow of the founder gave the Foundation all of her shares, just before she died. In December 1967 the Foundation bought the remaining shares that were owned by the Goldschmidt family, which was about 45% of them. We are not on the stockmarket and there are no shareholders, except for the chairman of the foundation who holds all shares. At the annual general meeting he is always asked by the chairman of that meeting "does the shareholder have any comment?" The purpose of the Foundation of course is to run the Lundbeck company but they also support research and other philanthropic activities. Some of the donations to research are larger than the Nobel Prize for instance.

### **P V Petersen, who was heavily involved in introducing the company to the psychotropic area was almost Mr Lundbeck at one point it seems. He was an almost legendary figure whom everyone I have talked to speaks highly of. Who was he?**

VP. PV was a chemical engineer who started here in 1943. It was his second company. He had been in KVK - Kemisk Vørk Kaege for a few months and then he joined Lundbeck. He was the one who started medicinal chemistry in Lundbeck and then later with Dr Møller-Nielsen, pharmacological research. He was first head of medicinal chemistry but later on he was appointed Director of Research and Vice-President of the company and then even later President and member of the Board of Directors.

When I joined the company, everyone knew him. He joined all the research meetings and was really the one who gave us the inspiration to try and find new drugs. He was also the one who started the research with the thioxanthenes.

When he started in 1943 the company was working with sulphonamides. Sulfametizole was actually the first Lundbeck development. This was done by Mr Hübner and some of his colleagues before PV Petersen came. Then PV was involved in planning the chemical production of that because that was very primitive when he joined the company. He was the only chemist when he joined. But later he became just as involved with pharmacology. Mrs Moller, a laboratory technician, for a while was the Department of Pharmacology. One of the pharmacologists from the Institute of Pharmacology in the University of Copenhagen was a consultant. This was quite impressive for a chemical engineer who had no background in pharmacology, he just did it.

#### **Where did his interest in the CNS come from?**

VP I think the invention of chlorpromazine really impressed him. He wanted, it seems, to find a better drug or a drug which caused less side effects.

KB We had ketobemidon and became involved in pain research after the war. In fact PVP was made a lieutenant in the Danish army and provided with a uniform by the Ministry of Defence in order to go to Germany where chemists from the Allied countries were allowed to penetrate into the German pharmaceutical industry - to look at the IG Farben Industrie patents. He actually found the synthesis of ketobemidon - the patents were open for use - and he brought it back. So pain research was of some interest to him. He put up animal models for testing pain and he made many derivatives of ketobemidon. This was before the thioxanthenes but it was CNS.

VP. Yes narcotic analgesics are clearly CNS products but I do not know if this was the beginning of his CNS interest. I asked Dr Moller Nielsen, who knew him from 1956 and he could not answer this question either.

#### **What kind of a man was he?**

VP I was interviewed by PV Petersen and Møller-Nielsen. I really got the impression that he was the man that everybody considered was the leader. He was very friendly. Never tough but he could motivate people. From the very first day, he came and worked with us himself. I was very impressed by him.

KB He was a very impressive man. He was tall and with a deep very characteristic voice, which you could hear from a long distance. So there was a lot of power coming out of him. I think his heart really lay in the research. He was not a typical executive. Even though he was research director and Niels Lassen was head of the chemistry department he participated in all the meetings about chemistry. He loved discussing chemistry and he tried to get into the laboratory from time to time. All the chemists really liked him because he was always interested in what you were doing.

#### **He was always called PV or PVP but what did the P and the V stand for?**

VP. Poul Viggo Petersen. He got a stroke at the party for his retirement and he was paralysed and lay immobile until he died more than a year later.

#### **Møller-Nielsen's is the other name that features on all the early papers, who was he?**

VP. He qualified as a vet initially in Copenhagen in 1948. Then he went to Michigan and later Wisconsin where he did a Master of Science thesis on mink. From that he came back to the department of pharmacology in Lundbeck in 1956. Dr Kopff, a German pharmacologist, was the head of the department for the first few years. Then Dr Møller-Nielsen became the head in 1958. He left the company after 24 years to go breeding laboratory animals in Jutland. He was also inspiring but a different type, quieter and a more thoughtful type and a rather short man. They complemented each other.

**There weren't any medical people then were there. They liaised with clinicians from the hospitals - Jorgen Ravn and others.**

VP. That's true. They had a close collaboration with psychiatrists from the big hospitals in Denmark first of all, later in Scandinavia and off course recently everywhere else.

**Psychiatry and psychotropic drugs seem to have had more respect in Denmark and Scandinavia than almost anywhere else. There seems, in particular, to be something of a contrast between Holland and Denmark in this regard. I'm not aware of any vituperative anti-psychiatry movement here. Herman van Praag would say that the problems in Holland stem from a certain Calvinism...**

VP. Well the Danish Church is not Calvinistic. I think we have always been more practical and we have a tradition in psychiatry. Psychiatry is highly estimated in Denmark, more so than in the UK. We have had big figures here in Denmark - Erik Strömgen, Mogens Schou, Ole Rafaelsen and the Saint Hans Research Institute which had a research department started by Ib Munkvad. He and Randrup were the ones who put forward the amphetamine-model of psychosis. They knew that amphetamine could induce a psychosis very similar to schizophrenia and then developed animal models using amphetamine and the antagonism of amphetamine induced stereotyped behaviours. We had a very close collaboration with them. Then there was Arbild Faurbye who first described tardive dyskinesia.

**Coming to the thioxanthenes. In a sense they were a very logical development - simply substituting a carbon with a double bond for a nitrogen in the phenothiazine ring structure in an effort to produce fewer side effects. Tell me about chlorprothixene?**

VP. Its still used. In some countries, for instance Denmark and Germany, it is used quite a lot because it induces so few extra-pyramidal side effects. Our colleagues in pharmacology have now made a modern receptor profile of chlorprothixene which differs only a little bit from clozapine.

KB Its interesting in perspective that the old drugs are "mixed" compounds with actions on many receptors, although of course that wasn't known when they were discovered. Then came the tendency to remove side effects by looking for selective drugs and many companies developed selective D-2 antagonists - at least they believed they were selective. But when clozapine came in focus again after it had been withdrawn and more and more receptors were cloned and identified it became clear that the mixed profiles had a potential and chlorprothixene also has a mixed profile. Its one of those with a relatively good ratio between serotonin and dopamine which might be the reason why it has relatively few side effects.

In Denmark its called by the trade name Truxal, which comes from a Danish magician called Truxa. His trick was that he and his wife would read peoples' minds. He would stand in the audience and his wife was on the stage and he would pick something out of the pocket of someone in the audience and she would have to say what it was. This kind of name has become almost modern again - x and z are now in fashion for drug names.

**Right from the first article by Jørgen Ravn there are these hints about chlorprothixene that it had antidepressant effects which is very interesting given how the story developed later with flupenthixol. Is there something about this group of compounds?**

VP. It seems as if they have a certain mood-elevating effect - I don't know if we should call it an antidepressant effect. But its quite clear that there are fewer shall we say post-psychotic depressions in patients treated long-term with the thioxanthenes than with fluphenazine for instance. There are quite a few studies which have shown that and we have never seen other antipsychotics coming out superior to the thioxanthenes in this regard. We haven't done any big studies with chlorprothixene but as you say the older studies do suggest it has

an antidepressant effect. Flupenthixol is not an uptake inhibitor, that's for sure, but the first metabolite of chlorprothixene shares some properties of antidepressants, although I don't know whether that has any clinical relevance.

**Part of the reason for asking is because chlorprothixene is a very similar compound to amitriptyline - same side chain, just a small difference in the ring structure and in some ways amitriptyline is somewhere on the spectrum between a drug with a pure effect on mood and an antipsychotic.**

KB Well imipramine and chlorpromazine share comparable similarities and imipramine is an analogue in a sense of chlorpromazine. The rationale to produce amitriptyline followed the same logic - it was a similar analogue of chlorprothixene. But the six-membered central ring structures are normally not uptake inhibitors, whereas the corresponding compounds with a seven-membered ring are.

**One of the other interesting points here is that both Roche and Merck were in the business of making the exact same two compounds at the same point in time. Can you take me through what happened.**

KB Well the reason that several companies could end up with the same compounds is that at that time you had process patents solely which meant that if you could find another way to produce a compound which the other hadn't covered in their patents you could have a patent position too. That is exactly what happened in the case of amitriptyline. There are several different chemical routes to the compound. I don't know if the idea to make this compound came at exactly the same time and then the companies found different routes or if one heard about it from the other but as I've just said when you know imipramine its an obvious change to make.

From a purely medicinal chemistry point of view, now when we have computers and pharmacophore models of the receptors, I would say that it is not at all obvious to "the modern eye" that the thioxanthenes would be dopamine antagonists. A medicinal chemist looking at these compounds today would not be so sure but back then they apparently thought that there was very high probability that these drugs would work too. It was only many years later that we could show that they fit into the same D-2 pharmacophore as the other neuroleptics.

As regards chlorprothixene, Lundbeck filed a patent application in 1958. Merck had a patent issued in the USA in May of 1960 but it could have also been filed in 1958. Roche's patent is published in mid-1959. This means that all three companies probably filed patent applications at about the same time but Lundbeck had not seen any applications from the other companies when we filed ours.

As regards amitriptyline, Roche has three patents with priority from 1958. These are compound patents in a few countries where this was possible at the time and process patents in all other countries. They filed process patents in the period 1959 to 1962. Lundbeck has a process patent with priority from Oct 12th 1960 and a later patent from 1962. Roche acknowledged that Lundbeck had an independent process and in the USA Merck's patent had priority over Roche's. We made a licence agreement with Roche in 1961, which respected another agreement between Roche and Merck. We made our own pharmacological and toxicological studies but "exchanged certain information" with Roche, sending them a report in 1961 and they helped us with 10 kg of the compound in June of 1961. So I think it is fair to say that chemists at all three companies got the same idea at the same time and all three companies were able to make a business of their discoveries in the years after.

VP. It was strange though that imipramine was the first tricyclic antidepressant and amitriptyline was the second but amitriptyline was by far the bigger one.

**As these things go, its often the compound that is second in the group that does best and also between Merck and Roche there was a lot of marketing clout behind amitriptyline**

VP. I think there were also clinical reasons. There's no doubt that amitriptyline has a much stronger anxiolytic effect than imipramine. This might be the reason why it became so popular although the side effect profile is certainly no better than imipramine's.

**Even though Roche and Merck ended up at war with each other over amitriptyline and even in the courts about it, in some sense the atmosphere feels as though it were more gentlemanly then, is this right?**

KB. Its my clear impression that the competition has become much more intense. You can see it on the number of developments and patents that we file. In the years 1970 through to 1987 we filed about one patent a year. The research was different, we made a lot of derivatives of the thioxanthenes. It was like there was a gentleman's agreement that you didn't interfere with other peoples invention areas. So in terms of patents, we normally didn't file a patent until we had a compound that we actually put into development but nowadays you know that everything can be stolen so you simply cannot wait to file a patent. From a principle point of view you wait as long as possible to give yourself scope on the development side but you cannot wait that long anymore and once you file the clock starts ticking.

VP Also 25 years ago compared to now there were differences as far as the promotional activities of the the different companies were concerned. We promoted and other companies promoted our products but we never mentioned the products of other companies. Now today you can find some nasty things being said about a competitors products. That was unheard of 25 years ago.

**On the question of derivatives, whether the thioxanthenes or citalopram, once you had one or two compounds why on earth make more?**

KB. Well the project was to eliminate side effects. When I started Truxal, Fluanxol and Sordinol were all made. While they have differences all three compounds were typical antipsychotics with extrapyramidal side effects. So when I came I got the story " we have these compounds but they have side-effects and we have to get rid of these". How did you do that in the 1970s - only by making systematic variations in the compounds you already had. You must remember we didn't have receptor binding models. All the testing was on in-vivo models - mice and rat models. We made a broad screening of every compound we made using reserpine ptosis and apomorphine gnawing for antidepressant effects and methylphenidate antagonism for antipsychotic effects. The induction of catalepsy was and still is used as a measure of the liability to produce neurological side-effects. We also tested for analgesic and anticonvulsant effects. And we did all of that for every compound. For the antipsychotics it was the ratio between anti-stereotypy effects, methylphenidate antagonism, and catalepsy production we were interested in and we tried to improve this ratio. And so we made hundreds of thioxanthenes but we didn't find what we were after, instead we found another thing.

We found some very, very potent compounds. In this work we started to put in fluorine atoms in the molecules and at a certain position in the ring structure this gave us some very potent and longer-acting compounds. Potency was very much the in thing; people liked potent compounds. They were thrilled when we made piflutixol which was one of the most potent dopamine antagonists ever made. That compound was put into development together with teflutixol which had a better profile as regards side effects. Finally we had a very long-acting compound Lu 13-135 but this was given up because about that time we discovered another group of compounds with a completely new chemical structure - the

phenylindanes which we have been working with ever since. Out of that came sertindole and it was then we let the thioxanthenes go.

### **So how did you find the phenylindanes?**

KB. We found them because we had an anti-inflammatory project. These anti-inflammatory compounds were amines and all other anti-inflammatory compounds at that time were organic acid derivatives. At that time the prostaglandin story was not known for these anti-inflammatory compounds and we had the naive thought that because they were basic rather than acidic they would give less gastro-intestinal problems. They were active in our tests of anti-inflammatory activity and we made some ring-closed derivatives of these compounds simply by connecting the side chain to the aromate. This gave us these indanes, which had some anti-inflammatory effects too but not in the final test model - the adjuvant arthritis model. But because we had this broad screening programme it was found that one of these derivatives inhibited methylphenidate-induced stereotypy and in this way we discovered this new class of antipsychotics. Of course then we started to make hundreds of them and we have since made 600 - 700 of them. These compounds have the problem that there are four stereo-isomers every time you make a new compound and it was difficult to separate the optical isomers. So we made some analogues where we removed the stereochemistry and one of these analogues was sertindole.

It would be fair to say that what first attracted our interest with these compounds was the very potent 5HT-2 antagonism, which in fact some of the old thioxanthenes also had. Its funny that several companies had the same idea at the same time. Janssen had a lot of 5HT-2 compounds which ended up in risperidone.

### **Can you recall the day that you found that this new compound had an effect on the methylphenidate model?**

KB. No, but I can remember another day. Because we had a trifluoromethyl group in the thioxanthenes I always wanted to make the same substituent in these compounds but it turned out to be extremely difficult and it took me more than a year to solve that problem. When we had the compound finally I said to Vibeke Christensen "Here is the compound - this is the compound". It was called 18012, like the Tchaikovsky overture, and when it was tested I remember Vibeke running down the corridor saying it was indeed extremely potent. The problem with the first indanes was that they were not very potent and potency was a god at that time. Remember, we had just had piflutixol which was a thousand times more potent than these compounds.

### **You've taken piflutixol Vagn haven't you?**

VP. Yes, and I was heavily sedated after a single 1 mg dose - I slept for about 15 hours. I have also tried teflutixol which gave me akathisia. We made a one or two week phase one study and we were the healthy volunteers. I got akathisia which was very unpleasant. So we discovered that it could cause extrapyramidal side-effects - if akathisia is extrapyramidal.

KB. Piflutixol was so potent that one of our technicians Peter Bregnedal who is still here, and who made the compound got very sedated, before we knew from the animal experiments that it was so potent, simply from a little dust which he must have had. He couldn't wake up the next morning so we had to fetch him.

VP. He was also a member of the Lundbeck badminton club and he had made piflutixol on the Monday and he was so sleepy that he had to stay at home on the Tuesday and the Wednesday. On the Friday we had the annual party in the badminton club in the canteen. I was sitting at his side and we just had a glass of white wine and he drank half of it and we had to order a taxi to take him home. Alcohol you see potentiated the sedative effects of piflutixol.

**In those days it was fairly routine for company employees to be the healthy volunteers but that doesn't happen now does it?**

VP. No it does not any longer. I think that's fair enough. It changed in the early 80s. Ethical committees won't approve a protocol like this because if you are a company employee there could be the suspicion that you are under pressure.

**I can see that but is there a drawback in that if you have had the compound yourself you have a much better understanding of what you are dealing with - as with you and the akathisia Vagn?**

VP. Yes, I realised what it was and I didn't know it was so unpleasant. Although it was a mild akathisia you couldn't watch TV, you couldn't do your work. As soon as you could find an opportunity to leave your office you did so. With piflutixol the problem was sedation. I got 1mg and I didn't come to work the day after. I slept until midday and I couldn't drive the car.

**After producing amitriptyline, Lundbeck produced nortriptyline which I suppose was an obvious step but then you produced melitracen, what was that?**

KB. Its also a tricyclic but just to contradict what I said earlier, now you had a dimethylated six-membered ring in the middle and still it was an uptake inhibitor. A rather selective noradrenaline uptake inhibitor but it has a strong anticholinergic effect and so the side-effects profile of melitracen was the same as that of imipramine.

**Talking about selective uptake inhibitors raises the question of citalopram, how did that come about?**

KB. In fact melitracen was the key. It was made in the early 60s and after that they were making derivatives of melitracen in the laboratory. They wanted to make a trifluoromethyl substituted derivative. But when they made the reaction in the way they used to make melitracen, they got a compound which they first thought was the right compound but after the analysis it became clear it couldn't be. They spent quite some time trying to find out what it was. It turned out to be the first phenylphthalane derivative. Melitracen everyone knew was a noradrenaline reuptake inhibitor - now if you make a wrong reaction in the laboratory and get a completely different compound what is the chance that this compound will also be a noradrenaline reuptake inhibitor? Probably one in a million. But it turned out that this compound and close derivatives were extremely potent and selective noradrenaline reuptake inhibitors. So in a serendipitous way they had discovered a completely new group of noradrenaline reuptake inhibitors.

The compounds that came into focus then were talopram and its sulfur analogue talsupram and both these compounds went into clinical trials. PV in the beginning was quite enthusiastic about these compounds but they were very stimulating and there were some suicide attempts. There always are with antidepressants but he was afraid that they were too stimulating.

**In what sense - they interfered with sleep?**

VP No this was a hypothesis that was put forward in the 70s but this has not been supported. In the papers put forward by Lizzie Stromgren who was the psychiatrist who worked on them, they speak of an activating effect rather than an antidepressant effect and that is the reason we left off.

KB Talopram was discovered in 1965. Then in 1967, there was the work of Carlsson which was published in 1969, who suggested that noradrenaline was involved in activation and 5HT in mood elevation. Arvid has been here a few times and he put forward the idea of going for a 5HT reuptake inhibitor, so when I started in 1971 I was presented with talopram and two derivatives which were dual uptake inhibitors and I was told we should try to produce a selective serotonin reuptake inhibitor. We made 55 compounds before we had it - citalopram. Until a few months ago it was still something of a mystery why two structurally

very close derivatives such as talopram and citalopram have such different pharmacological profiles - being one of the most selective noradrenaline and serotonin reuptake inhibitors respectively. But now we have a pharmacophore model upon which we have based a hypothesis about what this is due to. You know Eli Lilly have the same story because they also made a selective noradrenaline reuptake inhibitor, nisoxetine, and by making a very small change in that they got fluoxetine. We think we can explain that now.

So there you are. Its very few medicinal chemists that see one of his compounds come on the market. I've told you how I came into Lundbeck. Very soon after I joined I was caught by the excitement of not just making new compounds but having them tested and having a result. That's the suspense of being a medicinal chemist, a drug-hunter as someone has called it. I've always seen myself as a drug-hunter. Its always exciting. You always feel that the next compound is the compound.

**But if very few people ever see a compound get through to the market, it must be a very frustrating job**

KB. Yes that's the paradox but in the meantime you have the synthetic challenges. You wish to make this and that molecule but its not always very easy to do it. So you are always occupied with these synthetic problems and every time you succeed in making the molecule you want to make you have a success as a chemist. Then from time to time you get lead compounds which go into further development but most of them of course don't make it. Lundbeck, however, has very good statistics. You will very often see in journals that one in ten thousand compounds becomes a drug. We haven't yet made ten thousand compounds in Lundbeck but from 1958 to 1965 we got seven molecules onto the market and now we have citalopram and sertindole and others in clinical development, so that's more like one in a thousand.

**There are a lot of differences between the SSRIs?**

KB. Yes but only from a simple two-dimensional point of view. Two years ago I realised that nobody had actually made conformational studies or what we call pharmacophore models. Look at it as a lock and key model where all the drugs are keys and the receptor is the lock. When you don't know the lock, what you can do is compare all the keys and prepare a common key using all the shapes that have a sufficiently low steric energy. We have done that with all the serotonin reuptake inhibitors and found a very accurate pharmacophore model and from this you can see that they all fit nicely into the pharmacophore. But these tools were not available in the 1970s and its strange that so many companies succeeded in making so many selective compounds in such a short time. We made it, Astra did with zimelidine, which was the first but was withdrawn from the market and Rhone-Poulenc had indalpine but it was also withdrawn. Then later came fluoxetine, fluvoxamine and a little later paroxetine from Ferrosan and later again sertraline from Pfizer.

**You say you can see why they are all active on the 5HT uptake site but they are nevertheless structurally diverse, would you not expect there to be some differences in their behavioural profiles? Are you aware of any feedback from clinical use as to differences? - there seems to be some data particularly from use in the elderly and for aggression that there are differences as well as from behavioural models in animals.**

KB. Well on the uptake site they are similar but in recent years the number of serotonin receptors has risen from 5 to 17 and there are now 5 dopamine receptors not counting the isoforms of some of the receptors. Nobody has made the complete receptor profile of the 5HT reuptake inhibitors. So I would not be surprised, I would predict actually that differences on other serotonin receptors will be there and this might explain why psychiatrists say they are different.



VP. Clinically the selective serotonin reuptake inhibitors are rather similar but there seem to be certain differences. Especially in the elderly, citalopram seems to differ somewhat from the others but its difficult getting an explanation from clinicians that we can work with.

**Is there a problem here these days particularly with the antidepressants. In the old days a psychiatrist using a new antidepressant would maybe see a few hundred depressed patients a year and he or she could build up an impression of the differences between drugs but these days depression is treated by GPs who may be just as good observers but they haven't the time to pursue their observations systematically ..**

I think there was a problem but today there are increasingly close collaborations between general practitioners and psychiatrists and high quality research in depression is being done by GPs - in the Scandinavian countries anyway and so far as I know also in the UK.

**Lundbeck are one of the few companies who have both an antidepressant and an antipsychotic, is this in anyway linked to the fact that in recent years you have opted to go down the CNS route more exclusively than before?**

KB. The CNS has always been our major research area but in 1988 the strategy was changed to be only CNS. The size of the company dictated it. After Erik Sprunk-Jansen became the director he made the analysis that it didn't make sense for a company of this size to also be involved in antibiotics and a little involved in cancer research. Its very obvious these days in research you have have a detailed knowledge of the therapeutic areas you are in - from basic research to marketing. Previously you could in-license compounds from other therapeutic areas but this isn't a good strategy anymore. In CNS we have real expertise and we could see that there was enough to do just in the CNS area. But making that decision you are bound to continue research with both antipsychotics and antidepressants. If your turnover is dependent on just these two areas you cannot allow yourself to leave these research areas because if you do you are out of business when the next generation comes.

**Lundbeck, at least in Europe, have almost been the experts in the intra-muscular preparations of the antipsychotics. How did that come about?**

VP. Flupenthixol was not the first depot, fluphenazine decanoate from Squibb was the first. I think that gave us the inspiration to develop flupenthixol decanoate which we did successfully. We had seen from the literature that there were some problems with the stability of fluphenazine decanoate. It had been published that there was an early peak some hours after the intramuscular injection of the formulation which was due to a content of free fluphenazine base formed by hydrolysis of the decanoate. As far as I can remember our idea was to find an oil which could be almost completely free of water in order to get a better stability. We chose a thin vegetable oil which is based on coconut oil. This has another advantage over sesame oil - at least in Scandinavia - even when it is cold it is still a fluid whereas sesame oil becomes something like butter if it is stored in the fridge. I remember we compared flupenthixol decanoate with pipotiazine undecylenate in a double-blind study carried out in the north of Norway and we couldn't maintain the blind because the district nurses and psychiatrists kept their drugs in the boot of their cars and pipotiazine but not flupenthixol became extremely difficult to inject.

Zuclopenthixol decanoate came later and now we also have the acetate of zuclopenthixol, Acuphase. The idea for this was given to us by one of the psychiatrists at the Saint Hans, Lars Kirk. He came to us and said we have a problem with the severely disturbed patients who are admitted to our wards - they don't like to take their medication and both they and we hate to have to give them regular injections which is necessary sometimes, two three or four times a day so why don't you develop a formulation with a duration of effect of a few days. We made a lot of different things but ended up with the acetic acid ester of zuclopenthixol which is the most powerful of our antipsychotics. The clinical development was very quick and it became very popular and its quite clear that the duration of effect is about right. Its

seems that this really is an advantage - perhaps a bigger advantage than we had expected. The patient gets fewer injections and it gives personnel on the ward time for some other clinical work. Unfortunately Lars Kirk had retired by the time this became available so he has not been involved in it further.

KB. At the start it was not sure that this would be possible. Its kind of logical that going from a long ester to a short ester should result in a shorter duration of action but that's in a way a very primitive point of view so it was nice that it worked out. Nobody else has really done the same thing. We actually made haloperidol acetate also and discovered that Janssen hadn't patented this compound.

**The intramuscular forms are hugely useful practically and once you see how useful any possible ethical objections melt away but its often occurred to me that if depots hadn't existed and you proposed to make one today there would be a lot of agonised debate about the ethics of treating people against their will for a month. Were there any human rights type issues put forward in the early days**

VP. We were very careful in the beginning. All psychiatrist in the beginning gave a half dose first and watched the patient for any adverse reactions because as you say once you give the injection there is no going back. I think this test dose has disappeared now but initially they were a little bit scared and we recommended the half dose.

**Why is there such a huge variation in the use of depots from country to country with extensive use in the UK for instance and very little use in the US?**

VP. This question is very difficult to answer. I have heard an American psychiatrist say that if they suggested giving a depot because of bad compliance on the patient's part and they are relapsing frequently, he more or less needs signed informed consent to do it. But John Kane, from New York, has said to me that depots will ultimately be used much more in the US. As you said they are not used much at the moment - there are only two on the market, fluphenazine and haloperidol.

**Why is flupenthixol not in the US?**

VP. Because we don't have a US branch and there hasn't been a license agreement that has functioned. Its on the market in Canada and in most Latin American countries. But we were a very small company when this was being developed and it was not easy to find a license partner. We were more or less focussed on the Nordic and a few other countries. In the 60s, Europe and the Far East was enough - you could make a living there. Its no longer enough. Now we always look for a licence partner in the US and Japan, which is what we have with sertindole.

**Are Danish psychiatrists like US psychiatrists, do they prescribe home products preferentially?**

VP. Well if you look at citalopram its number one in a number of European countries - Denmark but also Sweden, Finland, Austria and Switzerland. In Sweden its between 50 and 60% of the antidepressant market.

**In the past I have used the "antidepressant effects" of flupenthixol as an example of very clever marketing but I wonder if I have had this wrong. As you will no doubt tell me there are a large number of studies which bear out this antidepressant profile but also as I've hinted above there seems to be something about the thioxanthene nucleus which has right from the start pointed to something of a profile in between the classical neuroleptics and antidepressants. How did the possible antidepressant effects of flupenthixol come into focus?**

Well Lars Sonne reported a few years after the launch of oral flupenthixol in Denmark that he had treated more than 500 depressed patients with low doses of flupenthixol and he was convinced that it was an extremely good antidepressant. We were very surprised because

we had expected that flupenthixol would be the most selective antischizophrenic drug that had been developed by the company. Later, a number of publications appeared supporting the use of low-dose flupenthixol in the treatment of mild to moderate and severe depression in general practice. In low doses it is almost completely devoid of adverse effects.

**After you distinguished the isomers of flupenthixol, in the mid 1970s there was the Johnstone and Crow study in the UK where they showed that the z isomer was the active one. For one moment there seemed to be the implication that they had almost proven the dopamine hypothesis of schizophrenia whereas in fact what they had done can retrospectively be seen to have demonstrated the dopamine hypothesis of neuroleptic action but it was an exciting piece of research. How did it look from your point of view**

VP. Yes we made the formulations. We were interested in the trial because we thought it would be interesting to have it confirmed that the clinically active isomer was the one that worked on the dopamine system.

**There were other pieces of science you chased which raises the question of how much is a drug company in the business of chasing scientific leads rather than drug development issues. One of these other studies was a study on the possible prophylactic effects of flupenthixol in depression after the early studies showing that it had an antidepressant effect.**

VP. Yes there was a pilot study by Kielholz and Poldinger who had treated a small group of 30 to 40 patients over one year with flupenthixol, a group of patients who may have been non-compliant with lithium normally because they said they couldn't treat them with lithium but anyway they noticed that flupenthixol had a certain antidepressant effect and we discussed a prophylactic study with a group of psychiatrists. Mogen Schou was the co-ordinator. It was an interesting study but flupenthixol did not, in that study, have a prophylactic effect but in a small group of bipolars it seemed to have a mania-protective effect.

**How does the future look in the CNS area.**

KB. If you are speaking about antidepressants and antipsychotics you have to ask what is the unmet need. For every group of drugs you have two to four generations. The first drug is a breakthrough but its not the ideal drug from the point of view of either side effects or efficacy. The next generations come nearer to the ideal drug. In some areas we are there: the ACE inhibitors for hypertension, I think probably cannot be much improved on.

In terms of the antipsychotics or antidepressants how close are we to that? Its too early to tell with the new generation of antipsychotics. In a few years after there have been controlled trials for treatment resistance, negative symptoms and other areas we will see what is left - how much it is likely that we can improve on what we have. In the antidepressant field everybody is talking about the onset of action and efficacy as the two remaining areas. That's what the competition is about now and of course we are competing.

There have been the claims for the combination of pindolol and the SSRIs where it was believed that there might be a faster onset of action. Now it seems that this might have to do with different patient populations. That the so-called fast onset is related to higher efficacy in some drug resistant populations but is not seen in a population where there is no drug resistant patients. I think onset of action and efficacy is probably very closely linked together. Pindolol is also a very dirty drug and a lot of companies are looking into what aspect of it counts. I am not convinced that anyone will make a faster onset of action drug but I think we might make a more effective antidepressant or an antidepressant that is more effective for a particular population. Is depression one illness?

**Probably not but surely from a marketing point of view it has to be kept as one illness. What about the idea that the SSRIs are as potent as some of the older antidepressants in terms of getting the severely depressed person well but that perhaps they are more prophylactic than the older drugs**

VP. I think there is evidence that they have a good prophylactic action and that they are very well tolerated during long-term treatment which is very important for compliance.

**Coming back to the antipsychotics we have a phrase in Britain which is that you can't teach your granny to suck eggs but I wonder whether that isn't just what you guys are doing with the new compounds. When clozapine was introduced there were all these marvellous stories about producing miraculous effects but listening to the people who prescribed it one of the things you find is that the patient formerly was on perhaps 300 mg of fluphenazine I/M weekly, along maybe with an oral neuroleptic and an anticholinergic and maybe even an antidepressant and all this was stopped in favour of a relatively low dose of clozapine as monotherapy. Now both you and Lilly have brought out drugs and you're almost insisting that the dose can only be what in the old days would have been a very low dose. Are you teaching us to suck eggs in the sense that you're saying that all these clinician grannies have got the dose of these drugs very badly wrong for a long time?**

VP. Yes but there is a difference between clinical development today and clinical development 20 years ago. In the case of haloperidol 30 years ago, Janssen didn't make a dose finding study, we didn't either with ours but today its a requirement. Today you must estimate the optimal dose and the minimum effective dose so there is a scientific basis to our dose recommendations. John Kane said when he saw the results of our studies against haloperidol where we used 12, 16 and 20 mg of sertindole against 4, 8 and 16 mg of haloperidol and the 4 mg of haloperidol was as good as 20 mg that we're only finding out now what the proper dose of haloperidol is. But its not just that we are not poisoning people anymore because sertindole in those studies was in a number of respects better than even low-dose haloperidol.

**I suppose that a longer clinical development time has its good and its bad points. In 1959 as I understand it chlorprothixene went from first clinical testing to launch in a matter of weeks. Jorgen Ravn's first use was in early November 58, his report to the company was in December, the license was granted in January and the drug was launched in March. The comparable period for sertindole must have been much much longer**

VP. Yes about 5 years - which these days is something like a world record. But its strange nevertheless that the products developed during the 50s and 60s were very safe products.

But to come back to the question of dosage, the megadose philosophy has almost disappeared because there was no evidence that there was any better effect when you gave flupenthixol for instance in 200 mg doses rather than 10 mg doses per day. The most I ever heard of being given was 1000 mg daily of flupenthixol. It was by some clinicians in Norway who phoned and asked what I thought about doubling the dose - giving it b.d. The strange thing about it apparently was the girl involved didn't have any side effects.

**What will happen in the case of the smaller group of patients who need immobilisation - who need chemical restraints.**

VP. You will need a product with a strong sedative effect. Perhaps use the old drugs. I heard a paper by Robin McCreadie in Melbourne who suggested that zuclopenthixol acetate had become almost standard therapy in the acute phase in the UK and that he felt this would remain the case for some time to come.

**What about the figures in Danish psychiatry - Erik Stromgren?**

VP. He collaborated with us on the noradrenaline reuptake inhibitors. His wife Lizzie Stromgren was the principal investigator on the talsupram studies for instance. He got the PV Petersen Prize, which is now called the Lundbeck Foundation Prize. It was instituted the year that PV retired. It is quite a big prize. It is given out every year, Stromgren got it, Arvid Carlsson got it, Gottfries got it. It alternates between clinicians and basic scientists.

We have had a close collaboration with Ib Munkvad and his colleagues at the Saint Hans but he has retired now. Per Bech and Jess Gerlach have advised us on many of our clinical studies. Rasmus Fog was another person. He is now the medical director of the Sct Hans Hospital. Some years ago he put forward a hypothesis that Mozart suffered from Gilles de la Tourette syndrome but there are many colleagues of his who disagree with this.

KB. We had a very close collaboration with Arvid Carlsson on the basic sciences side. No-one else has had quite as big an impact as he has. Otherwise in medicinal chemistry we have more or less been working with our own type of compounds. The biggest inspiration in medicinal chemistry terms has been the Janssen company because they are a highly respected company - both as a competitor but also a company we respect very much for their research.

VP In the early 1970s Dr Møller-Nielsen and I were invited by Janssen to his company to see it and how they had computerised their screening results. They were very open minded. That would never happen today. Paul Janssen himself showed us around.

**Chasing the history of the SSRIs another Danish Company comes into the frame - Ferrosan, who made femoxetine and later paroxetine. Can you tell me something about them and what happened them?**

Ferrosan was mainly a CNS company and the head of pharmacology there was Buus-Lassen. However they were bought by Novo-Nordisk and Buus-Lassen left and started Neuro Search together with key scientists from Ferrosan. Last year Novo-Nordisk abandoned CNS research completely but Neuro Search where Buus-Lassen is the chief executive lives on selling CNS projects to larger companies.

**Where is the field going now?**

KB Today we are moving into combinatorial chemistry. It cannot be used for everything, it is a supplementary technique but this combined with identification of disease relevant genes and new drug targets means that I see the coming years as most challenging. These genes for instance might identify what is responsible for onset of action of antidepressants. So the quality of the research group will be important, the cleverness and the enthusiasm and the possibilities of working with biotechnological companies. The winners may not be the very big companies, it will be the people who manage through the jungle of opportunities, who chose the right things and who have some luck. Citalopram and sertindole came about by serendipity or what is sometimes today called pseudo-serendipity. Both examples you could just have walked by. The chemist who makes a compound that is not the one he wants could just dismiss that compound and try to get back to his original goal. I'm sure the "prepared mind" will play an even bigger role in future.

We had a visitor from a company called Gene-Logic recently who are able to screen for these turn-on and turn-off genes - they can show hundreds of genes turned on and off when you give an anti-inflammatory compound, how do you go forward from there? I am sure serendipity will play a role, that the unexpected will happen. In all my time as a medicinal chemist I have looked at relatively simple structure-activity relationships such as effect in methylphenidate antagonism, catalepsy or on a limited receptor profile but now we have so many results for each compound and what are the efficacy profiles? Its already now known that many of the neuroleptics which we have been calling antagonists for so long are not antagonists - they are everything between a full agonist and full inverse agonist on every

single receptor they work on. We need to map out these efficacy profiles and then we will see that they are different. Then we will see differences between the ten derivatives of sertindole which look quite similar today. That's my picture of the future - very exciting but also very demanding. The people who just leave it to the machines will be the losers.

**If it isn't going to be left to the machines, what will it take?**

KB. It will take discussions about strategies for selecting the compounds. In psychopharmacology its not just affinity for one target. In many other diseases this will do - a selective ACE inhibitor, a selective H-1 antagonist along with one indication and one model such as lowering the blood pressure and you are there. Here you are playing on so many things. It will be what you believe in. It will be important to make clever evaluation of the strategies you will have to pursue.

**But where will these strategies come from. Once upon a time you could talk to clinical people but now do any of them have the same kind of feel for what the issues are. Knowledge wasn't so specialised on either side before, there were more people who knew everything.**

KB. Clinical people are still very important. They are the ones who will define the unmet needs. What are the clinical differences between the compounds.

**A colleague of mine Tom McMonagle has come up with a term that seems appropriate for the new antipsychotics - he calls them cocktail compounds. Previously when the idea was to have highly selective compounds with one target action, everything else was seen as side effects but now that you have more than one target action built into each compound, its as though the one compound contains a cocktail of active principles whereas previously the idea of treatment cocktails implied that you were giving more than one drug. But isn't there a natural limit to have many actions you can build into one compound ?**

KB. Its not us that build in the actions, the actions are there. Incidentally we have never pursued an antipsychotic with selective actions, except for a D-1 antagonist which we did not succeed with. Otherwise we have looked at both dopamine and serotonin antagonism, just like Janssen. As more and more receptors were cloned we found that our compounds were beginning to look more and more like cocktails as you call them. So they are already built in and our job is to understand which receptors are important and which are not and what is the right cocktail. Our job would not be to build in, rather it is to take out the things you don't need. For instance, sertindole is an alpha-1 antagonist; now there are some indications that alpha-1 antagonism can be important for lowering extra-pyramidal side effects but it can also lower blood pressure. If we take it out we need to design compounds that do everything else except that and that can be a difficult task for the medicinal chemist.

In addition to our antidepressants and antipsychotics we have a muscarinic receptor M-1 partial agonist/ M-2 antagonist in clinical development for Alzheimer's disease. We also have compounds for epilepsy, Parkinson's disease and a sigma-2 ligand for anxiety.

**The whole area of anxiolysis has been very tricky since the benzodiazepines, this will have to be quite a different therapeutic principle.**

KB. It is. The first idea about sigma compounds was that they would be antipsychotic because haloperidol was the first ligand used to identify the sigma site. But then by serendipity we discovered sigma ligands. We put up a binding assay for sigma compounds and in a project for 5HT-1A compounds we found some very potent and selective compounds for the sigma receptor. When it was established that there were two sigma receptors, we found that our compounds were sigma-2 selective which is unique because no other sigma-2 selective compounds were known. We put it into various behavioural models and found a very potent effect on certain anxious behaviours. If it is effective in the clinic it will be a very different kind of compound.

## References

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