FROM NEUROLEPTICS TO ANTIPSYCHOTICS
EDWARD WARAWA

Warawa is an unusual name.
Yes. My great grandfather came over from the Ukraine in 1898 to scout the area. He went back and told his brothers and they came over. They all ended up on homesteads in Canada. We recently had a family reunion in a small town in Alberta. It has 600 people normally and the population doubled in one day. Of the 1150 descendants that you could trace, half of them showed up for that two day event. So that's the origin of the name. It is very rare. When I lived in New York, I was the only one in the Manhattan phonebook.

Can I take you back and ask you how you ended up in the industry?
Well, I got my Bachelors Degree in Chemistry in the University of Alberta. I was Canadian in fact until 1996 when I became a US citizen. From Alberta, I went to graduate school at Stanford University with Carl Djerassi. My thesis was on optical rotatory dispersion - this deals with the absolute configuration of steroids and small molecules. I really wanted to work on natural products but this is the problem that Carl gave me.

I left Stanford and went to Columbia University, where I did a postdoc with Gilbert Stork at Columbia in chemistry. He was interested in methods development so we were looking at enamine chemistry. Enamines are related to ketones. You convert ketones to enamines, then you can do chemistry on enamines that are more selective than the ketones. This was largely just method development - it was not applying it to natural products.

Then I didn't know what I wanted to do. I had a chance to do a postdoc at Scotland but I figured if I went there I'd probably have to come back and do another postdoc to look for a job. I guess I didn't have enough confidence to go into teaching. There was a lot of competition - there were a lot of good chemists. I was looking at a magazine one day and it had an article on anticholinergics which are hallucinogenics – quinuclidine benzylic esters, written by a guy named John Biel who was at Lakeside Laboratories in Milwaukee. So I got an interview in Milwaukee at Lakeside and also at Aldrich Chemical Company. By the time I took it, Biel told me he was leaving and was going to Aldrich which was still Milwaukee. I interviewed at both places. This was the Aldrich part of what was later Sigma-Aldrich. John Biel wanted to set up a small medicinal chemistry unit there doing contract research. I joined his group in January 1963.

Where did the anticholinergic hallucinogens fit in?
Biel developed these along with a psychiatrist Leo Abood, while working on antimuscarinics. I ran into Leo about 5 years ago in Washington at a conference he arranged concerning receptor interactions. Biel had died of a heart attack in 1976. We talked about what Leo had done in psychiatry treating patients, really seriously disturbed psychotic prisoners, with piperidine. It worked well for some of them but not for others.

Anyway we worked mostly in CNS. When the contracts were hard to get with pharmaceutical companies, we worked with Government contracts, like with

Walter Read on anti-malarials. Then about nine years after I joined, Biel left and went to Abbott to head up their research. I took over the group for about two years – I think it would have fallen apart if I wasn't there, so I felt obliged to stay on.

I should tell you about one of the things I did while I was there. I was working on benzylidine-quinucleidines and I had a series of compounds which as alcohol's were anti-inflammatories if you had fluorines on the rings and CNS stimulants like methylphenidate, if you had no fluorines. With an amino on the quinuclidine ring, it was a diuretic. One of the intermediates for this diuretic was an N-benzylated compound. Because it looked good, we had about a kilo made. In fact it just sat there in the company long after I left. Alfred Bader, who was the man who set up Aldrich, - later the head at Sigma Aldrich – listed it in his catalogue.

What happens? Pfizer picks it up years later and it becomes their NK1 antagonist and there you have the start of the substance P antagonist story. All they had to do is put a methoxyl on my compound and they had their NK1 antagonist. As one of our guys once said, wow look what Pfizer did, they just went through a chemical catalogue and got a common chemical. That's not true – it came out of the compound collection of a Med Chem group. This Pfizer compound lacked oral efficacy though, so then the Merck people found you could modify it to make it orally active and then Sanofi came up with another NK1 antagonist. Everybody's chasing it. I think it's going to be an intellectual nightmare in patenting.

But anyway by the late 1960s, things started changing with the FDA. If you had a drug, there had to be more safety studies and you couldn't get into the clinic as fast. We had a contract with Bristol Laboratories that led to a couple of compounds going to clinical testing, as antipsychotics. But as soon as the clinicians saw extrapyramidal symptoms, they weren't interested. At Aldrich for about 10 years in fact, we were Bristol's med-chem group since their chemists worked on antibiotics. But gradually their own med-chem group built up and we competing in a sense so they just took off on their own.

At that time Aldrich merged with Sigma so I had a decision to make. Do I stay with the business end of the company but I didn't want to look for contracts anymore - it was too hard - or do I stay in med-chem or do I go to Miami into Med School and get onto an accelerated programme. If you've got a PhD you could get an MD in three years. I decided to stay in med-chem and I went to Abbott Laboratories.

When you say hunting the contracts what do you mean.
At Aldrich they gave us some money but most of the money we had to get ourselves. Biel had the contracts with Bristol Labs, which were very lucrative. Then I got one with Walter Read. But it got harder and harder to get contracts in med-chem. The company business was changing. At that time, Aldrich decided to get into biochemicals. The question was do we go on our own or do we buy a company. We were actually talking of buying a company and then the opportunity came for Aldrich to merge with Sigma. At that point I

decided I was going to leave. I hated to go but I wanted to stay in medicinal chemistry.

Why?
Chemistry is like model building. For me it's an avocation not a job. I'm doing what I like and I get paid for it. The business end I think I could probably do but at that time I wasn't interested in business or in making money. I was always interested in CNS.

I went to Abbott first. The situation there was they had hospital products, pharmaceuticals and corporate research. Corporate research only got part of the money they needed directly. It was the same sort of situation as at Aldrich in a way - going out to look for contracts with these other divisions except it was all internal. Why they set it up like that I don't know. But that's probably one reason why I got hired because I had been doing this before on the outside. After about two years, they were pulling out of CNS and I didn't like their philosophy to begin with - they weren't really gung ho in terms of good research.

I heard about this opening with ICI in Wilmington. I'd gone to school with a lot of guys who had worked at ICI. Neville Crossley was one who worked for Djerassi also. He later went over to the UK. So I knew that ICI did good research but when I got to Wilmington, I was a bit disappointed. The new building was just starting to be constructed. The UK had taken effective control of the other parts of the business but they had sort of left research at Wilmington alone. In a sense it wasn't really ICI yet. It was still really the Atlas Company. Atlas and Hercules were originally part of Dupont when the trustbusters came in and they made them break up. Much later ICI bought Atlas.

Who were the trust busters?
The Federal Trade Commission - they figured Dupont was too big. Dupont had General Motors also at that time and they had to split that off as a separate division. Hercules was a pretty big chemical company and Atlas was essentially chemicals plus a little bit of pharmaceuticals. Anyway when I came here, it was essentially the old Atlas company. But the building went up in three years and within a year they brought Barry Hesp in from the UK to head medicinal chemistry. The US essentially took the lead in CNS and respiratory diseases here and I stayed in CNS. The UK took cardiovascular, infections, cancer and the rest of the work. I joined in September 1976 and from the start I was working on antipsychotics.

What was the thinking at that point?
The thinking was everybody wanted to have the new Clozapine. Clozapine we knew had no EPS. We were trying to figure out how we could even pick up a drug like clozapine. What test would do it? We didn't want to chase the clozapine structure and we didn't have any really good tests. One of the tests we had was testing for dopamine antagonists and looking to see if they were pro-convulsive because all antipsychotics are pro-convulsives. When your patients with dyskinesias sleep, most dyskinesias stop. So this raises the

question, with clozapine are you sleeping while you're awake? Is that a way to look at it? These are the kinds of questions we asked.

I would have thought at that point that while people knew about clozapine it was seen really as a freak - the big story was going down the D2 route, getting more and more potent drugs acting on the D2 receptors. Was that not the main stream of thinking?
No I don't think at that point it was. You had haloperidol which was very potent but it caused TD and EPS. You had thioridazine giving less EPS but also causing TD. And then you had clozapine which was a weak D-2 antagonist. We didn't want to go down the structure route. Our position was that we were too late to chase the clozapine structure. Everybody was working on it, including Eli Lilly, and receptor binding was not much help since we would be looking for a compound with the potency of clozapine. So what do you do?

In 1979 we hired two biologists. One was Andre Salama who came from Warner Lambert and he set up the neurochemistry. They did the binding assays and looking for dopamine metabolites. Bernie Migler came from Squibb. He was a psychologist by training. He had worked in Walter Read and at Squibb, where he was involved in setting up tertiary screening models. The head of research Mort Goldberg also came over about a year before that from Warner Lambert. We stayed in antipsychotics and we picked our target. We looked at the profile of clozapine, which was very weak on dopamine, and we looked at what it's profile was in behavioural tests.

We looked at the literature and here's what we found. First of all clozapine fails to work in blocking apomorphine-stereotypy in rats. There's a review article written in The Chronicles of Drug Discovery by Schmutz and Eichenberger, the people from Wander who discovered clozapine, and they said that the apomorphine stereotypy test wasn't available at the time they created clozapine. If it had been clozapine would have failed in that test which probably would stopped its development.

Schmutz and Eichenberger looked at the profile of clozapine and the fact that there was no catalepsy and compared it to the profiles of haloperidol and chlorpromazine where it looked more like chlorpromazine and that was enough for them to go ahead. But actually what they don't mention is the first compound in the series they took forward was called perlapine. This was a very strong sedative but it failed clinically. They haven't published much on this. It's in the literature though and they say it had practically no antipsychotic effect. Perlapine is an interesting story, as you'll see.

This was the early 60s. Clozapine then was obviously a clinical discovery, at least in terms of recognising its lack of EPS. Now this probably relates to apomorphine induced stereotypy but crucially clozapine does not block all stereotypy in rats. In fact if you gave mice sub-threshold doses of apomorphine, clozapine actually potentiates the biting or gnawing produced by apomorphine. So it will potentiate one effect of a dopamine agonist but it will block others. Normal mice in cages don't climb. Apomorphine induces

climbing in mice and clozapine in a dose-related way will knock down the climbing. So that's what we said we were going for. Behaviourally we wanted it to be able to antagonise climbing in mice, while at the same time potentiating biting. We figured that would give us a compound that would not produce tardive dyskinesia.

Our measure for the susceptibility of our compound to induce EPS was based on a biochemical assay. If you give haloperidol chronically to rats, the number of D2 receptors increases in both the striatum and limbic areas, without change in affinity, and you can see a behavioural supersensitivity to apomorphine. Clozapine also produces this but not in the striatum. The other thing that clozapine does is this. If you give it chronically and you look at it in terms of metabolites, like DOPAC and HVA, in the striatum you do not get a tolerance. If you give haloperidol, the metabolites increase for a while in the striatum and then after that they tolerate. Whereas in the limbic area, there is a tolerance to both haloperidol and clozapine.

If you look at this electrophysiologically, in the striatal A9 area after clozapine chronically, the dopamine cells are just fine they don't stop firing but in the limbic A10 area, they do. All clinically effective antipsychotics cause the A10 to shut down. This is referred to as depolarisation inactivation. In the lab, the on-set of dopamine blockade is fast but in the clinic it takes time to get an antipsychotic effect. This led to a theory by Bunney and Grace that its when you produce this depolarisation inactivation that the antipsychotic effect kicks in. This is what clozapine had in common with all the other antipsychotics. And the fact that it doesn't do it in the striatum would correlate with the fact that the EPS was coming from the striatum and this was why it doesn't have EPS.

We had three series soon after I got here. In one, a chemist had designed a compound around apomorphine. The second came from compounds that we were bringing in from the UK and screening looking at mouse climbing and mouse biting. We had compounds that could knock down climbing and they wouldn't potentiate biting so we tried to change them around. This went on for about a year. Then we had compounds that did both. Mort Goldberg at one of our meetings got angry and slammed his fist down and said that we had to have a compound that has the same IC 50 as clozapine on D2. These compounds didn't. They were active at a micromolar level, whereas clozapine was active at about 350 nanomolar. At that time I switched my programme and within five compounds we had a compound to test our hypothesis.

We knew that propranolol would potentiate biting. And I knew that orthomethoxyphenylpiperazine increased HVA. I had my guys put the two compounds together. I made the first one but it was one of the others that was the first one submitted. And this compound did every thing we wanted – it potentiated biting, knocked down climbing and had the same IC 50 as clozapine. Very recently there were compounds coming out of Glaxo that look like this that they say are D4. This was our test compound – U11117. Now all we had to do was go into the rats chronically.

So we took rats and chronically dosed them with this compound and clozapine for three weeks. Then you sacrifice them and you look for whether there's an increase in the receptor number or affinity and there wasn't any. Neither with clozapine nor with this compound. Now then we had something that matches the profile we wanted. But we said okay, what if we do it at higher doses and go longer. Then we started dosing again for six weeks with the last two weeks being higher. This compound was well tolerated and you could go to higher doses. With clozapine you couldn't do this because of its lethality. At that point we got an increase in receptor numbers. So we were in a position, what do we do now? What does this increase in receptor numbers mean?

It turns out that about 6 months before this, there was an FSAB meeting at Atlantic City, where a guy from Lederle by the name of Frank Cahn gave a talk. He had sensitised cebus monkeys with haloperidol and then showed that once they were sensitised you could give them any antipsychotic you want and it would show dyskinesias. What you do is you give the monkeys haloperidol about 1.25 mgs orally per week. At the end of 14 to 16 weeks, they look normal but the next time you give them haloperidol they produce dyskinesias. It could be tongue flicks, it could be arm movement, it could be neck movement, it could be bar-biting, it could be twisting of the torso. It's very tardive dyskinesia-like. According to Cahn, all antipsychotics thioridazine, chlorpromazine etc, all show dyskinesias except clozapine.

So, we set up a colony here and we showed that clozapine did not show any dyskinesia. Then we gave our compound, U11117, and it produced numerous tongue flicks. The compound was dead. Our project was over and we moved on to a new approach for coming up with an antipsychotic – a presynaptic approach.

Now the presynaptic approach is linked to Arvid Carlsson's and his compound - minus PPP.

Yes but years ago it was known that low dose apomorphine is an effective antipsychotic in man. That was known in the 20s and 30s. At the time, Carlsson's group was pioneering this approach and this is where we went after U11117. What you do is you give low dose apomorphine to rats and these animals get very quiet and hypoactive. They're not sedated because if you clap your hands they'll take off. If you increase the dose, mice will climb or rats will run and if you go higher they will bite stereotypically. At a low dose, the theory was that there is a presynaptic receptor, an autoreceptor, that shuts off dopamine. So that's what we were working on.

What Bernie Migler found was that if you repeatedly treat them with low doses, within a week the effect tolerates out and you no longer get it. But we were very neurochemically driven as opposed to behaviourally driven on this one. The neurochemistry department was the science here and they looked hard at it neurochemically to see if they could find a correlate to tolerance and they couldn't. So the question was is it tolerance or is it tachyphylaxis, what's going on?

We were ready to go to clinic with low dose apomorphine in Canada with a guy named McNair. Then we decided we'd look at it electrophysiologically. And if you measure your dopamine cells electrophysiologically, you see a rapid tolerance after a couple of days of apomorphine. Just at that point, Carol Taminga published a paper where she had given n-propyl apomorphine to human subjects. This is a little longer lasting than apomorphine and she said it tolerated. With minus PPP, we got some tolerance but not as fast as apomorphine. After that the whole area just quietened down without anybody really saying why. I think it's because everybody recognises you're getting this tolerance.

Behaviourally if you look at the rats on chlorpromazine, haloperidol and things like that, they look indifferent. Does low dose apomorphine produce the same behavioural effect – indifference. Why is it antipsychotic?
I don't know. I do know that it's not sedation. If you clap your hands they're moving so they're able to do it. I think you're going to have to find another descriptor for this behaviour stemming from a lack of dopamine. It may not be the same as just blocking a dopamine receptor, which triggers all kinds of feedback loops. Low dose apomorphine is a much more natural process and maybe you don't activate all the other feedback process.

Would it be worth doing clinically, even though it isn't much use in the long term, because it sounds like it might minimise some of the dysphoria that can be caused by acute D2 receptor blockade.
Yes it could. I think it was described as a rapid onset effect. It also produces depolarisation inactivation quicker than dopamine blockade does, so it might also give you a quick initial response. For long term use one would have to learn more about receptor desensitisation.

So that's another approach dead. What happened then?
Let me go back to perlapine. As you'll see we picked up on perlapine again but shortly afterwards, in January of 84, the Wander Group published on fluperlapine, which is perlapine with a fluorine where clozapine would have a chlorine. This was an effective antipsychotic in the clinic without EPS. We made it in house and looked at it in cebus monkeys - no dysinesias. It's a little bit weaker than clozapine. But it died because of liver toxicity.

This made us feel good that we had picked on perlapine and moved forward this way but it also bothered me that they could have gotten another patent on fluperlapine because it presumably was part of the patents with perlapine. I think they got it because they could show that it did have antipsychotic effects and the original perlapine compound didn't – it was too sedating. This was their second line of bad luck whereas we were very lucky. We would really have been whipped if fluperlapine was out there and didn't have agranulocytosis. Wander were very unlucky.

Just before this, Bernie took perlapine, the first compound that Wander had, and he put that into monkeys and found there were no dyskinesias. So he said well why don't we work around perlapine. I said wait a minute there's

another compound that Wander published on - they said it was a good antipsychotic in the clinic with no EPS but it was prone to convulsions. And so they dropped it. This was a compound called NT201252.

Perlapine is very close to clozapine but it has a carbon instead of the nitrogen and it lacks the halogen. NT201252 is like perlapine, in that its got a carbon instead of a nitrogen but it does have a halogen, just like clozapine, and one of the benzene rings is a thiophine ring. We got that compound, put it into cebus monkeys and it caused dyskinesias.

Then Abbott came up with a clozapine analogue. They took clozapine, which it is an n-methyl-piperazine and they put on a piperazine which came from the old tranquillizer, Atarax. They patented this. I made the compound after they patented it. It potentiated biting, it knocked down climbing and in monkeys it caused dyskinesias. Now here's a compound that got around the clozapine patents - there were only a few times I'd seen that happen – but it was very close to clozapine in structure and at the same time was dyskinetic.

So this put us in the position where we had the clozapine series, which is dibenzodiazepine, in which we had one compound that was dyskinetic and one not dyskinetic. And we also had the perlapine series, dibenzapines, and one compound was dyskinetic but the other one wasn't. At that point we said we should chase the structures.

Now while we're working on a presynaptic approach in the Spring of 1983, we made our first hybrid of perlapine. We simply took the Atarax piperazine and put it on perlapine's structure. This compound knocked down climbing but it lacked potency. It only worked at 80 mgs IP. But it did have efficacy. So we put it in cebus monkeys and there were no dyskinesias.

I was working on another project at the time, so I only made this compound on the side. When we found out there were no dyskinesias, we put a chlorine on the ring and we found it looked pretty much like clozapine. Again no dyskinesias but now its more potent than the first compound. This must be September 83, so we're talking about 5 months later. After we finished evaluating it, in February 84, at our next antipsychotic meeting project meeting in May, we got an okay to chase this new group of compounds. But we were also advised that we should look for other types of structures. And so we had another team on this looking at other compounds.

I stuck to this compound and went into the sulphur series and into the oxygen series but we weren't getting much improvement. Then I remembered the very first compound we had, which lacked efficacy. It didn't have any substituents on the rings, so I had my guy make it without any chlorine and that was Seroquel.

But we also continued to look at perlapine. A pharmacologist named Stanley Wilk said that perlapine should be re-evaluated in a clinical setting at a higher dose, on the basis that it increased dopamine metabolites in rats - HVA went up. Now we took the perlapine series which looks just like clozapine except it

misses a chlorine and has a carbon. If you put the chlorine on - its inactive. If you keep the chlorine and replace the middle carbon by sulphur its also inactive. Put on an oxygen, dead again. But all these compounds, if you take the chlorine off, they're all active.

We said wait a minute, maybe Wilk is wrong in saying it should be tested again. Maybe it's just an active metabolite that's giving it activity. So Bernie pretreated his rats with SKF258, which is a p450 inhibitor and all the resulting compounds turned out to be essentially inactive. So what was happening in the case of perlapine is in the animal you're getting a very active hydroxy compound, a good dopamine blocker, but man doesn't make the metabolite. So we knew that the hydroxy compounds were potent and I made a couple others. We isolated the perlapine metabolite I made it and I made the sulphur metabolite and they were all dyskinetic.

At this stage would you guys not have been prepared to go ahead with one of these compounds even though they did cause some dyskinesias?
No. That was not the philosophy. In retrospect maybe that was a mistake. But the thing was that clozapine did not cause dyskinesias at all. And that's what we wanted. When we gave Seroquel to 13 cebus monkeys, 2 showed dyskinesia. Let me tell you about this test. You're giving the drug in something like Hawaiian punch. Monkeys like that. You're observing them for 6-7 hours. A person's there watching them, scoring them every couple of minutes. You can assign scores to the dyskinesias - weak, strong, medium and you record what type they are. In one monkey, I think we saw a dyskinetic movement for 10 seconds and they still said that one monkey had a dyskinesia, even though in over 6 hours this lasted 10 seconds. The other one lasted like 20 minutes. The others didn't have anything. If you take olanzapine and you put it in these monkeys its dyskinetic. Risperidone is very dyskinetic.

Then we had to see what Seroquel looked like in terms of neurochemistry – HVA etc. It was selective for the limbic area just like clozapine was. We looked at its electrophysiology and it did exactly what clozapine - it knocked down the A10 and did not effect the striatum. It looked like clozapine. Weak IC 50 the same as clozapine.

So, when did you have the compound.
When the project started we had these two precursor compounds fully evaluated and management said go ahead. This was 1984. Seroquel was actually made in March of 85.

I'm trying to work out what people would have thought at this point in time because clinically this was the height of the dopamine hypothesis and the D2 receptor binding story - people were doing post-mortem brain work and reporting raised D2 receptors to the brains of people who had schizophrenia. There was no hint of clozapine - it had gone. Clinically very few people knew about it.

But when we first started we knew that clozapine had a history in a clinic that said no tardive dyskinesia. First of all we showed that our first hypothesis that a potentiation of biting is somehow associated with whatever property clozapine has that will suppress and not induce TD is wrong. U11117 showed that this hypothesis was wrong. Our fall back position was in looking at perlapine and the NT compounds and saying wait a minute there are holes in this series. Even before we started, we said that if we found a compound and went to the patent office, they're immediately going to cite these compounds against us. The Abbott compound showed severe dyskinesias and the point was that our compound doesn't do it. You'd have to look at what the closest structures that appear in the prior literature are that are known structures and show that they're dyskinetic and ours aren't. And that's the basis on which we were able to get the patents.

You're saying that you can't get a patent by simply having a slightly different compound just putting on a chlorine.
No the patent office would say its obvious. There has to be some difference in your compound that produces different properties. The other thing we had was this compound was never known – it had never been made. Not that it couldn't have been made but it never was. And as long as its not exemplified in the literature you can now get what they call composition of matter patents. You can get it patented on both the compound as well as its utility.

So we had enough to go to the patent office and get the patents. And they responded just the way we thought. First of all they came back and said what's the closest structure and everything else about the functions. We had to file affidavits to show that the closest compounds are dyskinetic. The patent was granted in November 1989.

Right this was when the clozapine story had begun to unfold because Study 30 had been reported about 88/89 and clozapine was all of a sudden big business. Where were you and all the rest of the competition at this point ?
Olanzapine was out there already - it was published. I think they went on a lack of catalepsy and a couple of other tests. Essentially what they did was work from the clozapine structure. They took the chlorine off and they kept the thiophene. NT101-252 is a thiophene ring and its dyskinetic. Olanzapine is also dyskinetic in our monkey model.

So the monkey model what does it mean? It's just a model after all. What impressed Bernie about it was the type of movements induced in the monkey. These were reminiscent of what you see in people. The onset after 14 weeks of haloperidol is pretty fast compared to the occurrence of TD in man, so some people would argue that it's tardive dystonia, or they call it an EPS of some sort, rather than tardive dyskinesia. The other problem is you can block this effect with an anti-cholinergic, like you can with EPS, whereas tardive dyskinesia may worsen with an anti-cholinergic or at least it's not helped. So we said that we couldn't go to the FDA and get a label to say it won't produce tardive dyskinesia unless its got a reasonable history and that remains to be seen.

Regarding olanzapine at low dose there are few EPS, do you think it's a mistake to say on this basis its clozapine-like?
Well you know a low dose is one thing a higher dose is another thing. Seroquel in terms of prolactin also wasn't quite like clozapine because clozapine doesn't increase prolactin. With Seroquel it went up in rats for a half hour and then came down and stayed there. The other thing is it did block 5HT2 better than it blocked D-2. What we're saying now is it's a balanced D-2/ 5HT-2 blocker and that may be true but it's not how we found it.

I've interviewed people in the field like Klaus Bogeso, who was involved in making Sertindole, and the impression I got from him was that through to the 80s, mainly because clozapine had nose dived, they were still trying to chase potency at the D2 receptor. They may have been doing other things as well but this was the main thing. Were you guys only going down the clozapine route or were you playing two horses - you know lets have the standard program and lets have the atypical program at the same time or were all your eggs in the atypical basket?
No. This was our program. We had no choice but to look for dopamine antagonists at least with the potency of clozapine because we didn't know of another mechanism that could be responsible for clozapine's activity. But it was essentially a behaviourally driven programme.

What would happen when you'd meet the guys from Janssen or other companies, where they were chasing a fairly potent D2 receptor blocker. They wanted it to do other things to it as well but they were much more traditional.
Right, well I'll tell you that risperidone certainly is not clozapine and neither is olanzapine. We did know as we got into the neurochemistry that clozapine also had a serotonin antagonism. Later on Stoof and Kebabian at NIH showed that it had a D1 antagonist properties. Clozapine also has alpha-1 effects and it's also a potent antihistamine. Neither Seroquel nor clozapine are the most potent dopamine antagonists. Olanzapine and risperidone work at the milligram per kilogram level. Seroquel has to be at chlorpromazine like or clozapine like doses to show an effect.

Do you need potency? Potency was what drove Paul Janssen to produce Risperdal?
Clozapine has serotonin antagonism. Going down the potency route you would have to decide on what percent of serotonin block you need versus what percent of dopamine block. I don't know what their measures are but if you come down to the cebus like we did, risperidone is clearly dyskinetic. When the hype first came out on risperidone it said you didn't get the EPS etc. but its clear if you go a little higher with the dose you get it.

You didn't win the race to get the first post-clozapine atypical
Olanzapine beat us to the clinic. Lilly got there first. I think we could have been there faster. Accolate was being pushed in the respiratory area here and I think that delayed Seroquel. The other thing that had happened was in toxicology studies in dogs they observed cataracts in some of the dogs, you

didn't see it in rats. That set us back - we had to do a tox study in monkeys and we didn't see any cataracts in monkeys. But because of that we had this label that says you have to have your eyes examined before you use it but we're trying to remove that label.

The other thing that set us back was that ICI had very little experience in the CNS area. The clinical studies moved very slowly at the beginning. We went into very severe patients first, which was maybe not the best way. Then Lisa Arvanitis came here and sorted out the later clinical trial program. She's a neurologist by training. As of last Thursday I heard she left to move to Sanofi. This was possibly because of the merger with Astra. With the restructuring, a lot of people have left, mostly older people in upper management who've retired. It's hard to say what would have happened if Seroquel had beaten Lilly to the market.

Clozapine is still selling well but its just come off patent. I saw a generic form advertised this month for the first time. How are you all going to do compared to it?
Well if conventional drugs don't work and you put them on clozapine and it works then you're not going to take them off clozapine in case it may not work again. When we went to the launch for Seroquel in Fort Lauderdale, they set up scenarios one of which was a community hospital, another a psychiatric hospital, another different settings. They had some patients, some families and some psychiatrists there and asked them what they thought of the new drugs. Basically they said that if they give a patient a drug and it works then they are not going to take them off. They are not going to switch. That's one of the problems we have with Seroquel, which is we're not going to get them on Seroquel unless they get it first.

Where are things going now as regards development?
Let's go back for a moment to clozapine not inducing TDs. In 1979 the pharmacology literature is suggesting that potentiation of biting is important. I started reading the pharmacology literature, asking who's working on this problem. It turned out there was a pharmacologist at the University of Nijmegen in Holland named Alexander Cools. I thought he was a real genius, he writes beautifully. Looking at dopamine and antipsychotics and how they interact, he took behaviour and tried to make wiring diagrams like you would from receptor systems. He had his own nomenclature. He said for example there are two actions to dopamine, an excitatory one DAE, and an inhibitory DAI. The terminology can be confusing but that didn't bother me. He had taken a compound called DPI, which he could inject into the brain and DPI caused tongue flicks in cats. He found serotonin blocked that. He also found norepinephine given into the brain blocked it.

So I said I'll look for a norepinephrine agonist that can cross the blood brain barrier and see what happens. In the literature, about the same year, there was a paper by Cannon's group from Iowa on a 2 aminotetraline series, where some the compounds were able to antagonise apomorphine. He concluded that this was not due to dopamine blockade but indirectly to alpha agonism because they were also potent alpha agonists. SmithKline picked up

this series and made some sulphur analogues and also found them to be alpha agonists. Anyway I also picked up this series and made some compounds, one of which we put it into a mouse climbing test and it knocked down the climbing but it didn't potentiate biting.

Now Bernie I told you was really good at developing tests. Mouse climbing is a very non-specific test. Any sedatives will keep them from climbing. There was though a Russian paper that gave him an idea. He came up with a swimming model. If you take a circular pan with a circular obstruction in the centre and put a mouse in it, the mouse will start in one direction and swim around the pan and in two minutes it may do 20 swims. If you give it apomorphine, it just stays in one part, clings to the wall and doesn't swim at all. You have to rescue it. If you pre-treat with an antipsychotic and give it apomorphine, they swim. In other words, they don't need dopamine to swim. We called it a normalisation test because what you're doing is taking a behaviour, which is not normal, and you're renormalising it as opposed to the mouse climbing which is not a normal behaviour for a mouse.

This normalisation test is very specific - the only compounds that work are antipsychotics. And so we used this test on some of our Seroquel series of compounds. Both our compound and clozapine did this. I tried it on this alpha-1 agonist, 2 aminotetralin, and it worked. It normalised the mice. I got it into the cebus monkeys - no dyskinesias.

This compound has an amino group on an asymmetric carbon - that means that it can exist in enantiomers, so at that point we separated them. We looked at the plus enantiomer and it worked very nicely as a dopamine blocker but the minus enantiomer didn't. When we put the plus enantiomer into the cebus moneky it showed dyskinesias but the mixture didn't. So that tells you that the minus enantiomer was suppressing the dyskinesias due to its plus enantiomer. So then we put the minus enantiomer with haloperidol, with thioridazine and with chlorpromazine - no dyskinesias. So we have a patent on this compound now.

One of the lessons of this is that when you're looking at in vivo work and you're talking about receptor properties and feedback systems, you've got to watch out for active metabolites - they can totally mislead you. I don't know how clozapine works. I know in some way it suppresses it's own dyskinesias. We know it suppresses early genes - that may be it. These genes are translated into proteins and plasticities and that may be it. But how it does it, I don't know.

So is this going to be the next generation?
I don't know what's going to happen with this one. We did a lot of structure activity relationships that showed that you can only have certain moieties in certain places – there's a very tight SAR around this compound. When we say we've got a compound that can suppress dyskinesias, the response is "so what, in 8 years you won't need it". All the compounds out there - olanzapine, Seroquel etc won't require anything like that. I don't know, I think you could

use a compound like this to suppress the dyskinesias due to l-dopa in Parkinson's patients.

But the thing is clozapine has a property that suppresses its own dyskinesias. They showed that clozapine increases a marker for something like c-fos much more in the limbic area than in the striatum where haloperidol does both. Maybe this is how clozapine inhibits its own induction of dyskinesias. Seroquel also inhibits dyskinesias. How? Is it 5HT? Well that's what we say but it also has effects on norepinephrine.

What about calcium channel blockade? People always focus in on alpha receptors or 5HT or dopamine systems but there's a whole lot of other things such as sigma receptors and calcium channels. Jerzy Vetulani and his group recently showed that if you give haloperidol to rats chronically you can show very marked withdrawal dyskinesias. But if you give pimozide you don't have the same problems at all. Why not – well it's a calcium channel blocker.
It could be anything. We've looked at calcium channels. One of the things about verapamil was they used to say it never got into the brain, whereas it's now clear it does. If you take something like verapamil, you can block out L channels but if you still look at the neurones current is still flowing. If you take conotoxin then, you can block out the N channel but there's still residual current flowing. So when we got into this area we recognised there's still residual current through what we called the O channel – O for other. This was done by Richard Keith at Zeneca. They are called RP channels now.

You need calcium to release transmitters and the calcium that releases a transmitter is working either through an N or an RP channel but not through L channels. We found that the RP channels are good at blocking the release of glutamate, where the N channels were better at blocking the release of norepinephrine. So yes there probably is something there. How you translate it I don't know. We know also that a lot of the anti-psychotics, haloperidol etc, are very potent on sigma receptors.

From what you've said, there's been three very different approaches. There's been yours, which was behaviourally driven. There's been the Lilly one, which was structure driven, and a Lundbeck and Janssen one, which was receptor driven. It's fascinating there were such different approaches. But whatever about 5 to 10 years ago, can you not now with a pharmacophore model work out exactly what it is about clozapine?
Yes it was a behavioural approach. We could have done an assay on binding but what's the difference between 200, 350 and 800 nanomoles in some binding assay? We could measure it but what did it tell you? We have all the modelling capability you describe now no question, we can work on pharmacokinetic factors and everything else but you don't still see what the difference is.

In CNS we've usually gone by sponsors. Somebody has an idea, we work on a project, get it to a point where we say okay lets present it to management to

see if they'll give us the go ahead. I think CNS has gone that route a lot, whereas asthma has gone by known receptors or known systems. It's a lot easier to develop Structure Activity Relationships around binding than structure activity relationships on behaviour, which could be subject to so many other variations. Every CNS project I've been on calls for a dual action. It's never just give me a straight antagonist.

Talking about receptors, James Black used to work for ICI, did you meet the man?
I don't know him personally I've heard him lecture here when he came over. Definitely he was a receptor man. He left ICI because they wanted him to move into management and he didn't want to do it. But ulcers are an area that's interesting when you throw in the pylori issue. ICI was very close on this. We had a great compound, a much more potent antagonist than cimitedine but it caused tumours in mice and we killed it. Some people say we got scared too soon. It would have beaten Zantac to the market.

We were very strong in CNS up till the late-80s but since then we slipped for a while. Part of it is looking at where you're going to be in the next 5–10 years. At the end of the 80s, we started structuring around genomics and built up a big target discovery group. This is the group that is supposed to identify the targets that we go for. I think initially they hoped for too much. Things were disbanded in many companies I think because they all thought genomics was going to come with targets very quickly. But targets were slow in coming. Now we're getting back to animal models and some more conventional approaches to balance off the programs. With the merger with Astra, Wilmington is going to be the site for CNS and pain research and my feeling is we're going to get back to where we're going to be a real CNS company again. The genomic work has also begun to come along nicely.

We're heavy into neurology now, going for stroke compounds. When I was working in CNS, I used to read a lot of pharmacology and try to make sense of the things and see what agents people were using to get effects and whether there was a handle that I could get from that. I've been in stroke and calcium for the last five years and as a result I've stopped reading the antipsychotic literature so much.

Every so often though when you step back from the field you can see things a bit more clearly. Working on Alzheimers and strokes might well be the way to come up with really new CNS compounds.
Yes there are a couple of theories. Marsden argued that it was a development problem affecting the learning of language. I've always been told that schizophrenia's age of onset is young adulthood, no matter what part of the world you're in. If you say it's a problem of development, then you go back to genomics and genetics to see if you can find a gene and but they haven't been able to show that yet.

People are also chasing potassium channels. That may be another area, one where you could maybe get some antipsychotics because you're dealing with hypo-polarisation. I think there's still probably hope for the channel story.

In the Alzheimer's and stroke areas, there is a difficulty screening. The models have a lot of variation and they have a very slow throughput. We heard a lecture the other day where they talked about a compound in the periphery that binds ferritin to produce a complex. Now in the case of complex molecules with two dimers, four units, for instance, if you put these into some microsomes, where PH is a factor, when the PH gets low these things dissociate. In the case of ferritin, one of the monomers, or a product of one, self-aggregates giving you neurofilaments, just like you see in Alzheimer's disease. So if the neurofilaments and the tangles are coming from a very natural process like this, by working on the kinetics of this process and just stabilising the tetramer with two molecules of mefanamic acid, which is an anti-inflammatory, it may be possible to block this process.

This is an approach that a lot of people are taking. You're not working on a receptor and you're not working on a channel, you're stabilising things. It's probably a genetic mutation in one of the monomers that allows the thing to fall apart and degrade and if you can block that and make it stable then this is not going to happen.

Given your early lead in this area what about substance P antagonists? They were supposed to be anxiolytic, antidepressant and antipsychotic. But the Merck compound has come a cropper.
Well we're up in that area too. The problem in the tachykinin series is to get orally active compounds. I think Merck probably had some bad luck in having a clinical trials with such a high placebo effect. These peptides, substance P antagonists and so on, the area of co-transmitters and how do they function. I think there's still a lot we have to learn. There's another difficulty with some of these compounds like phosphatase inhibitors. You've got a double problem which is you've got to get your compound through the blood brain barrier and then you've got to get it through another barrier inside the cell. That may not be so easy to do.

The Substance P antagonist and the D-4 antagonist stories leave me feeling there must be some scope to go into man first to find out what things do?
Well yes, it's done in a situation where your binding assay doesn't tell you anything but you have some model, say an electrophysiological model, and the compound works there. You can then go into a rat and find it does work in some way. But about all you know is that it has some effect. So the question now is will it be the same thing in man and this is probably the type of compound that we'd push forward right to man and find out if it does anything. You'd have to do some preliminary toxicity and then go to man.

Our guys took bets when we sent Seroquel off for D4 binding. They were betting that it would because clozapine has D4 but Seroquel doesn't. Compared to the D4 receptor, in the serotonin area there are even more receptor subtypes that could be important. I would guess if we had a very clean, very selective compound, we might want to go to man and try it out.

Are we leaving the era of receptor chemistry do you think?
No I don't think so. But I think you're going to have to look at other approaches too, for example this business of self aggregation and the question of prions, which is the same sort of the same sort of thing. If we ask where's chemistry going in the next decade, well the new areas are nanotechnology and making molecules that self aggregate. Very different structures which when you put them into a solution have this tremendous ability to self aggregate into channels or whatever. Now if that's a principle of nature, why shouldn't a peptide that's unfolded be in a position to do the same thing? If you're missing a chaperone that's got a folded peptide in the right place, a mutated peptide could substitute. This takes a whole different technology to assess what's happening. The principles are all on the basis of kinetics, how you can block something so it doesn't degrade too fast. Built in somewhere there has got to be genetics.

It's a question of mechanisms. We always have this argument - we've got a compound now that can suppress dyskinesias. It's gone through toxicology studies and it's clean. People will say well what's the mechanism and I'll say I don't know but what difference does it make if it works. Now you can ask the question at an early stage and start a project because you think this is the mechanism you want and you can then chase that. But if you get a compound that works then why bother asking that question.

Marketing people like to be able to have a slogan.
That's true but you don't want to hold back progress because you may never know the mechanism.

Sure but "it works" has never worked as a marketing slogan. They have to be able to say it does such and such – its got to sound like the latest science.