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Approaching rationality?

How did you start in the area?

I started as a chemist and oddly enough I've ended up in exactly the same field I started in. I did a PhD on alpha-adrenoceptor antagonists, as they then were. We didn't know about Alpha-2A, 2B, 2C and presynaptic control of catecholamine release was still to be described. That was from 1962–1965 which seems an awfully long time ago now. I went to the University of Hull, which had a chemistry department that was well known for its pioneering research in liquid crystal chemistry. I did a PhD in chemistry and pharmacology because Reckitt and Colman was still a very active pharmaceutical company in those days and they were just down the road.

Then I did a post-doc in the US with Alfred Burger. He was an Austrian who emigrated to the US in 1929 and worked initially for a government organisation located in the University of Virginia. When the Drug Addiction Laboratory moved to Bethesda he stayed on at the university and became Professor there eventually. He invented the concept of medicinal chemistry.

Which is what.

The study of the design of drugs, looking at what structural features are important for a particular type of biological activity and trying to predict biological activities from chemical structure. In a nutshell, it's the relationship between the chemical structure and biological activity and trying to manipulate the structure to modify and further refine biological activity. It used to be called pharmaceutical chemistry and chemical pharmacology but the phrase that was eventually settled on was medicinal chemistry. When he and Arnold Beckett founded the first journal in the field in 1959, it was called *The Journal of Medicinal and Pharmaceutical Chemistry*. This was renamed *The Journal of Medicinal Chemistry* in 1963, which is now the major journal in this area. It is now published by the American Chemical Society, so it's still perceived as part of chemistry rather than part of biology. Burger was the founding editor and he remained editor for 12 years. In the 50s and 60s, he was the doyen of medicinal chemistry worldwide. In 1951, he wrote one of the first and now the standard textbook, *Burger's Medicinal Chemistry*. This is the equivalent of

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Gray's Anatomy. Other people write it now, of course, but although he is now over 90, he's still active reviewing books, refereeing papers, writing occasional articles. He still has a very good mind. In those days, in 1965, if you wanted to work in medicinal chemistry he was the person to go and work for.

Structure-activity relationships were a big thing in the 60s at CINP meetings etc but today you only hear about 5HT-2 receptors and alpha-2 receptors – people like me would never hear about the actual structures.

They still are a big thing. If you go to medicinal chemistry meetings or chemical meetings you will certainly hear about the structures. I think the accent in psychopharmacology meetings is much more on the functional end. But, using much more sophisticated technology than in the past, people are still trying to relate structure to function. These days we have the ability to model complex structures like proteins and to manipulate their structures on the computer screen. Modern medicinal chemistry is very much about visualising the structure of an enzyme perhaps and finding the active site and then searching databanks for molecules that will fit that active site and then going away and making those molecules or their analogues. But the basic idea is still to relate structure to function.

Peter Waldmeier suggests that there's only so far that can go¹. Chemists can optimise for one or two things but once you get into optimising for 3 things there's problems and because of that chemists don't like the dirty drugs, they like the clean, the specific and maybe they're making a mistake.

It's degrees of complexity of course. It's easy, as Peter said, to identify and manipulate the structural features that will determine one or two biological factors but as you move on to 3 or 4, the interactions between them become more complex. It's fairly easy these days to sit down and design a serotonin reuptake inhibitor but we don't need another. What you really need is the innovative leap in concepts. If somebody were to say depression is due to some change in glucocorticoid receptors, for example – the chemist is the servant of the biology in this instance – the chemist will come up with any number of possible structures. But somebody has to have that innovative idea that this is the target we are going for. The first lead is what you want to find.

If you have got an unusual target for which there are no known active compounds you have to find a lead compound which has some sort of activity. There are large scale technologies such as combinatorial chemistry, which are very heavily touted these days as the answer to the maiden's prayer, to identify a substance which is active at a certain level in your biological assay. People thought it would be the death of traditional medicinal chemistry but of course all that these very capital intensive programmes do is identify a compound with some activity. That is not your drug. Having found it, you have to do tra-

¹see Waldmeier P in The Psychopharmacologists Vol 1

ditional medicinal chemistry to modify that compound to the drug that you want. So medicinal chemistry as it was in the past still exists, although it's been overtaken in the screening stage by these very highly sophisticated techniques.

So you went to Virginia. What was Burger like ?

I went to Virginia for 2 years. He was really nice, hospitable, very slight in build, a very sharp mind, highly interested in the arts especially music. When I went he must have been nearly 60, so he was nearing the end of his academic career. It was a very interesting lab. The University of Virginia is an old traditional southern university. It looked like a scene from *Gone with the Wind* with marble columns and town houses. The town of Charlottesville, in those days, was 35,000 people and when the University was in it was 50,000. The students were very elegantly dressed. These days it's a modern University with a top academic hospital and a very fine law school. Charlottesville is a much bigger town although it still has the same charm as it did in 1965. The Chemistry and Pharmacology Departments were housed in an extremely ancient building. You'd come in at night and the cockroaches would dash away. The facilities were not exactly the best. When I went back 2 years ago it was unrecognisable because there were new buildings, new equipment everything. But in my day it was still very much a traditional, very old lab, of the sort you would associate with Britain.

Surely this was the kind of man the industry would have been supporting.

Yes they did. He had a very long standing relationship with SmithKline & French to the extent that my first year was financed by a fellowship from SK&F working on sympathomimetic agents. He had quite a number of advisorships with pharmaceutical companies but his main research support money came from SK&F in those days. Because of his contacts within the pharmaceutical industry in the US, he could place his students. There is a sort of Burger's old students group now in the American pharmaceutical industry – so his influence is much greater than it might seem.

This doesn't only apply to Burger. Certain individuals with a good reputation attract students or Post-docs and if it is well accepted by the industry that these father figures are good trainers of people, they can get their students placed everywhere, so they have a much greater influence all over the industry than it would seem at first sight. Burger is a fine example but you can think also of people like this in the UK. A lot of people will go and work with Sir James Black for example. He's that kind of figure because he has worked in the industry before. He has got good contacts. He is a famous figure and he was responsible for sub-classifying 2 or 3 of the major receptor families, beta receptors and histamine receptors, for example.

Was Burger responsible for any receptors?

Well he was responsible for the whole science of medicinal chemistry as I've said. And also Tranylcypromine is Burger's drug. He synthesised it in the 50s

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and later of course it was an SK&F drug. It came onto the market in round about 1960. He was interested in cyclopropane chemistry and this was just one of the things he made.

I've thought for a while that tranylcypromine is one of the most interesting compounds around. Have we dismissed it as an MAOI? In actual fact in extremely low doses it inhibits monoamine oxidase completely but this isn't enough to get some people well who at a higher dose do get well. So between that and isoniazid which has been shown to be antidepressant but is not a monoamine oxidase inhibitor at all, have we been too synapto-centric, calling these things monoamine oxidase inhibitors, and thinking because of that that we know what they are?

I think that drugs tend to get labelled and people forget that they have a spectrum of effects. We always try and classify things. But by grouping disparate drugs together you often forget that drugs like Tranylcypromine can be something entirely different than an ordinary monoamine oxidase inhibitor. This is also the case with the group of SSRI's now and the group of double action antidepressants and within these there are individual drugs with a very diverse pharmacology and action. I like tranylcypromine although it has fallen out of favour. It was never used very widely but it's a very good drug. It has almost a psycho-stimulant action. The original chemical publication was in the Journal of Medicinal Chemistry in the early 60s and it's still on world markets.

There was another famous drug that emerged from Burger's research activities, in my second year in Charlottesville. It was the heyday of the Vietnam War and I was drafted because I was on an immigrant visa. I was called by the draft board and classified 1A for immediate shipment to Vietnam but my wife just happened to be pregnant and I was re-classified to 3A. Fortunately I avoided it. But anyway in my second year, because of the Vietnamese War they had a lot of falciparum malaria resistant to the then standard drug chloroquine. So the US Army instituted research at the Walter Reed Hospital and were pouring large funds into chemical and microbiology labs to develop new anti-malarials. We worked on a series of compounds, one of which became mefloquine, which is now the standard one shot prophylactic. Our publication came out in 1968 in the Journal of Medicinal Chemistry. Mefloquine is the one that's causing all the problems with psychotic reactions that you've read about in the press. It's been on Watchdog and other programmes. It was financed by the US Army within a World Health Organisation context but they had to have a company to market it which was Roche. So it's not a bad record to get 2 major drugs out.

You worked on alpha receptors – before they became alpha 1 and 2 ?

Ahlquist had already suggested in 1948 that there were possibly 2 types of adrenoceptors (α and β) but it was not until 1973 that Delbarre and Schmitt proposed a subdivision into α_1 and α_2 . Pre-synaptic control of catecholamine release was absolutely unknown. That was a 1970s concept. Sol Langer really invented pre-synaptic regulation. His first major paper about pre-synaptic reg-

ulation via auto-receptors appeared in 1973. In 1965 there were simply alpha receptors but now of course we have α_1 and α_2 , sub-families, hetero-receptors and we have all these complicated inter-dependencies of neurones which rely on one neurotransmitter for their main actions but are also influenced by other neurotransmitters. In the context of depression also, noradrenaline and serotonin have lots of interactions with each other in the brain.

After Virginia, what did you do? How did you end up in the industry?

After returning to Britain I worked for 7 years in the Chemical Defence Establishment in Porton Down on hallucinogens and dopamine agonists. I had quite a nice research line in hallucinogens. We did a lot of original work looking at structure activity relationships of hallucinogens, and published the definitive paper on the ecstasy type molecules in 1974. The military world-wide, especially in the US, were interested in the dangers of hallucinogens being used to incapacitate soldiers in the field. Counter measures were required including antidotes. To design antidotes you needed an awfully good understanding of what hallucinogens were and what they did in biological terms. Now we realise that 5HT receptors are involved in the actions of many of them. This period included my first contact with Brian Leonard, then an earnest young pharmacologist at ICI². He visited Porton Down and we discovered a mutual interest in psychopharmacology after his lecture. I supplied him with a number of compounds for his research work. Unfortunately, and we still joke about it today, he failed to acknowledge my contribution in his subsequent publication. Nevertheless, an inauspicious start was the basis for a friendship which has lasted.

The other strong interest was dopamine as a result of the military's interest in emetic agents. I did a lot of work on dopamine agonists. I got associated with all the Parkinson groups and worked a lot with Brenda Costall in her early days in Bradford, with Leon Goldberg in Chicago and David Marsden and Peter Jenner in London. I collaborated with Geoff Woodruff who was then in Southampton and also with Les Iversen and Alan Horne in Cambridge. With that group we worked on what has now become the D1 receptor. We didn't know in 1973 that there was a D1 and D2 receptor but the structure activity relationships of the compounds that I provided them with were so strange that when you look back you can see that it was two receptors we were dealing with.

That work was all going very nicely but my wife and I got fed up living in England and we wanted a change. Adis Press, which was then called the Australasian Drug Information Service offered me an interesting position and transported us to Auckland. But we didn't take to life in New Zealand – it was too far away, too isolated. After a while we decided we were Europeans and we wanted to come back. In New Zealand you were always treated as an immigrant, whereas we didn't feel we had emigrated; it was merely another

²see Leonard B in *The Psychopharmacologists* Vol 1

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job and a step in one's career. Anyway I wrote to many friends in industry and academia, one of whom, David Savage, who died a few years ago, worked for Organon in Scotland. I had met him at a medicinal chemistry congress years ago in Lyon, when I lost my baggage and he lent me a shaver and so we had known each other a long time. He passed my letter on to Organon International and after a few negotiations and interviews in Australia and Holland they offered me a position. So we came back in 1977. I had several other job offers but this was the most interesting position which was to ultimately manage world-wide CNS R&D. They were just about to change their research structure to therapeutic area programmes so I suppose my application arrived at the right time. Life is about being in the right place at the right time.

Mianserin, historically I've always thought has been one of the most important psychotropic drugs. It links back to drugs like cyproheptadine. It catalysed a change to a receptor mode of thinking within psychopharmacology yet, just like tranylcypromine in a sense, it cannot be pigeon-holed in terms of its receptor profile and of course difficulties surrounding its use provoked one of the most important regulatory debates in recent years. You joined Organon soon after the Mianserin story started, didn't you?

I joined Organon in March 1977 by which time the drug was on the major markets. It was already becoming well established, particularly in places like the UK, where it had been introduced in 1974/75. It was first synthesised in 1966 as an attempt to make a better anti-allergic drug. The chemist, Wim van den Berg, tried to combine the structure of an anti-serotonergic drug – cyproheptadine – with an anti-histamine – phenbenzamine – and succeeded quite well. It began life, in fact, as an anti allergy drug. It was tested in asthma, in migraine and it is effective there. Patients in the first hospital study for asthma felt reasonably happy on the drug, more happy than they should have done and astute clinicians realised perhaps this might represent a psychotropic effect. So the drug was subsequently investigated for antidepressant activity.

Where did the EEG profiling come into the story?

Pharmaco-EEG was just beginning as a technique for detecting the activity of drugs and it was used to look at mianserin which displayed the same sort of EEG profile as an antidepressant, like amitriptyline. That helped in deciding that it could be anti-depressant. In fact, Itil, the Turkish-American guy who did that work, I believe, tried to claim the credit for having discovered mianserin, but I think the psychotropic properties were already evident. But this happy coming together of some scientific evidence and a bit of astute clinical observation pushed the drug forward at the time. Subsequently we have used pharmaco-EEG for profiling our potential psychotropics. Max Fink was our adviser for many years and he suggested that ORG 3770, which is now mirtazapine, had an antidepressant profile. We have also developed an extensive rat EEG system for pre-clinical evaluation.

So it was about 1970/71 when it began to switch over to being an anti-depressant?

The company had a 50th Jubilee in 1973 because Organon was founded in 1923 and they desperately wanted to have a new drug registered, launched and preferably something which was outside the company's normal insulin-related, steroid-related activities, so a CNS drug they thought was great. They had a symposium in 1973 to celebrate the 50th Anniversary of the Company, focusing on Mianserin. It was a bit early I think. There might have been a bit of pressure to get everything ready for this symposium and I think the data were a bit deficient at that time. Although the data were subsequently quite sufficient for gaining registration in the UK and in places like Switzerland and Germany.

What went wrong in the US.

The US is an interesting story. I think the file as it existed in the mid-70s as used in Europe was insufficient for the different conditions in the US. The studies that had been done, by today's norms, you would not regard as of very high standard and the FDA even in the 70s was quite exacting in its demands. A clinical trials programme had been initiated by Akzona, which was the American arm of Akzo, the parent company. Organon Inc. operated virtually totally independently in those days of Organon International as it was in Oss. They took their own decisions, although they obviously consulted Organon International. They were relatively inexperienced in psychopharmacology and they put themselves in the hands of Donald Klein, then and now a very distinguished psychopharmacologist, who advised them on a set of investigators including John Feighner and Tom Ban. They started a series of studies which included amitriptyline control without placebo in seriously depressed patients, the sort we would still take into trials today. It's a shame it wasn't placebo controlled as we would do today. It was amitriptyline controlled because Klein advised that mianserin was perceived in America and in some parts of Europe as a sedative anxiolytic rather than a hard core antidepressant and that it would be quite difficult to demonstrate the drug was better than placebo.

He suggested a special placebo-controlled study to test the hypothesis that anti-depressants would be effective in endogenous depression and not in chronic dysphoria or disappointment reactions. In a way this had a good scientific rationale but it was inappropriate for registration of a new antidepressant for major depressive disorder. He designed a study where people entered with Hamilton's between 4 and 18. We now know, and I think we knew then, that between 12 and 18 is the most difficult group in which to demonstrate placebo, antidepressant differences and it is almost in principle impossible between 4 and 12. It was a nice hypothesis to be tested from the psychopharmacological point of view but it was inappropriate for a new antidepressant. Donald Klein felt at the time that he would still be able to convince the FDA that Mianserin should be registered for the treatment of minor depressive dis-

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orders as they were then. We disagreed. The study was subsequently published in 1985 in Neuropsychobiology, with the amitriptyline study appearing a year earlier in the same journal.

When the parent company, Organon International, took over responsibility from Akzona in 1981, it was realised that the file being generated in the US was not appropriate for the registration they hoped to get for the drug as a major antidepressant. Subsequently new studies were started and completed, some of which have been published, very fine up to date studies – placebo as well as active control, big groups of patients – the sort of thing we would really do today for any modern antidepressant and Mianserin turned out to be very effective in these studies. If we had not had Mirtazapine coming along at the same time, we probably would have filed an NDA for Mianserin in the late 80s or early 90s.

So we ended up with the oddity that a drug which was the best selling antidepressant in quite a few European countries wasn't registered for the US market at all. @First Para:

I think it had a very unfortunate history in the US. If Organon Inc had got the studies right in the early 80s, I think you would have seen mianserin as a major drug in the US market. As it turned out, Trazodone, which in my opinion is an inferior drug even though it is an anxiolytic sedative type of antidepressant like Mianserin, was the first new non-tricyclic antidepressant in the US. When you look at the new drugs that are coming out, they are all better than Trazodone but Trazodone made a great splash in the US, because it was simply the first that was different. Mianserin could have been that first one. So US psychiatrists don't know the profile of Mianserin or the concept of alpha-2 antagonism, which may be advantageous for Mirtazapine.

One of the things that Mianserin partly did was to help catalyse the change to a receptor view of things – partly perhaps because it came at the right time, partly because it had no effects on reuptake or on monoamine oxidase.

Up until then people had focused on noradrenaline and serotonin – we still do, I think we are stuck in a time-warp really. It all comes from the fact that all our new antidepressants and all our thinking about depression is based on the old work about reserpine and catecholamines and we can't get out of this vicious circle we're in. I am sure one day we'll come up with an antidepressant and it will have nothing to do with noradrenaline and serotonin. But until Mianserin, people thought in terms of uptake and monoamine oxidase inhibition. Mianserin was the first drug where people had to think about a receptor approach – still focusing on pre-synaptic events but on release mechanisms in a totally different manner than uptake. This ushered in an era where people focused more on receptor selective events. I think drugs like venlafaxine and milnacipran are the Last of the Mohicans in terms of the uptake inhibitors.

While it helped to change things and to usher in the alpha-2 and 5HT receptors and all that, do you think we have become too much synaptocentric? We think because we know

this drug blocks alpha-2 and 5HT-2 receptors for instance, that we know what it does. But Mianserin in one sense is another of these drugs that tear up the receptor copy book when you hear that the Japanese are using it for delirium – you would never predict that thinking about it just in terms of receptors.

Oh course it has a lot of pharmacology attached to it – it's an antihistamine, it interacts with various serotonin receptors. If its any one thing it's probably an anti- serotonin agent. Multiple pharmacology can lead to multiple potential uses.

Is there a difference between it and Cyproheptadine – which for my money is another of worm-holes in the psychotropic firmament, which if followed can lead to a totally different universe.

As I've said part of its structure was based on cyproheptadine, so the essential structural elements of cyproheptadine are in the molecule and, like cyproheptadine, mianserin was often used for increasing appetite in people who are seriously under-weight. This is a common property of what we now know as 5HT-2C antagonists. It looks as though the 5HT-2C receptor is involved in the control of appetite and weight – 5HT-2C agonists would be fine anti-obesity agents and may be responsible for the anorexic effects of the SSRIs. In those days of course we just knew about serotonin receptors, we didn't know about sub-classification. That's another thing that has happened in the last 15 years which has really got the whole antidepressant receptor specific approach off the ground as people are now looking at drugs which will interact specifically with sub-sets of receptors.

Well that raises a point that was made by Claude de Montigny in a plenary lecture at this meeting when he made the claim that we have left serendipity behind and we're into the rational design of treatments but are we?

I still think it is very much serendipitous. I think most drug companies these days run programmes where they identify target mechanisms that they are interested in – it may be a receptor or an enzyme. Then they scan millions of compounds because people are now using combinatorial chemistry where you synthesise very small amounts of very large numbers of compounds and you have a high throughput robotised screen that goes 24 hours a day, 7 days a week. Companies build up huge databanks of millions of compounds in this way, but they've identified before that a target mechanism. So in one sense it is much more rational, but that target mechanism is based on current knowledge. In depression you might do it for say a certain type of serotonin receptor. To make that quantum leap to a totally different mechanism you have to take something quite unknown, which might not have any connection with depression and screen the compounds past this. That then is a form of serendipity because you don't really know what you are in for – whether it's going to work in depression or something else.

The ability to screen very large numbers of compounds means there is a lot of structural diversity but narrowing down to one target means there is a risk

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that you are going to miss some of the old chance findings where pharmacologists in the lab were working with a group of compounds and found something quite unexpected. That chance has been lessened by modern drug screening techniques. Combinatorial chemistry has been likened to the search for the same needles in even bigger haystacks.

Does the capacity to design things so easily leave you increasingly vulnerable to the claims-makers in the field? For example, two or three years ago there were big claims made for the D-4 receptor in Schizophrenia, made by one of the senior figures in the field. This looked good for a while and at least one large company went out and did trials on a D4 receptor antagonist, showing if anything it made schizophrenia worse. The field is repeatedly assailed by this sort of claim. Are you likely to get de-railed even quicker because these days you can go on to test these claims out because of your ability to design drugs as readily as you now can.

I think psychopharmacology like most fields in medicine has always been subject to and will still be the subject of speculation and claims – there are fashionable areas of research. If claims are made by the appropriate person of high reputation, they will be followed and believed and drug companies will actually go out and design compounds which have the requisite specific properties. Often these things take you down a blind alley. I think the finest example in recent years has been the 5HT-3 antagonists. A very nice concept. It all came from Gaddum's work in the 50s on the then M-serotonin receptor. The 5HT-3 antagonists were specifically designed to work in emesis – and they are the best thing since sliced bread for chemotherapy induced emesis.

There was a whole series of experiments, mostly carried out by the group in Bradford of Brenda Costall, indicative of an antipsychotic effect, as well later of an anti-anxiety effect and an effect on cognition. And these were shown in nice animal paradigms which we all believe are predictive of antipsychotic effects or effects on cognition. Testing in the clinic has gone on for the last 8 or 10 years but one by one the indications for psychosis, anxiety and for Alzheimer's or old age memory impairment have fallen by the wayside. One has to ask oneself does this mean that the animal paradigms we use are not very indicative or were people over-enthusiastic – did they extrapolate the animal data much further than they should? It's a very difficult point to tease out but certainly 5HT-3 antagonists for CNS indications have been a major disappointment for Glaxo and some other companies. I think there's a lesson to be learned there. I think we shouldn't over-interpret our animal data. I think animal models of CNS diseases are very far from the situation in the human. We still don't know what most CNS diseases are in neurobiological terms and to try and reproduce in a behavioural model or even in a simple biochemical model in animals what you think might happen in schizophrenia or in depression or Alzheimer's is probably stretching the science a bit far. We have to have these models and hypotheses to test but it was a little unbelievable that the 5HT-3 antagonists would work in every psychiatric condition known to man. Ondansetron may actually have some psychotropic effects but insufficient to justify an indication as an antipsychotic, anxiolytic or cognition enhancer.

But isn't the issue also that it was the claims of one group in essence that really made the issue.

That comes back to the point that if the group or the personality of a member of the group is so strong and influential in science they can override the objections of others and even in this case override the caution exercised by major pharmaceutical companies in their investment in a project. And the whole project sort of fuels itself. At every conference that you went to, people would talk about ondansetron in this and that indication. Then it all went very quiet as slowly the news emerged that it wasn't an effective antipsychotic or a useful anxiolytic and that it isn't very good in cognition. There was a presentation in this meeting (ECNP 1996) by Mike Palfreyman who was involved in this research when he was at Merrell Dow in Strasbourg – in fact it all began there with John Fozard. Anyway he admitted that of the wide range of CNS indications they might be suitable for, nothing had come out. This was a fine example of the way individuals or groups of individuals can push along an idea, which is taken up and people run with the ball for nearly 10 years.

Mianserin began running into trouble around the same time as Nomifensin.

Before Nomifensin. Mianserin had a long history, particularly with the British, although other countries like the Germans for example kept it under surveillance for quite a long time. The first case of agranulocytosis was reported in 1979 in the BMJ and slowly more cases began to appear. We had a number of cases in our pharmacovigilance/product surveillance – not enough to be worried about taking the drug off the market or anything. Organon was very responsible and when the first case came in the package information was changed and slowly the warnings and the precautions became stronger in the product information. I think the problem with Nomifensin and Hoechst was that they were overtaken by events. They must have waited until there were sufficient cases of haemolytic anemia for it to be seen as a major problem and at that time they hardly had anything in their package information.

On the other hand it was quite an interesting development because in the UK the CSM tried to restrict Mianserin to the treatment of patients in whom anti-cholinergic effects were unacceptable – people with very severe reactions to tricyclics, old men with prostate problems for example and the elderly particularly with problems with tricyclic anti-cholinergic effects. We fought that proposal very hard at that time because we believed the risk-benefit ratio was very much in favour of the drug. I think companies should always do that if they believe they have got the benefit-risk ratio on their side – even if the drug has a major rare side-effect. You have to balance that against the relative benefits and the benefits within the class of drugs in which the compound exists. At that time, in the early 80s, there were no SSRIs and so mianserin was in a class with nomifensin, trazodone and the tricyclics and we fought the issue on the basis that mianserin had a well deserved reputation for safety in overdose. The same should have been done for nomifensin, which was a very useful drug especially in the elderly and quite benign in overdose.

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We had very rapidly to generate data from mortality statistics of the OPCS in the UK, which every year publishes tables of causes of death including suicide. You can find out which drugs are associated with suicide and we could at the same time look at the company sales in kilograms of drug and the defined daily dosages and duration of treatment and come up with a very crude estimate of the number of deaths per million patients.

Where did The Fatal Toxicity Index come from?

Well the Fatal Toxicity Index was John Henry's invention. He did a very fine job on looking at data both in England and Wales and Scotland – but he had access to the NHS prescription database. He combined that with exactly the same data as we did – OPCS mortality statistics – and came out with the Fatal Toxicity Index, showing that the old tricyclics were very nasty, causing about 30-50 deaths per million prescriptions whereas a drug like Mianserin was near the bottom with single figure deaths. We were doing this, I guess, simultaneously with John as he published in 1987, while Stuart Montgomery and I had a letter to the editor of Psychopharmacology published in the same year. There was a remarkable consistency between his data and ours. Obviously our individual figures are different but the rank order of toxicity was identical. So we used the data in our discussions with the authorities. I think that idea of looking at the whole benefit and risk ratio and the whole pattern of what a drug is doing has become firmly embedded in the psyche now. People are not prepared to take drugs off the market for a side effect and I think authorities have learnt their lesson that they shouldn't just focus on one side effect but should take the whole profile of the drug into consideration within the context in which it is used.

Why was the CSM so awkward?

Well the CSM and then the Medicines Commission didn't want to accept that you looked at the whole benefit risk ratio. They focused entirely on the fact that Mianserin produced agranulocytosis and that's dangerous per se.

Is the rate at which it actually does that much higher than for tricyclics?

I think it's probably comparable to tricyclics although getting at tricyclic data is very difficult because none of it is reported any more. Tricyclics were available long before the Dunlop Committee and yellow-card reporting and doctors are so used to the fact that they produce blood dyscrasias that they never report them anymore but if you go back to the old literature of the 60s, there are a lot of imipramine, amitriptyline and clomipramine cases. In contrast, new drugs are particularly focused on and I think these days agranulocytosis will be reported for new drugs if it's seen. In my opinion mianserin was not very much different, there may be a slight increase compared with the tricyclics but we couldn't get that data and so we were working on our own problem and trying to relate that to the benefits of the drug in terms of overdosing. But the CSM and the Medicines Committee were very obdurate. They interpreted the law very tightly...

Why?

I don't know. Most of the clinicians on the CSM are not psychiatrists but I don't see why any clinician cannot see the argument of balancing what is a major risk in that therapeutic class and in that particular type of patient – suicide and overdose – within the overall profile of the compound. Balancing the benefits of a drug which was safe in overdose against its potential danger in terms of agranulocytosis. They listened politely but they didn't accept the case. I really don't know, even to this day, why they were so obdurate about it because in the end we were so convinced about the merits of our case that we actually took the Health Authorities in the UK to the courts. At that time the British hadn't taken the European law on medicines into their legislation so potentially it could have gone on for a very long time but we won in the High Court.

There were very expensive and long discussions in court over whether overdose is to be considered. The British law at that time stated something along the lines that the authorities should consider 'drugs in the dose in which they are normally used'. They strictly interpreted that as an overdose is a dose that is not normally used and so they could, therefore, not take the overdose argument into account. But in fact the Judge ruled that you should take overdose into account in depression. The British authorities appealed to the Court of Appeal, so we went through another very long process.

What was in it for them to appeal ...

A point of principle I guess. The scientific debate, which obviously went on outside regulatory circles in psychiatric congresses and so on, had accepted the argument that suicide and overdose fatalities are an important aspect of depression. The CSM even produced in their regular publication *Current Problems* a review of mianserin and agranulocytoses where they actually published a league table of ADR fatalities per million prescriptions for all available antidepressants and we used that data and stacked it up alongside the Cassidy and Henry generated overdose data and you could see that the total fatality index was much greater with other antidepressants. This should have convinced them because this was their own data on ADRs along with other quite independent data on overdose fatalities. Nevertheless they appealed to the Court of Appeal where they again lost and were refused permission to appeal to the House of Lords, which they intended to do. The Appeal Court judges decided enough was enough. In fact, it could well have ended up in the European Court because as I have said European law was different from the UK law at that time. It then stopped and we made a minor change in the package information which could have been achieved without all this fuss, many years before.

We have had another illustration in the company recently with third generation oral contraceptives and venous thrombosis. Here the MCA have taken a very strange attitude – treating it as a public health hazard. OCs were restricted overnight with very little time for the company to present any evidence. It should have been dealt with like the mianserin case should have been dealt

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with, in my opinion, by a proper discussion and the company agreeing to make the appropriate change in the product information. With the OCs what you have had is a well accepted risk – there has been an accepted incidence of venous thrombosis over the last 25 years. These new studies, although they demonstrated for what ever reasons, apparently a 2-fold increased risk of venous thrombosis with the third as compared with the second generation OCs, that 2-fold risk was still within and below the old accepted risk. So it wasn't that there was a new enhanced risk for which immediate action must be taken. What had happened was the risks for the older drugs had gone down and the risk for the newer drugs seemed to be like the older drugs were 25 years ago. This may be a cohort effect and a prescription bias. New, young and at-risk women receive the third generation OCs and it seems as though women may get a thrombosis when they are first exposed to a surge of oestrogen either when they are pregnant or when they first get an oral contraceptive. So the generally older women who have received second generation OCs are in essence healthy users and are less likely to experience a thrombosis. Recent epidemiological evidence suggests that when such biases and confounders are corrected for there is no difference in risk for venous thrombosis. Furthermore, the risk for acute myocardial infarction seems to be less for third generation OC users.

So why did this extraordinary fuss happen – it was front page news on the newspapers in the UK. There was severe criticism about the way the MCA went about it and the interesting thing is that it's your company again.³

I have been heavily involved with this and it's so reminiscent of the mianserin case where actions were going to be taken of a public health nature when the data did not suggest that degree of urgency. I think the OCs are even worse than the mianserin case because here are drugs which are used by healthy volunteers in essence, whereas mianserin is a drug used by sick people. The MCA acted in a way that caused panic. Not only did women stop using third generation OCs, they stopped using OCs altogether and there has been an increase in abortions in the UK and in other countries where it happened. The only other country which took precipitate action was Germany. In the rest of the world it has been treated in the way it should have been treated with a change in the product information.

The UK action has in fact destroyed confidence in contraception, which is a major thing to do over such a trivial business. The perception of women in Europe to oral contraception has changed. There is resistance to what is a fairly safe group of drugs, which has come about purely by the action of one Health Authority. But the discussion is still on-going. The CPMP, the

³on Sat 2nd Nov, the Guardian newspaper in the UK reported that UK official statistics indicated a 7% rise in abortions and a 25 % increase in live births for the first 3 months of 1996. Abortions in England and Wales were 2,688 higher in the first quarter than in the same period in 1995.

European Authority, believe that we were right. We are still supplying data to the CPMP and one of these days there will be another discussion. A lot of distinguished epidemiologists are studying the problem and publishing data and I believe in the end we will win through. But to come back to your point about why Organon and why .. twice

And mirtazapine has now been licensed in the US, which is supposed to be the hardest arena to enter but is still not licensed in the UK...

I don't believe in conspiracy theories but yes we feel again the demons may be working against us because we still haven't got a UK license. As you say, if you talk about the countries that are usually regarded as having the most stringent regulatory authorities, the FDA in the US and the British, the Swedes and the Australians, well we are approved and on the market in the US, we introduce in Sweden in October (1996) and Australian approval is in, but we are still arguing with the British about the benefit and risk ratio.

We have had one symptomatic neutropenia which we think is possibly attributable to the drug in our clinical trial programme but we also had one with imipramine. The FDA handled it in a very sophisticated way. They accepted that this happened. It's in the labelling, in heavy type. They even quote a so-called incidence of severe neutropenia but it's obviously difficult to quote an incidence on so few patients. But they thought the drug was of sufficient value and novel with good data on efficacy that they were prepared to accept it with this risk. Indeed the FDA Psychopharmacology Advisory Committee thought that the efficacy part of the file was among the strongest that they had seen in terms of positive studies. And that has been the case in most of the European countries and Australia, but the UK and France are still being difficult about it. One of these days we will go back to talk to them when we've got much more pharmacovigilance data from Germany, for example, where it's been on the market for 4 or 5 months. There has been no symptomatic neutropenias in the 50,000 patients we have treated in the last 6 months, so the incidence is falling. Trying to explain the situation to British psychiatrists is very strange.

When the mianserin story was building up a head of steam, as I remember it some German pharmacovigilance group wrote 'asking what you going to do about it' and you mentioned the issue of overdosage to which they replied that they weren't interested in overdosage because suicide isn't legal. I used to tell this as a comment on German 'principles' but the MCA attitude seems even more strange.

This was Moebius and his famous Arzneimittel Telegram, a monthly newsletter that is put out in Germany, highly critical of the pharmaceutical industry usually. There is a clinical pharmacologist associated with Moebius, Schönhoffer who is Professor in Bremen, and the two of them are part of the anti-industry group in Germany. They've popped up again in the OC business; they had a long running campaign against Schering but we have been caught in the flak. But yes they had a very big go at Mianserin in the 80s with

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messages in their newsletter, calling upon the German authorities to take it off the market.

They wrote to us, as you have said, but to give them their due, they did accept that there was a case to be made although they maintained their point of view. The suicide point was actually made but in fact it was almost exactly the same with the CSM. It was a very fine legalistic point to argue. I think in discussions about drug safety anything of relevance to the benefits and risks of medication should be on the table to be discussed. If the law has some fine points which can be used to eliminate public discussion I think it's incumbent on a body like the CSM not to focus upon those elements. I think the company's view was that they were eliminating the discussion of a proper topic which is very relevant to the use of antidepressants.

Since 1962, regulators have been in the business of trying to persuade the industry to produce drugs which have a good risk benefit ratio and they achieve this partly by restricting them to a disease indication. In contrast before 62, the drugs that people wanted weren't necessarily disease based – they wanted a tonic or pick me up or an anti-halitosis drug. Now if you look at what actually happens today, the OC market is not a disease based market and it's not clear that steroids for minor skin complaints or nasal inhalers for rhinitis are disease based – these seem more a discomfort market than a disease market. So drugs work but not necessarily for disease indications which sets up a conflict with regulators taking a very purist or categorical view of things. Medical people such as Juan Lopez-Ibor or Pierre Pichot will still say we should have to make a diagnosis and that we abandon the medical model at our peril but is the industry being tied to a medical model, when this is not the way drugs are developed and it is not clear that that is what people want.

I personally think that things like homeopathy and alternative medicine should fall under the same rules as conventional pharmaceuticals. There should be the same standards of proof for any medical procedure be it drugs or whatever. If we are obliged for a new antidepressant to prove efficacy and safety in a large body of patients, I think it's incumbent on the authorities to ask for that same evidence for what passes as a drug and is used by many people and prescribed by physicians for the same conditions. Homeopathy is not as popular, I think, in the UK as it is in Holland and Germany for example. Germans like to take natural type of medicines and in fact if you look at the depression market in Germany it's dominated by St John's wort, which probably has a very mild euphoriant effect but it's certainly not a proven antidepressant.

But is this happening partly because of the regulatory framework. For you to sell mirtazapine, you've got to sell a disease model. You have got to tell people they've got a depressive disease before they can have it. Whereas for St John's wort you don't have to do that. They don't have to go to a person like me and be evaluated by me. They can take the stuff when they want. And there is a stigma associated with all disease models. Even if you've got a tumour, you become a diseased person, a leper of some sort. Whereas the homeopathic market is a problems of living market – its life we are talking about not leprosy.

Exactly. There is stigma associated with all disease – you're different, you're stigmatised, but I think mental illness is particularly stigmatised. People can

accept that a physical problem like a tumour is a disease, but to be mentally ill is unacceptable. Particularly with depression, where if you see surveys that have been done of the general public, like what do you think of depression, most people don't see it as a disease, they think it's something that you grow out of, a weakness of character, people who are just giving in to a stress. It's not seen as a serious treatable disease.

On this point, when I came to North Wales first there was still an old GP there who was using a lot of cyproheptadine – as a tonic. Its a perfect tonic – it will increase your appetite, improve your sleep and people would buy the idea of having a tonic and having it for a few months, in a way they wouldn't buy the idea of being depressed and needing an antidepressant. Now is the regulatory framework doing this to us?

Yes. I guess there was no regulatory framework before the days of thalidomide and companies made drugs and marketed them for what they liked. In that sense I think we are in a better situation today because drugs are for diseases rather than just out there for anyone to use and you need a prescription to get the drug for your disease. But I still think mental illness presents a major problem and I think depression within mental illness is the worst example of all because it is under-diagnosed. Doctors don't recognise it. Patients don't want to admit they've got it. They often present to doctors with all sorts of other strange symptoms which they are really presenting instead of the underlying depression.

Well if you were to ask them are you depressed, they would say no. If you were to ask them have they psychological problems, they might say yes but if you were to ask them are you a bit under the weather, would a tonic do you good, an awful lot would say 'yes'. They'd be keen to have a tonic but you can't get one these days.

Yes indeed.

Can I hop to what may be a related issue. In both Holland and Germany, to have a career in the pharmaceutical industry was a good career to have. But somewhere it seems to me in the late 1960's, perhaps associated with the 1968 events, the industry became evil and biological psychiatry in particular was a problem. Here in Holland Herman van Praag ended up being escorted by the police for his own safety⁴. What's going on?

I'm not Dutch but I think we had in Holland in those days a reaction to society like the students in Paris. There were the provos here which was a group that was very much anti-society in general, not only anti-industry. In those days psychiatry was perceived as something evil because it was regarded as a sort of manipulation of minds. I think this was a very prevalent view, not only in Holland but in many countries. Here it was particularly strong. You can see this in the interview that you had with van Praag and yes it got to a very serious stage where the more famous people in Dutch psychopharmacology like van Praag, like David de Wied in Utrecht, were pilloried in the press, were

⁴van Praag H in *The Psychopharmacologists* Vol 1

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physically intimidated and were threatened. I think psychiatry in Holland suffered for a long time. ECT for example which is a very useful technique and has never been out of fashion in the UK, was virtually banned here for 20 years and only now is there a resurgence of interest but it is still very much less used than in other psychiatric communities outside the Netherlands. You still have the feeling that here psychiatry is not quite respectable. There's an awful lot of psychology and of non-drug psychiatry practised. The general standard of biological psychiatry and drug therapy, I think is less well developed because of this history of the anti-psychiatry movement, than it is in other parts of western Europe.

How is the industry perceived.

There are only 2 major pharmaceutical companies here – Organon and Solvay Duphar. The rest of the industry is mainly local offices of large multinationals. It's quite difficult to get young physicians to join the pharmaceutical industry in the Netherlands. The industry is regarded as a good career for young managers and scientists. Dutch universities produce a lot of good basic scientists and there's not enough jobs to absorb them so we have more than our fair share of good chemists and good biologists but finding good physicians and psychiatrists to join the industry is very difficult. I think in Holland specialist physicians, psychiatrists, cardiologists and the like are extremely well paid. Their rewards outside the industry are more than their potential rewards within the industry which is a quite different situation from say the UK, where relatively it's more tempting to join the industry.

Organon have recently decided to focus on two areas gynaecology and CNS. Lundbeck have also decided to focus on the CNS only. Is this the way the companies are going – specialising on just one area.

I think it depends entirely on the size of the company, and of course on their traditional expertise and niche areas. I think companies like Roche and MSD and Glaxo can quite happily, with their size, afford to be in several therapeutic areas. A company the size of Organon, which in world terms is currently in the 30s – we move up several places each year as companies fuse above us – can't afford to be active on a broad front across all therapeutic areas. Gynaecology, of course, has been the traditional area of the company for many years. It is very much a steroid based company. Actually we do steroid based work in the CNS.

We have in fact 4 therapeutic programmes within a system of therapeutic area research. So in addition to CNS and Gynaecology, there is a small vascular programme focusing on thrombosis which also does work in stroke, which has a connection with CNS, and a small innovative experimental programme in immunology. But the company has decided that because of its past strengths, it will focus on reproductive medicine and CNS. In reproductive medicine we have the OCs but also fertility drugs and hormone replacement therapy. In CNS, depression and schizophrenia, which of course are only 2 of the many possible diseases you could study in the CNS but a small company with the limited resources it has for R&D can't cover all of the CNS diseases.

In the last year the company has made a real commitment for going for CNS as a second leg to stand on next to reproductive medicine. The other 2 programmes, thrombosis and immunology, are regarded as experimental. They may become things which we would want to spend a lot more money on if they turn out promising or they may wither away. I think it's essential for companies not to become too focused. If you become too focused and the field dries out or if your innovative compounds don't come through, then you can find yourself in very serious difficulties because pharmaceutical research is such a long-winded affair that what we are doing today in the research lab will not be on the market for another 12 or 15 years. If things do foul up you've no time to catch up before the company goes bankrupt, so you always have to have a good pipeline of compounds. The job of a research director is to see across the whole company that there's a pyramid of compounds with 1 or 2 coming into registration, 3 or 4 in phase III, 6 or 7 in phase II and so on down to the bottom of the pile. Within each therapeutic area, there should be a similar pipeline but for the overall research manager it doesn't matter whether they are gynaecology, CNS or vascular projects as long as that pipeline is adequately filled with new innovative compounds. As soon as you perceive that there's a gap, that's the time when you should take some action like licensing in a compound to fill the gap or co-develop a compound with another company.

It is fatal for the future of the company if you end up with a 5 or 6 year gap in your pipeline. This can happen by default. If there are very successful drugs like Tagamet or Zantac, they can become such a major part of the company sales that everything else goes to the wall for it and you can forget that behind it you have to have several projects coming through. For all the the Tagamets and Zantacs, its nice to have half a dozen smaller products in your portfolio which are selling in total as much as the major product because when a block-buster comes off patent, its quite a serious matter. You need to maintain the revenues to fuel the research organisation you have built up on the back of your block-buster. Some companies have been successful in living on after the block-buster, others not so successful.

At the ECNP AGM yesterday you were critical of the motion to increase the membership fee. There was also a big fuss, as you know, at the CINP AGM as well this year and at the BAP AGM, what's happening. Are all these organisations hitting some kind of crisis?

I think all organisations go through periods of crisis. I don't think psychopharmacology societies are any exception, but I think we got into a position in all 3 organisations where we had a fossilised situation almost, a coterie of people who had been in the organisation for a long time, a self-perpetuating group. In BAP the constitutional changes proposed by council and the officers would have kept all the power with those who already had it. The meeting was dramatic. Most members objected to the proposed changes. I think the CINP is the example to which the BAP would have headed if they had changed its constitution in this way. The CINP already has a self perpetuating oligarchy. I don't like organisations where the constitution allows the current committee to appoint the next president and the officers and so it goes on.

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ECNP is now the most expensive psychopharmacology society by far, which will discourage younger psychopharmacologists from joining. Lets face it, even you and I who can afford to pay the fees, are members of more than ECNP – between other pharmacological and chemical societies and so on, it adds up to quite a large sum of money. For this organisation which, after all, had a massive balance of cash and assets, to increase the yearly fees by 25% is asking a lot. It will put off a lot of the younger people from joining, who already see it as a slightly elitest organisation.

But not elitest in the ACNP sense, which they may be aiming at but rather elitest in the sense of owned by an in-group, which is exactly the wrong perception.

It is exactly the wrong perception. I was particularly upset at the ECNP AGM because I don't think there was a proper debate about the fees and the finances. They had made a decision and they wanted it pushed through. Both the BAP and the ECNP have used their journal as an excuse to increase the fees. I think one should have the right to be able to chose whether you want the journal as in the British Pharmacological Society. Many of us don't want journals lying on our shelves as personal subscriptions. I can see in the beginning of a new journal it's essential that the membership supports it, so a construction whereby for a short time while the journal gets going, you are obliged to take it would be all right but I think there should be a choice once the journal is established, as European Neuropsychopharmacology and the Journal of Psychopharmacology now are.

Coming back to the point that ECNP looks owned. This translates on the ground into a feeling that the meeting are not quite right. This may reflect the constitutional issues and the fact that ECNP isn't alive in some sense. The automatic response to that is to blame the industry.

Yes the industry has got flak at ECNP and CINP because the last few congresses of CINP and ECNP have been in the eyes of a lot of psychiatrists dominated by industry. There have been sessions which purported to be part of the scientific programme and not satellites which were dominated by industry speakers who gave the same talk in the real sessions as they did in the satellite symposia. There's a general feeling that industry has taken too big a role in the psychopharmacology associations. It's a fine line. You can't do without the industry because without us paying for exhibition space and satellite symposia, the organisation would wither away to be simply a learned society, which you don't want in fact. But there is a fine dividing line and I think Venice last year (ECNP/1995) was a good example of over-commercialisation. I think this meeting (ECNP/1996) probably got it just about right.

I think companies have to have the opportunities to have satellite symposia where they present new drugs, and exhibition space where they can pass out information. I think a situation where you separate satellite symposia from the rest of the programme where the speakers and the topics are chosen by the scientific committee is quite acceptable. But gone are the glory days when our

budgets were growing. We want to see something for what we are giving to ECNP for example. I have had the same argument with ECNP about companies' educational grants to specific symposia of interest to the company. In addition to a satellite, for instance, we might want to see our money assigned to a speed of onset of antidepressant action symposium, without the company having any influence at all on the choice of speakers, Chairman or topics. This year the ECNP committee decided that they couldn't have particular symposia sponsored by an educational grant and decided on just a blanket listing in the front of the book of the companies who have sponsored. But we are not giving money to the ECNP just to support ECNP, we are giving it to support particular activities and we have to find a formula with the psychiatric organisations and societies, where the company's support can be identified as being associated with a particular activity and not just as a general grant to the organisation. ECNP, and all societies for that matter, have to find a balance between commercialism on the one hand and pure academic interest on the other. The confusions were symbolised in a sense by a fuss that happened this year at the AGM where the recipient of a prize had problems with the fact that Lilly had their logo on the plaque for what is the Lilly Prize. If it is the Lilly Prize I can't see any objection to having the Lilly logo on the plaque. If it was my company I would certainly want the Organon symbol on it.

A theme I've had for some time is that scientific concepts don't work just because they are right. There has always been the idea that they work best when they come from Harvard, Yale, Oxford or Cambridge but there's also the question of commercial viability and in addition there's the question of the friends a concept has. For instance, the Galway panic disorder study which involved Brian Leonard and Tom Fahy was one of the best pieces of research in the field but it didn't have any friends in the sense of commercial viability. They weren't working with drugs that one of the companies was going to register for panic. Neither were they working with the non-drug lobby. They produced disinterested findings but disinterested findings have no friends. And that study has vanished.

Yes and you find people reinventing the wheel and forgetting that the study was ever done. I think it's very difficult unless you have a powerful set of friends, either on the academic side or in the industry, who will pick up the ball and run with it. The ball has been dropped with the Galway study in fact. It's best, I guess if you want a study to be well known, that you've done it with drugs which are going to be also well known.

There is an issue of friends in the whole thing. Because when Mianserin ran into problems in the UK there were a few friends who were outside the industry who came on board...

I think both academics and the industry need friends and the industry in particular needs friends in times of crisis. I think most of my job really is about creating networks, creating friends for the company who might be useful one day, people you can call upon in times of crisis, or for advice generally. With any study or drug you do need people who are going to talk spontaneously

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about your drug or study to their friends. It is important to be perceived by the psychiatric community as a serious and responsible company which deals properly with people and which thinks seriously about R&D in psychiatry.

Within groups like ECNP there is also that kind of networking but there was a stage, perhaps with the Venice meeting, when people were talking, almost openly about the networks being the wrong kind of networks. From the outside, a person might think well it was the industry to blame but the insider story was that there were networks within ECNP that the industry probably weren't too keen on either.

Yes I think within ECNP and the other international psychiatric organisations there can be networks of people who are perceived to be manipulating events and you have to be very careful I think within organisations that you don't create such groups. The International Academy of Biomedical and Drug Research, an independent organisation which operates to organise congresses and do research, made up of current or former committee members of CINP or ECNP, is an example. I don't think it's good for science and organisations if 3 or 4 core people, however benign their motives, are in a position of being able to influence several organisations. There are enough interested scientists who would join committees if it were possible. We should never end up in a situation where a few people are always there in all the societies.

In the mid-1970s, catecholamines were where the action was in depression, then the SSRIs came along and you heard about nothing except 5HT. The catecholamine story was dead but Organon hung on in there.

Yes. We tried other things. We had an SSRI of our own, which was killed in Phase II. Not because it wasn't effective. We had decent pilot studies to suggest it would be effective. But we had this toxicological problem common to all SSRIs that it causes phospholipidosis in tissues of rats and dogs. It was regarded in the toxicological world in those days as a really killing effect for drug development. We stopped our programme and it also delayed fluoxetine for a number of years while they considered the problem. Now it's not perceived as a problem – it has no relevance to human toxicology. All the SSRIs do it. We were one of the first caught by it. We might have been one of the first companies with an SSRI. It was a compound from a series being worked on in our Scottish lab in Newhouse and they had certainly been working in that chemical area for quite a long time before I joined the company, since the early 1970s in fact.

But we hung in with alpha 2 agents or rather we hung in with the chemical series, shall we say, the tetracyclics, because within the group you could also find dopamine antagonists. We, in fact, have a tetracyclic, Organon 5222, it's an SDA for schizophrenia. I was in the scientific group within my first few years in the company that selected mirtazapine as a potential anxiolytic antidepressant. Only later did we realise the very attractive extra effect it had on serotonin release. We always knew that there were alpha-2 hetero-receptors on serotonin terminals but because Mianserin was equipotent as an alpha 1 and

alpha 2 antagonist, we didn't realise you could have this facilitating effect on serotonin firing, via the α_1 adrenoreceptors on the cell bodies. So we carried on with the chemical series and out of that chemical series came other alpha 2 antagonists and other types of drugs.

In terms of the alpha-2 story, there has been a range of things that have been linked to it like the speed of onset of effects in depression and actions in schizophrenia.

In depression, Per Bech has recently shown that mianserin accelerates the onset of action of fluoxetine. There is also nice work by Bill Potter suggesting that addition of idazoxan to fluphenazine gives an extra effect in drug resistant schizophrenia and mianserin has long been used to augment antipsychotic therapy. Clozapine has a very strong alpha 2 effect in its profile of course. If you look at some of the newer antipsychotics coming along now, some of them have retained this alpha-2 effect and others have not. It will be interesting to compare them. What you should do of course is a study adding mirtazapine to a standard neuroleptic because not only is there evidence that you can add serotonin antagonism into dopamine antagonism in one molecule (the SDA concept) but you could also unhook them and give a normal dopamine antagonist together with a serotonin antagonist and an alpha-2 antagonist. Sulpiride and mirtazapine would be a very good combination. I think mirtazapine could find a place as add on therapy in schizophrenia.

We come back here to the regulators because a few people have said to me that the way we need to go is in terms of rational polyprescribing. But the FDA will never license claims for this. They're just geared to deal with one drug.

They deal with one indication and one drug. It's a shame. It's left to clinicians to do these combinations in the US but it leaves them very vulnerable to litigation if something goes wrong because this is not in the listed ways of using the drug. I hope that situation never develops in the same sense in Europe.

But isn't part of the problem that the industry won't support anyone with a good hunch of this kind either because you won't be able to get an application to the FDA out of it.

I think if there's an established basis and a reasonable market drug companies would do studies. One of the suggestions with mirtazapine is that it would be a great drug to combine with SSRIs to bring about an earlier onset of action and to eliminate typical SSRI side effects. A lot of people take a long time to respond to SSRIs and if you had a drug which you could add to them, it could present quite a large market. We are going to do such a study, although whether we will ever pursue it to a stage where you could file a claim, that's different. What you can do is to do some studies which provide good evidence, publish those and you can on the basis of those get a small additional wording in the product information and that's probably sufficient to establish it as a technique which could be used by clinicians without any fear of them being later accused of using it for an unlicensed indication.

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This situation throws up some interesting ambiguities. The rational way for Janssen to go a few years ago, after they had first produced the 5HT-2 antagonists, ritanserin and ketanserin, might have been to add these into depot haloperidol as a treatment for schizophrenia. This would have made perfect sense but they would never have got a separate licence for ritanserin in schizophrenia because it is not independently antipsychotic and if they have brought it out under a sleep architecture assisting or appetite stimulating label, arguably everyone using it in schizophrenia would have been using it off-licence.

Developing combination products is more difficult and expensive than single entities and modern regulators tend to frown on combinations. Take Limbitrol, for instance, where despite a large US study demonstrating the combination to be superior to the individual constituents in the treatment of depression, it is no longer available in many countries. Augmentation strategies are easier because they usually involve drugs that are already approved and not given in inflexible fixed combinations. However lithium is the classic example of an unlicensed but well accepted augmentation therapy based upon a body of evidence that may actually be insufficient to achieve regulatory approval.

Data from a trial of mirtazapine and Prozac came through a few days ago and I understand that it almost immediately boosted your share price.

Yes. It's not as bad as in the biotech industry where shares are up and down on the basis of one drug having a result in Phase II. Analysts are very strange. They regard the pharmaceutical industry totally differently from the biotech industry. Whether we lose a compound in development doesn't affect us at all but the biotech companies go up and down depending on where products and projects are going. I think it was the way it was written up in the press release – people said 'well it's better than Prozac, Prozac has a \$2 billion market. Organon's ambition is to be among the top three antidepressants with this drug' ... so this was interpreted by analysts as 'hey they are going to get a third of \$2 billion and it's better than the \$2 billion drug maybe'. Akzo Nobel shares are usually very stable. They don't vary between wide margins and it's quite remarkable to see this sort of dramatic change. And on good news! It was nothing to do with gynaecology where it was surprising how little the share price was affected by the OC crisis even though the company lost a lot of sales in the UK and Germany. And yet here we have a drug which is hardly selling anything at the moment but the share price is massively affected by just an announcement that it's better than Prozac. I think without that study, this wouldn't have happened – it would have just been another new antidepressant.

But it is interesting that all these new antidepressants are turning out to be better in the trials that have been done than the SSRIs especially in the more severe forms of depression. It has been rare in the past to find differences between 2 antidepressants. It's fascinating that not only mirtazapine but also venlafaxine and milnacipran have got these studies – there must be something peculiar about the new drugs, with their dual mechanism of action.

Perhaps catecholamines are important for speed of onset. It would be a nice touch if the area you did your original work in came into the frame again after being eclipsed for two decades. But these ideas about what works in depression are something that you'd imagine a department of psychiatry or even of neuroscience should be testing but they can't – they don't have the resources. Is there a sense in which companies like Organon have become the only departments that count?

Yes, in terms of the big programmes of trials needed to prove that a new drug is both safe and effective. But departments of psychiatry and neuroscience have major roles to play in teasing out new uses and new mechanisms of action. They, and not the industry, are the vehicles for innovative research into the neurobiology of psychiatric disorders. The industry will capitalise on their findings, doing what it does best – medicinal chemistry, applied pharmacology and drug development. We can also support collaborations with university departments and the biotech industry, initiatives which may eventually lead to product development.

The process of drug development you've described has been rational but empirical and maybe pragmatic rather than theory-driven. I'm hoping to see Les Iversen next who has seemed to be on the opposite side of the theory/empirical divide. How do you see his approach compared with what you think works

I admire Les and I enjoyed our brief collaboration in the dopamine area when Alan Home was still alive and working in Cambridge. Les had a chance to put his philosophy into practice at MSD when he was the first director of their Neurosciences Centre in Harlow. Innovative research, however, does not always lead to drug development, although it can add considerably to the body of knowledge. Les was unfortunate in that a lot of fine research did not lead to new product opportunities. I believe that a judicious mix of innovative academic research and opportunistic product development is the best way to proceed, and that the industry can sometimes better achieve its aims by actively supporting outside research and incorporating the results into its drug development programmes.

References

- Aldous FAB, Barrass BC, Brewster K, Buxton DA, Green DM, Pinder RM, Rich P, Skeels M and Tutt KJ (1974). Structure-activity relationships in psychotomimetic phenylalkylamines. *Journal of Medicinal Chemistry* 17, 1100-1111.
- Brimblecombe RW and Pinder RM (1975) *Hallucinogenic Agents*. Wright-Scientific, Bristol.
- Costall B, Naylor RJ and Pinder RM (1974) Design of agents for stimulation of neostriatal dopaminergic mechanisms. *Journal of Pharmacy and Pharmacology* 26, 753-762.
- Miller RJ, Horn AS, Iversen LL and Pinder RM (1974) Effects of dopamine-like drugs on rat striatal adenylyl cyclase have implications for CNS dopamine receptor topography. *Nature* 250, 238-241.

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Pinder RM (1971) Recent advances in the chemotherapy of malaria. *Progress in Medicinal Chemistry* 8, 231-316

Pinder RM (1988) The benefits and risks of antidepressant drugs. *Human Psychopharmacology* 3, 73-86

see also interview with Brian Leonard in Vol 1 *The Psychopharmacologists*.