24 Peter Waldmeier

From mental illness to neurodegeneration

Let's start with how you came to be in chemistry and then with Ciba-Geigy.

Basically, my mother wanted me to be a lawyer and she wanted it so badly that probably I decided not to be a lawyer. At that time in school I had a teacher in chemistry who was somehow able to interest me in chemistry, so I went to Basel and studied chemistry. But before reaching the end of my studies, I realized that synthetic chemistry was not really what I wanted to do. When I was finished and I was looking for a job – at that time it was not really general practice to do a postdoc, you looked for a job in industry if you were a chemist – I tried to get a job which was not linked to synthetic chemistry but there were none. So I found a job with Roche in medical marketing. I was with them for a year and I was mainly involved in the marketing of CNS drugs and that raised my interest in that kind of business. After a year I felt that marketing wasn't what I wanted to do either, so I called my former biochemistry Professor at the University, who had a Department at Ciba-Geigy, and asked him whether he could offer me a job and he said 'oh yes, fine, come over'.

When was this?

This was during 1970. I had two possibilities. I could go either into what was a precursor of molecular biology – DNA biochemistry – or into CNS and because of my involvement in Roche in CNS drugs, I picked CNS and that's how I came to Ciba-Geigy with barely any knowledge of the field. What I brought with me was a solid background in analytical chemistry and, at the time, this was of interest because the methodology to determine neurotransmitters and things like that was just evolving. So I grew into that business and we did, for years actually, CNS biochemical pharmacology – determining the effects of drugs on noradrenaline turnover, release or synthesis or 5-HT turnover and so on. In Ciba-Geigy, at that time, our main area of interest was antidepressants. The second area was neuroleptics, where we actually never got a drug into the market but nevertheless in terms of research the emphasis was rather significant. So I got to work with those drugs.

About the time I entered the company, maprotiline was in its final stage before getting approved so I joined actually long after anafranil and imipramine entered the market but before the last tricyclics made it. I used to work on antidepressants up to about 10 years ago, and then the interest started to shift a little. We got into more neurological diseases, starting out actually with epilepsy. There was a programme on epilepsy and then we started a programme on Gaba-B antagonists and so I moved more and more away from antidepressants. I still kept busy with brofaromine, which needed a lot of backup work, but there weren't actually any active programmes for antidepressants any more for almost 10 years. Now I am purely working in the neurodegenerative area.

Did you join before the merger? Why did they join?

I started in 1971 about two weeks after the companies had joined. I think Geigy was in trouble actually. Geigy had been in trouble once before after the War and was then saved by a concerted action of the three others.

How much competition is there between the three companies here in Basel? It would be hard to believe that there's quite the degree of competition that there's been between some companies like, for instance, when the minor tranquillizers were in trouble, part of that trouble seems to have come from the companies that were trying to produce 5-HT-1A agonists.

There is definitely some kind of competition in the market place but still I think the market segments don't overlap too much but we don't try too much to hurt each other.

Maprotiline was about to hit the market in 1970 – how did it look at the time, because it was in a sense going to be the logical development from everything else before and this was the most specific catecholamine reuptake inhibiting.

It was in the last phase, just before production. As always in a company, there was heavy opposition against the compound inside the company, there were supporters and opponents.

And this is always for each drug.

I've never seen anything else. You see you cover yourself by being negative. When you argue in a company that a drug shouldn't be developed for this or that reason, the chances of being right are much larger. If you say, you must develop this drug because it's going to be a big success, you can be proved wrong. When you oppose and destroy a drug, you can never be proved wrong

How much of a hazard is this building up large groups of sceptics within a company?

Oh Ciba-Geigy has a pretty good record of that. We have been too hard with our drugs for 20 years and so we have never finished one since

maprotiline in the CNS area, at least. I think it's a big problem. In order to get a drug to the market you have to go past a point of no return. You have to commit yourself to a decision once made and not always be questioning it after that. If something is proved toxic that's another thing but to reiterate the question whether is it really worthwhile to do it and do that every two weeks, that really inhibits development.

Maprotiline is curious in that it became for a long time the best- selling anti-depressant in parts of Europe but in other parts of the world, the UK for instance, it didn't really seem to take off. Can you account for this variation?

There may be two reasons for that. The reason which I would invoke first, is the marketing. The more you do for a drug in terms of marketing, the more it will sell. This will not necessarily positively affect the benefits, because it costs a lot more to do the marketing, but it will certainly increase the sales. The other reason may be that the Anglo-Saxon countries were the 5-HT countries and the more German-speaking and orientated countries, including the Scandinavian countries, were more catecholamine countries. It has to do with specific single researchers involved in the area. Alec Coppen was one of the dominant figures in the UK and he was pro-5-HT and Arvid Carlsson and a few other people in Europe, Norbert Matussek, were noradrenaline people. So one group preached one story and the other preached the other story and this has some impact on the practising psychiatrists.

Maprotiline led to Levoprotiline which is . . .

Oxaprotiline is a hydroxylated derivative of maprotiline. It had two enantiomers. Levoprotiline was the non-noradrenaline reuptake inhibiting enantiomer. We originally wanted to have a double-blind comparison of plus versus minus oxaprotiline, that is of 'dextroprotiline' and levoprotiline. We wanted to test the catacholamine hypothesis and this pair of enantiomers seemed ideal. This was a good idea and it would have been possible to finance it but there was a legal problem. The toxicity studies were available for the minus enanatiomer but we would have had to provide additional toxicity studies for the plus enantiomer, therefore this direct comparison couldn't happen.

The first trial that was made was levoprotiline against the racemate. There were several small trials, and one of these small trials seemed to indicate a positive effect and then it got out of control. There was a clamour in certain corners of the company – 'oh, gee, we have a breakthrough, we have something which doesn't work according to the catecholamine mechanism'. This is something totally new. From then on science had no control over it. We argued that these are limited trials, these are not placebo-controlled trials, these may be biased trials but nobody listened. It was the big thing.

Then they went into big, still poorly controlled trials in East Germany

and Czechoslovakia and so on. The drug got better from one trial to the other, until it finally collapsed. Because when the double-blind trials came, no efficacy could be shown. Interestingly though, there are still a lot of clinical investigators, especially in Germany, who stubbornly say this drug is active. They saw changes in patients, which they interpreted as positive. One guy said, look this drug doesn't really affect the core symptoms of depression, but it makes those patients who sleep badly, sleep better. It makes those who have eating disorders shake off their eating disorders. It sort of takes care of the peripheral problems. In any case, it all collapsed because the pivotal trials were negative. It was sad because had we chosen the plus-enantiomer to develop, we would have ended up with a drug – not a very innovative one but at least we would have had a drug.

Roland Kuhn was involved in this, wasn't he?

Yes. Roland Kuhn tried for a long time to convince the company to continue to develop levoprotiline, because he considered it to be an active drug. He actually wrote some pretty tough letters to higher ups in the company because he felt that Ciba-Geigy was doing wrong in abandoning the development of the drug. There were others as well. It is very difficult to judge who is right and wrong because this is not a black and white story. It is definitely clear that the drug did something but what it was, nobody could really properly describe it. I think to reach registration with such a drug would have been extremely difficult. It was obvious that in a normal depressed population you couldn't reach a significant effect with the given armamentarium of clinical investigators. So to try and register that compound as an antidepressant was hopeless and nobody had a brilliant idea of what other indication we could chase.

There's a curious irony in that Kuhn would say 'well, I found the first antidepressant and I knew it worked without clinical trials to prove it'. He was still saying in 1989 that 'all these clinical trials are a complete waste of time, what have they ever found'.

In a way, I understand this comment because the more controlled the clinical trial is, by our standards, in terms of done right by statistical considerations and things like that, the more it tends to obscure any finesses. I would believe Kuhn if he says that if he treats a number of small number of patients and observes them carefully that he can tell you more about a drug than a big clinical trial. The big controlled clinical trials against placebo, they are good for establishing firm data on the efficacy of the compound in a given indication but they are no good for finding an indication. When you are sure about your indication, you need to do one of those big trials to nail it down. To convince authorities and health care managers.

The next antidepressant that Ciba were involved with, was of course brofaromine. Do you want to take me through its development?

Well, I'll try not to be emotional because this for me is a kind of emotional case. I devoted a lot of time to that drug and I still think it was a grave mistake to abandon the development. We were working on 5-HT uptake inhibitors back in 1972/73.

Sorry for interrupting but that was very early to be working on 5-HT reuptake inhibitors . . . Who started the 5-HT reuptake story? Hyttel has suggested he did and Arvid Carlsson was talking about this idea back in 1969.

I think Lilly did. You see, as always, these things germinate and then eventually they get tackled and at several places at the same time. I don't know how the publication dates compare but publication dates don't tell you when they started because the publication policies of companies are very different. Some publish early, some publish late. And the same is true for patent dates. So unless you ask the people involved, you will never know. I, for our case, know that we started almost immediately after I arrived.

And why did you want to make a 5-HT reuptake inhibitor?

We happened to screen compounds for noradrenaline uptake inhibiting properties because we were still in the phase where maprotiline was still being prepared for introduction. And we hit upon a compound in the screen, which inhibited noradrenaline uptake but also inhibited serotonin uptake and MAO-A. We only found out about the MAO-A inhibition because it increased noradrenaline levels and, as a pharmacologist, when you see that your first reaction is let's see if that inhibits MAO-A. So we were there with a compound which had in similar doses, noradrenaline uptake inhibiting, serotonin uptake inhibiting and MAO-A inhibiting properties. Although it was relatively weak with respect to each single property it was a potent drug in pharmacological models. We thought wow this is just the right thing. Unfortunately this compound died in toxicity because it killed the dogs. But the series was born. The chemical structure was entirely different; it had nothing to do with tricyclics.

This was all the more interesting. So, one of the chemists, Raymond Bernasconi, was particularly productive. He produced about 300 analogues of that compound. And the next thing we hit in that chemical series were very selective and at that time very potent 5-HT uptake inhibitors. They were more potent than fluoxetine, for instance, and so we thought when we have them why shouldn't we try something with them. We had a number of candidates which dropped out one after the other but one of them, the most potent one, made it actually into early development and it was then killed because of some dubious results in clinical pharmacology studies. It was thought that it might change the blood clotting time or

reduce thrombocyte numbers or something. After the compound had been killed, it was shown that it results were erroneous and brought about by a wrong manipulation but it was too late to save it. The next analogues, all of a sudden, showed again 5-HT uptake inhibitory and MAO-A inhibitory properties and at that time we said why don't we try to select MAO inhibitors – if they are selective for MAO-A and reversible they might get around the tyramine problem.

Just before we go onto that can I quickly ask you, when you found the reuptake inhibitors, did you know what you would actually use them for – it's not clear that Lilly had depression in mind for fluoxetine.

Oh, it was absolutely clear that it was depression. There was no question, because we were aware at that time of the two mainstream theories of serotonin on the one side and noradrenaline on the other side. We had taken care of noradrenaline appropriately, so why not try the other area. There was never any doubt.

So we found drugs in this series of benzofuranylpiperidines which did not show much 5-HT uptake inhibition but were pretty good as MAO inhibitors and we selected one of them which was brofaromine. At that time we were openly declared almost insane because people had these stories about the MAO inhibitors in mind. We fought a long fight to get the compound into development. It was put into Phase 1 development in 1977 and there it stayed until Peter Bieck opened this Human Pharmacology Institute in Tubingen in Germany. He started to do phase I studies of that compound and it proved to be a good MAO inhibitor and he also did some pioneering work in tyramine potentiation studies.

So it got to the end of Phase I. It looked good but clinical development was not able to take it from there. It was in Phase II for an extraordinarily long time. Eventually they managed trials of something like 12 patients a year. There was no urgency until management realized that Roche was developing moclobemide. For a certain period of time we kept alive brofaramine by saying Roche develops moclobemide so MAO inhibitors must be good and they said Ciba is developing brofarmine so MAO inhibitors must be good – so we kept each other alive. And then at one point in time, perhaps 1987/88, Roche took a decision to develop moclobemide. Until this point we were ahead and from that point on we lost because they did something and we didn't.

So the whole development phase of brofaramine was much too long and then at the end when it became clear that maybe depression wasn't the best indication for that compound, that panic disorders or OCD, or post-traumatic stress disorder or one of the major anxiety indications, was a more appropriate target for this compound, it was too late because the patent life left was so short that management considered it just not worth it. They were there with a package of clinical data which could not be used for registration and the indications that had crystallized they didn't

have enough clinical trials to go for. They would have had to invest another two years or even more to do it properly and that was the end of the story of brofaramine, which I find particularly sad, because I think it was a good drug.

Why?

Well, I have spoken to a number of clinical investigators, particularly those who have used it in atypical depression or in major anxiety states, and not one of them said this drug doesn't work; on the contrary, they said we have never seen anything as powerful as that. Especially the Canadian guys, who used it first in panic disorders and it was absolutely dumbfounding. In some cases, it was almost 100% success and in many cases, it was 80% success. Most of the guys said this is the most powerful antipanic or the most powerful antisocial phobia drug they had ever seen. So from this kind of second-hand information, I believe it would have been worth developing the drug further. There was one little glimmer of hope where we thought we could get a patent for social phobia but unfortunately someone had mentioned the possible use of MAO inhibitors in social phobia in an abstract the year before and that spoilt the possibility of that. That killed it finally. That was about two years ago now.

There's actually something about this whole group of drugs that hasn't crystallized out properly. People have been saying from very early on that the MAOIs are not the same as the tricyclics. They do something different. Yes, they can get a large number of people who have got a major depressive disorder well, just as a tricyclic can, but there are some other effects – personality strengthening effects is the kind of phrase you hear.

It's very difficult to resolve. It's conceivable that they're different because most of the tricyclics at least have a large number of additional properties, for example, they are antihistaminic to various degrees, they have antiserotonergic properties which most of the MAO inhibitors don't and so the idea that they might have an overall different profile is understandable.

Are companies trapped by looking at the market size and finding that the only thing they can apparently afford to develop is an antidepressant, because it's the only thing that's got a sufficiently large market size. Then antidepressant trials all get done with instruments like the Hamilton Rating Scale, which pick up tricyclic type effects, so other drugs which may be subtly different are going to have a hard time trying to get on the market.

Well, look at how long the 5-HT uptake inhibitors took and there has been an argument for years and years that these drugs are not truly antidepressants and I don't even know whether the question has been settled yet. There are still people who say that these are 'feel good' drugs – they are not really antidepressants. I think the clinical armamentarium is just too coarse to allow fine differentiations like that.

296 *What happened to the neuroleptic programme. Why did savoxepine not happen?*

297 The story is almost analogous to the brofaromine story. When it finally
298 came out that the drug was good, it was too late. So the development
299 efforts of Ciba-Geigy during the last 20 years have not been very success-
300 ful. It took too long to generate too little data of too poor quality to
301 suffice for registration. I think they've realized that and they are trying
302 to do something about it. It was about time. But savoxepine again is a
303 sad story because from the evidence that we got it seemed to be a drug
304 which relieved the positive symptoms of schizophrenia with relatively
305 little restraint put on the patients. The interesting thing about this actually
306 is that patients said the difference in terms of motor side effects wasn't all
307 that great but what patients said was 'I don't have that straight jacket
308 feeling as with haloperidol'. It was a kind of, more or less a more subtle
309 difference in terms of mental restriction, which made it different from
310 other neuroleptics. The plan was that it should be better with respect to
311 extrapyramidal side effects and when that didn't turn out to be too clear,
312 the decision was made to kill it, together with the expiration of the patent
313 life and things like that. The Ciba-Geigy system was not able to say 'oh
314 look we were looking for something which was better than classical
315 neuroleptics in terms of extra pyramidal side effects. We haven't found
316 that but we found something else'. They couldn't do that.

317 *Sobering isn't it?*

318 Yes well I tell you life in a pharmaceutical company can be very frustrating.
319 I've seen a number of colleagues who had mental problems because they
320 felt they were useless and whatever they did was for nothing.

321 *Or seeing compounds go forward that are inferior to some of the ones worked on.*

322 This is normal. Normally it is hardly ever the best compound, from a
323 pharmacological point of view, which makes it. It's always the second or
324 third best because of other properties. Maybe your best compound is not
325 adequately metabolized or has too short or too long a half life or has this
326 or that. The compound which finally makes it is a compromise of all
327 those things.

328 *How do we solve this problem that a company will only bring a drug on if it's*
329 *going to be a large market share compound.*

330 The companies will, in one way or another, have to change their philo-
331 sophy. When you go for a mechanistic approach, you have to be consistent
332 and say look I'm going for this or that mechanism but I don't know the
333 indication yet and we will have to go for any indication where we think
334 we can prove efficacy. We will have to do that first, irrespective of the
335 market size and take it from there. Now if you are not willing to do that,
336 you put too many restrictions into the system. If you say I want a

mechanistic approach, we should go for something which interacts with a target protein or whatever, but it must make $300 million a year, then the restrictions are so difficult that you will hardly ever make it.

They will have to ease up on either of the two restrictions and the more logical one for me is to ease up on the financial restriction and say look we are going to try to develop a drug which acts on this mechanism and we are going to try and see what it does. Now you can't take that to the extreme either because it costs a hell of a lot of money, so you'd better have some idea of the indication in the first place but this indication need not necessarily be a big one. So an indication like petit mal, with a market size of $100 million or even less would, for me personally, be enough to start with, because it has quite often been seen that the first indication was not the last one. But it should be an easily testable indication; it should not be something like stroke which is a very difficult indication to test. It should be something with a clear endpoint, where you don't have to treat people for two or three years. But asking for both a mechanism and for a big market share reduces your options considerably.

We don't seem to have been able to decide what we really want out of this do we?

Well we want to make money. I'm speaking for the industrial manager, now. The industrial manager, at least the ones high up don't care whether you develop an antihypertensive for them which makes money or an antidepressant – all that counts is that it makes money.

Yes. The point that I'm actually trying to get at here is that there seems to be some confusion at the moment about whether we should be going down the route of producing pure and clean drugs that are acting on a particular mechanism or whether we produce drugs to treat illnesses and for 20 years or so we have been going down the route of purer cleaner drugs but with increasingly confusing results.

This is true. The least thing we could have expected, and I think something which many of us expected when we went down the way to cleaner drugs, was that we would find out which aspects of which illnesses certain mechanisms affected. We were somehow expecting illnesses to be composed of modular pieces. To give you an example, we could have expected that serotonin was affecting the mood component of depression whereas noradrenaline was controlling more the drive aspect of depression and perhaps you could argue that acetylcholine was controlling the vegetative aspects and so on.

I think we have to get away from this thinking because illnesses are not puzzles composed of different pieces. It's not like a car, which is made of wheels and a motor and a gearbox and things like that. It's not as simple because these things interact and when we hit one system directly with a drug, indirectly we induce alterations in other systems which will finally rearrange the equilibrium of the system as a whole and leave us with an altered system and from the alteration in the system you couldn't say what

initiated the alterations. Likewise, it may prove wrong to try and interfere with one particular mechanism to achieve a good therapeutic effect because the system has so many possibilities to compensate and to neutralize the original impact, so that of the anticipated action of the drug very little remains. In contrast, if you block a system in different places you restrict the degrees of freedom and the system can't evade that easily.

The main driving force behind trying to get cleaner and cleaner drugs was chemistry. Because for the chemists to optimize a drug for one parameter, they considered that as a possible task. To optimize for two parameters is much more difficult and to optimize for three parameters is just impossible, at least today. So chemists have always wanted clean drug . . . they know exactly what they have to do. I should not say nasty things about that but I can afford it in a way because I'm a chemist by formation. Chemists are simple minded, at least as far as biology is concerned. They think in boxes and as soon as things become complicated, they suspect the biologists have got it wrong. As long as chemists have the say in big companies this won't change. At present, there are companies in which chemists predominate in terms of the managerial hierarchy and there are companies where this is not so.

Could this problem get worse because all the people who now work in the various aspects of drug development are going to be molecular biologists as well and they are also thinking in . . .

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It accentuates the problem because in the past decade the chemists were going for the interaction with a particular receptor. Now they are going for a clean and pure interaction with a particular receptor subtype and in two years from now they will go for the pure and clean interaction with the splicing variant of a particular subtype. So it gets smaller and smaller or from bad to worse if you want. It reminds me a bit of the attempts in the middle ages to explain the movements of the moon by all sorts of strange spirals.

And it's going to require someone like a Kepler or a Copernicus to turn everything around.

I think it's a fashion and perhaps in 10 years people will revert to the integrative view.

But will we be able to revert – because we'll be going down so far down the road of producing junior scientists now who will be in the middle management then who have been thinking in this way. Will they be able . . .?

In 10 years from now or maybe 20 years, someone will stand up and present whole-animal pharmacology as a totally new idea and there will be nobody there who remembers that it has actually been done before.

I've heard people recently come out with things that I know were around in the 1960s but they make it sound like it has just be thought up.

Yes, I occasionally see that in the literature. Stuff is published now which I know has been done before. It has not been done in exactly the same way or by the same techniques but the conclusion that was reached was quite the same and these guys weren't even quoted because the literature is too old. I think the danger of re-inventing the wheel is pretty serious. The literature is getting too vast. The old literature is hardly accessible any more, it's somewhere down in the basements.

Is there anything about this whole idea about trying to get more and more pure, more and more specific drugs that stems from people's wish to have more technical control over life, as it were. I was brought up short recently when somebody on some radio programme said that cabbages, for instance, have something like 47 different natural pesticides in them, few of which would get through the FDA, if people tried to actually extract them and get a licence for them actually as a pesticide, but yet these are what give cabbage its taste. Do we all – both us as consumers and you in industry – want things increasingly sanitized . . .?

Yes, dirty is out. It is interesting though that I've seen very recently some articles by people who have a background in the area, who have come back saying 'look, we're running down a blind alley by going for purer and purer drugs'. So the voices can be heard now but they are not being heard by the management of the pharmaceutical industry. The main driving force for this craving for pure drugs is that we want to know how it works. If something works by two or three mechanisms, how can we know which ones give what, and this is not satisfying. The other very strong point which is one I made already before is that the chemists say I can't optimize for three properties and I want to optimize. This is what I can do and so I am going to optimize. Pharmacological purity is also important when it comes to screening drugs in an *in vitro* system, using a high throughput screen. This is not possible for things that have three or four different properties. For these you will have to resort to animal models, which are not fashionable nowadays. It's slow, complicated, expensive and laborious and causes problems with the animal rights people.

So there are all the reasons why people are going for clean drugs now but whether these reasons suffice to lead to good drugs is another question. Sometimes it reminds me of the guy who had lost his purse in the night and he was actually looking under a street light and was looking for something and someone else asked him what are you doing. I lost my purse he said. Did you lose it here? No I lost it on the other side of the road. The other person said why don't you look there. Because there is light here. We may be doing something similar by going for clean drugs, I fear.

But it's tricky isn't it? You don't either want to go to the opposite extreme of saying well let's go back to herbs.

I don't think it's the question of herbs or not herbs. I think those people who do not put the emphasis so much on the cleanliness of drugs are not arguing that we should go back to herbs. You could say that they are more aware that the nervous system is more plastic and reactive and tends towards homeostasy.

But people will say that herbs are the ultimate integrative view.

Well, there are people who argue like that but I don't take that seriously because herbs are mixtures of chemicals aren't they? I think herbs are nice and herbs are perhaps good to make tea and they are also good to have a look into them for active ingredients but to eat herbs to treat my illness because I think it's better than drugs, I don't accept.

Things seem to have changed since the 1960s when you trained. Back in the 1960s when we produced the first compounds there was the feeling that nature is tricky, nature is dangerous and human beings try to control nature and using drugs is a clever way to use human intelligence to control things for the benefit of mankind. Now we've got the opposite. Nature is good . . .

Mankind can't be moderate and intermediate. They have to be extreme. The pendulum was on one side and the pendulum is now on the other side, and I think either extreme is wrong.

But is it just purely the chance swing of the pendulum or have the kind of developments over the last 20–30 years given credance to the idea that nature is good and man's efforts to tamper with nature are not so good.

Oh, we have begun to realize that what we were doing to nature wasn't doing nature or ourselves any good. But instead of bringing us back to an intermediate position and trying to control what we do, it has for some people at least swung the pendulum to the other side and now everything that man does is bad and only nature is good. But nature is neither good nor bad. Nature is nature and herbs are herbs. They are good source for finding a drug, for instance, and it's a good approach to look in Chinese herbs for a new active ingredient but that wouldn't stop me from trying to improve that ingredient by chemical manipulations.

But for some people that's almost heresy. There's an awful lot of people out there who would think that if a compound actually exists in nature that it oughtn't to be changed. It's very presumptuous to try and improve on nature.

I have no sympathy for this view at all but I accept that it exists. Why should we not try to make that stuff better than it is. There is always something which can be improved, even if its only bioavailability and pharmacokinetics. I can give you an example. There's a compound that

has been isolated from a Chinese herb and the herb was used for 4000 years to treat epilepsy and hypertension. The active ingredient has now been found and it is a very complicated molecule with an extremely short half life. Why not take that compound now and make some modifications which keep its activity and increases its half life. You've got a more useful the drug – what's wrong with that? I think many of the people who advocate the use of herbs in a dogmatic way are fundamentalists in a way, aren't they

Are they?

I think they are. They believe in almost in a spiritualistic way in forces. It's comparable to homoeopathy. Our generation of natural scientists have been educated in a way which has no room for something like homoeopathy. I can't understand how things get more powerful by diluting them to the extent that you can hardly find one molecule in a bottle. This is against everything which we have learnt. We are probably so much impregnated by modern natural sciences that we will never be able to grasp that. I have serious problems with this way of thinking and I have exactly the same sort of problems with people who think that an ingredient in a herb is in any way better than the same ingredient outside the herb.

There seems to be this interaction at the moment between scientific thinking and popular culture, so that, for instance, we have these hysterias about health, about holes in the ozone layer, etc., etc. It seems as we generate knowledge and as health becomes the media event it is becoming world-wide, people are being exposed to information about holes in the ozone layer and they don't have a feel for the risks, they just get hysterical – herbs maybe seem safer.

For the non-fundamentalist and, more or less, neutral observer, it's very difficult to understand how serious a situation is. The ozone hole. You hear all sorts of messages but to know exactly how bad it is, because even the measurement data that are reported in the newspapers are very different, so we don't really have the data available to make an appropriate judgement. Again this information is used and abused by all sorts of groups for their interests and they are then distorted and communicated that way and they have an impact on the public and depending on the nature of the individual of the public they will react differently. They will say 'to hell, I've heard enough of this – I'm not paying attention to it anymore' or they start screaming and shouting and jumping up and down and saying 'the world is coming to an end'. To have a take-home message from such reports in the newspapers is almost impossible because you don't know what has happened to the message before, from the moment it was sent off until it got to you.

You have this uncontrolled amplification of facts and you don't know the amplication factor. By the time it comes to you, you don't know what

the original message was. We used to play that telephone game when we were kids – there was a row of kids and one started to say something into the ear of the next and it went round the table and it was compared when it came back from what it was originally – that's probably what we are witnessing with the media now.

Is it a thing that needs to be controlled in some ways because the problem is if drugs are the issue – if fluoxetine is causing suicide is the issue and any expert intervenes to say well look the evidence really isn't there, the disinterested view never seems credible; besides, it's not newsworthy to say that fluoxetine isn't causing suicide.

I think with drugs it's a different issue than with the ozone hole because it's probably easier to control issues with a drug than issues on the ozone hole, so lets keep with the drugs. I think if something emerges like the question 'does fluoxetine cause suicide or not?', this is something that really affects patients who are treated with such a drug and it should be clarified as properly and as cleanly as possible and the result of this should be communicated. There is nothing worse than this situation of rumours. I think it is in the interest of the patient, the doctor, the authorities and the industry to clear up these things rather than to try and cover them up. It is also probably for the concerned company, the worst thing they can do because eventually the truth will come out and the damage will be all the greater if it took longer for the truth to come out. I don't think the industry, even in purely financial terms, has an interest in covering up things because you can't cover them up for eternity.

Let me introduce another angle on this which is a phrase I picked up from you, so I need to give you the credit for it because I've been using it ever since. This may be linked with the development of modern drugs but people now seem to feel that they are 'born with a warranty' in a way that they didn't 20 or 30 years ago. Any thoughts on the origins of this kind of feeling?

Well, I think maybe the critical event was the availability of antibiotics because until antibiotics became widely available to me and you, you could catch an infection and die. It was normal. Nobody knew anything different. The idea of being born with a warranty goes back to an incident in my childhood where I was pretty sick, I had what they called at the time a renal inflammation and I had to be in bed for six months. I complained to my doctor about having to be restricted in that way and I obviously complained so hard that he got mad and shouted at me 'do you think you have a right to be healthy'. This made a really strong impression on me and that's probably the reason why I started thinking about this warranty business.

Surgery also in this century made advances and you could rescue someone from a situation where in the last century there would have been a death. So death or illness had another value for people a hundred

years or more back from now and they accepted illness and they accepted death. Whereas when the treatments became available, some hopes were raised and people expected more and more from medicine and drugs. So in one way or another, people expected that whatever happens to them someone can help them and they are terribly disappointed if they learn that in some cases this is not possible. I think this is something new. The roots are probably in the availability of treaments and the raising of hopes.

I'm absolutely sure that's it's new. It's a feature of the last 15 to 20 years only I think. In this regard, did the thalidomide tragedy have much bigger, long-term effects than was ever thought at the time? It's eroded trust in all sorts of ways; it's eroded trust in the industry; it's eroded trust in the medical profession.

It showed for the first time that things can get out of control. It eroded let's say the claim of science to be true and helpful under any circumstance. I think it still has an impact – it undermines the trust and this is the thing But it hasn't detracted from most people's belief that they are born with a warranty.

No, but do you not think it's caused the belief which is the flip-side of born with a warranty that we would have been okay if some drug hadn't done something awful to us. If some outside agency hadn't done something awful to us.

Is that such a frequent phenomenon? What I often hear is another argument that is, why does the state spend so much money on research and you still haven't found a treatment against this and that. This I hear much more often than it is a drug that has done that to me and that's why I'm like this now.

Yes, but there's a feeling that if things go wrong that there has to be a reason and increasingly we feel the reason will be something man-made; it isn't just nature, it isn't just an act of God.

This is what I would call the paranoiac fundamentalist view of things but there are not many paranoiac fundamentalists. This is a small minority. People may complain about side effects but they rarely blame a drug for an illness.

Well, it's big enough to influence practice in the US. I think the feeling there is that if you go for medical treatment and things go wrong there will be a law suit.

Yes but you have to turn it the other way round. Because you can sue them and you often win, that's why you claim such things, because otherwise you couldn't sue them. So you make your story in order to retrieve money from them. Not necessarily because you believe in it.

Let me hop back. One of the points you made earlier was that when you actually entered the field first there was a more open approach towards things and now you find that the junior people working with you are theory bound.

Yes. Part of this is the almost dogmatic belief in the idea that the drug must be perfectly pure in order to be a good drug and I find that this dogmatic belief is almost scary. You can't argue with them because they would say look it doesn't make sense to look for anything other than pure compounds. Interestingly, they wouldn't really argue with you when you say if we test it out maybe you will find dirty drugs are better but they say I don't want to go for this because I have no control of it. So the control over the mechanism of action, 'knowing what you do' is more important for them, than to find a good therapeutic agent. And this reflects a sort of selfishness. It's not the patient which interests them, it's not the therapy which interests them. They want to see how it works. They want to enjoy getting it right and these are elements of a dogmatism, I think.

So where does that attitude come from? Do you think it's just the maturing of the field because when you guys went in first, things like the amine theories were fiction. They were obvious fictions – you could be sceptical about them.

None of the theories that are available now are any better than that. I would even say that at that time although it was clumsy and the bases of the theories were no good, one tried to develop a drug with a rationale. Now they go for the next clean receptor or the next clean target protein and they try to find something which interacts with it and they say 'we'll see what it does'. They don't spend a lot of time in figuring out why something could work and trying to get experimental support for the theory before they start. Now if they develop a drug, when they have a clean drug, they say now let's see what it does. Somehow research got mechanized.

Why is that so? It's difficult for me to say. It must be a product of their education at University. Perhaps the basis of this is the idea that if we try hard enough we will find out how everything works. There are no limits. And with the event of molecular biology, which is definitely a very useful technique, the expectation that everything is doable is much more common than it was. We were more aware of the limits that we have because the limits were more obvious. Young researchers nowadays think if they've got a target protein, they know it all. They are not aware of the fact that they've just got a step farther but they still don't know why interaction with this target protein causes a beneficial effect in an illness. They don't realize that from the target protein to the illness is probably a much longer way than they had from the receptor to the target protein. Maybe we were the same and we thought we knew everything if we knew the receptor but we haven't been that dogmatic – we were allowing for dirty drugs.

It's a time of change within the industry, here in Switzerland.

Not only in Switzerland. It's happening everywhere. The conditions have changed. The economic situation of health care management in the widest

sense has changed. It has become overtly clear that the costs of health maintenance were rising disproportionately and something had to be done about it. There are a number of possibilities. You can investigate which are the largest cost items in the whole bill and then for each of these items think about what you can do. The largest item is definitely not the drugs. The drugs are somewhere between 10 and 15% of the to total costs. But they are an easy target. You just tell those who sell the drugs how much they can ask for them and you restrict the number of drugs allowed on the market. That's relatively easy to control.

In Germany, they started three or four years ago a process of controlling drug prescription both in terms of pricing and in terms of quantities of drugs prescribed very seriously. This has led to a pretty big decrease in the market size in Germany. Other countries are following more or less rapidly. We don't know how the situation will develop in the United States. So perspectives for the pharmaceutical industry have become less predictable than they were. In any case, if you're a company manager you are probably wiser to expect a worsening of the situation than an improvement so you better take care that you are not caught on the wrong foot. And you had better slim down, as long as you can slim down in a controlled way, before you are forced to. And this is precisely what's happening.

Leading to considerable job losses?

Oh yes, especially if a merger of two larger companies like Roche and Syntex, is added in on top; this will end in major bloodshed. Not all the people who will lose their jobs have lost them already. This is a process that is ongoing now. They are determining who, and why and when – nobody knows exactly who exactly will be hit. I don't like to make forecasts like this but it is clearly possible that the number of pharmaceutical companies will diminish and only a few will remain. The weakest will drop out . . .

And is this good or bad?

Depends on your point of view. From the point of view of health care costs, it's probably good. On the other hand, from the point of view of new drugs, new developments, new ideas getting translated into possible treatments, it is probably not good because from the statistical point of view, the more people working to reach a goal by different means, the higher the chances that one of them will reach the goal. So definitely I expect that this will lead to a poorer armamentarium of drug therapy than if there were more competitors in the market place. It is also possible that if there is only a few remaining that they will even break up the market into different segments, where they are more or less alone, and there is no competition any more and this will stop any impetus to improve. So the danger that we are moving to an industrial situation

which is comparable to what they had in the Eastern block before the end of the Cold War is quite real.

Allied to the current situation as regards health care generally, though, the industry seems to be less enthusiastic about mental health at the moment.

Yes and no. It is certainly true with respect to psychiatric diseases. Most of the industry had its major emphasis, at least as far as CNS research is concerned, in the psychiatric area. The reasons were probably the availability of hypotheses, whatever good they were. They stimulated ideas, they stimulated research, people have a kind of framework to operate within and that's why these theories were more or less well explored in terms of drug therapies. Two elements may have contributed to the change now. First of all the perception that neurodegenerative diseases are becoming more and more important in terms of social and economic costs. Then there is the idea that animal models for at least some of the neurodegenerative diseases are more reliable and 'better' than the animal models for psychiatric diseases. There were some ideas about mechanisms by which, for instance, the negative effects of strokes and other impairments could be controlled. So companies are shifting their resources towardf the neurodegenerative area. Of course, there is also the big market that they expect to be waiting out there, which is getting bigger with increasing life expectancy.

It's also a market where small amounts of improvement will be reimbursed whereas marginal improvements in antidepressants won't be reimbursed.

Yes, it's much easier to get an antineurodegenerative drug into the market, the best example is Tacrin. Tacrin is debatable whether it has any effect at all and a compound with a comparable improvement over placebo could never be introduced for the treatment of depression but for Alzheimer's because there is no treatment, they take whatever they get and this is going to be so for some time. So it also offers a kind of perspective – they are looking to introduce drugs in a series, so that different companies can always be a little better than their predecesor and so you can make money for a while. When you are beginning to make a reasonable improvement it's harder to do better than that. The lack of pharmacotherapeutic agents is one of the major reasons why people have moved into these areas. The official version is that this is a serious problem and as an ethical company we have to do something for mankind, but the driving force is money.

An interesting possibility about the movement of companies out of the psychiatric area is that it actually may be the best thing that has ever happened because you can't work in the CNS without the work you're doing having implications for mental illness generally.

You and I know that, but the managers may not. It's good for two reasons.

It is interesting because it makes people work on different mechanisms and it may turn out that these mechanisms have some implications for psychiatric diseases as well. It may also be that some of the psychiatric diseases finally turn out to be neurodegenerative diseases and the other thing is that is may just prove beneficial to take a step back and to look at it from a different angle.

We may be in the situation of Chicken Erna, who is enclosed in a fence which is U-shaped and open at one end. On the other side of the fence, there's food and chicken Erna tries to get the food desperately and runs back and forth along the fence but it doesn't occur to it that by going through the open back side and going around the fence, it could get the food. It may well be that we have been in a similar situation with the monoamine hypotheses and receptor research on psychiatric diseases. By leaving it for a little while and coming back to it from another side, we may find alternative solutions to the problem. So turning away momentarily from psychiatric research may ultimately prove beneficial for biological psychiatric research.

It's an interesting thought, isn't it, but it does mean that the period we have been in is closing as it were?

We are definitely at a turning point, yes. Well let's not put it as dramatically as that but the way biological research in the CNS area was done is changing now – definitely. I don't think that's a bad thing. We need some changes because when a particular way of doing research continues for too long, it is self perpetuating and it will not produce anything new, so we all need a break.

Curiously, though, some of the classic mental illness drugs and in particular deprenyl have for some time pointed the way towards the neuroprotective area. So in a sense, there's a continuity there that people from outside the field may not appreciate.

It is, I think, only seemingly a continuity because the interesting things which deprenyl does don't obviously have anything to do with MAO. It's probably a coincidence that one of these old MAO inhibitors is the spearhead leading into a new area. But it's nevertheless funny and it's also funny that at least part of those people who had been involved with the old MAO stuff are now again in business with this new stuff. This is not accidental because some of the people who have been working with the MAO inhibitors were attentive enough to see other other properties of the drugs and were interested enough in the other properties to more or less change their direction of research.

But now where did the other properties come from because those of you who have been working in this area have gone on working on the neuroprotective aspects of

these compounds even though the most recent clinical trials came out with fairly disappointing results. You haven't been deterred at all.

No, because nobody in the field expected major beneficial effects of anything. Everybody was happy with a small effect and I think by today's standards the effects of deprenyl in the data top study, that is the protraction of the disease for one year, is pretty good because there's nothing better and there is no reason to assume that you cannot improve on deprenyl.

My hunch though is that the reason why you are all working on in the area regardless of a reasonably small clinical effect is that you have hunches about what's actually happening with the drug.

Well, if we had an improvement with the antidepressants it all depends on the likeliness that you can make it credible to the authorities so that they will allow you to register your drug. A marginal improvement in the antidepressant area will not lead to that but a marginal improvement in the neurodegenerative area will. That may be too cynical because we believe deprenyl's neuroprotective effect will lead to something that is more than marginally better.

Yes, but perhaps like the early amine days, if you have a marginal improvement that you can't explain you've got something of a blind alley. Whereas in this case, lots of people have theories about what's happening with deprenyl that you can build on.

With all theories of course it's better to have a theory which is plausible than none. It needs not be true but it must be plausible. You cannot sell a drug only, you have to sell a story with it. The better the story, the higher the chances of your success in getting the drug into the market. A drug faces usually its hardest time within the company. Once you have overcome the difficulties inside the company you meet less resistance outside. And so the story is good for the introductory brochure and to convince the registration authorities but the best and the most important purpose of the story to go with the compound is inside the company – to convince management that it is solid reasoning and all that sort of thing. Many drugs that got into the market based on a theory that proved unsatisfactory have proved very useful.

Politics. Talking about politics, some time back you introduced me to the idea of the little Machiavelli. How big a part of the company culture is this?

Well, a very big part I think. We are all human beings and human beings are fighting for rank order and rank order is finally what it's all about. I just don't believe those people who say that they do something for the company's sake and the louder they say it . . . there was a book published recently which was discussed in the newspapers which goes even farther than the little Machiavelli. It was written under the pseudonym, I.N.

Sider, and nobody knows who is it. It was thought that it could be a former manager of Sandoz, but it has not been confirmed. It describes the power play, the politics, in much more colourful detail. I don't think it is in English. I haven't read it yet, I just read the discussion in the newspaper and it is interesting. This journalist thought it was largely overdone, so they showed it to a guy from Sandoz, who after having read it said 'I haven't learned anything new'.

But linked into all this is the idea that companies make various decisions because the managerial people involved are looking after their careers rather than trying to develop the field.

Oh, I think it would not be realistic to say that this is not true. Maybe the non industrial players in the game do too little to clarify certain things. For instance, we still do not know whether there are particular populations of depressed people who react specifically to one type of drug or another and whether this is reproducible from one episode to the other. They are all complaining of the Hamilton Rating Scale as an instrument to evaluate drug effects but who makes a serious effort to develop something else?

Why do you think the medical profession are doing so little?

These things are major efforts – they are not something I think that one person can do. So it's a question of getting organized, a question of getting finance. Clearly, especially at the present time, the drug industry has no interest in financing such things because they've got enough to do with financing their drug developments. So this would be in a domain where the public or the universities or whatever would have to finance that sort of thing. For some reason nobody is taking the initiative. I assume the same career thinking is involved because it is obviously a lot of work which will not lead to immediate results which can be published and so people might want to do fancier things.

In a sense, compared with 20 years ago, the psychiatric profession doesn't exist any more. When the drugs came out, they were able to dictate to the industry – these are the medical conditions that we want to treat, this is the way we want to run trials, these are the scales we want to use. But the big names in the field, the Martin Roths, the Mayer-Grosses, the Hanns Hippius's, are all moving on and not being replaced by comparably big figures and at this stage trial procedures have been globalized, they are multi-sited and the industry dictates to us, this is the protocol, this is how we do it. So the capacity for independent thought and action has decreased.

This has probably been an inevitable development because the industry had to change the procedures for clinical trials because the registration authorities asked for proof of the efficacy of drugs and the statisticians said that it has to be done this or that way to be able to reach a conclusive

answer and that finally led to devising trial procedures which were devised so as to provide a clear cut answer as what was effective and what wasn't. In the end, you might argue that this is to the benefit of the patient and of the health insurance costs because it will prevent inactive drugs from entering the market, which previously you couldn't do. But I admit it ties up efforts and also available patients to an extent that makes other trials difficult but that doesn't detract from the fact that these trials are sorely needed.

What are the groups like ACNP, ECNP, CINP going to do in the new neurodegenerative world?

I think they've got to change their character. At ACNP, there is more and more neurodegenerative stuff coming in. I haven't been at the last CINP but I hear that neurodegeneration is taking more space. So I think the shift in industry will be reflected in the shift in programmes. It depends how ECNP, ACNP and CINP adapt. If they provide room for these topics there will be no need to fund new groupings. If they show resistance new groups will form, there's no question.

How long is it going to be before we have a compound to treat some of the neurodegenerative disorders? A really new compound.

Let me give you an optimistic assessment – five years from now. I think this is perhaps overly optimistic but I wouldn't be surprised if we had something with a better than marginal effect within 10 years actually in the clinic.

So at this stage you feel there are a few compounds you actually have that are going to be those compounds.

Yes. They are at an early stage and they may still fail for pretty trivial reasons and that will prolong the process.

And there will be a few more nervous breakdowns if that happens?

Well, yes, I guess so. Not from my part. I've been in so many that it doesn't hurt anymore.