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The changing face of psychotropic drug development

I was born in Belgrade and I have spent my childhood and adolescence there. Pharmacy and medicine were the tradition in my family. As a matter of fact one of the first pharmacies in Serbia was founded by my great-grandfather Antoine Delini, a French physician who apparently came to visit the country and then never left it. To study medicine was for me therefore obvious and natural since very early. I went to medical school in Belgrade.

Why did you leave Belgrade?

My decision was primarily influenced by a stay in Dusseldorf, where I had lived and spent some time studying and working. I would have probably stayed there, but life plays some tricks – the man I was in love with lived in Belgrade. Since he didn't want to leave the country, I came back to marry him. But thereafter and for many reasons, my decision to leave was firm. Among these reasons the beginning of my involvement in reseach was certainly an important one. I came to Switzerland in 1966 and this has been my home since then.

Did your early research have anything to do with the CNS?

Primarily not. When I finished medical school, due to the fact that there were no immediate positions in the Institute for Child Psychiatry, which I wanted to specialize, I started a training in pharmacology at the Institute of Pharmacodynamics in Belgrade. The project I was working on was related to the investigation of some plant extracts and their allergenic properties. How we got a sample of metoclopramide, a benzamide derivate with a request to have a look at the compound, I don't exactly know. But my debut in psychopharmacology is related to this drug, a predecessor of sulpiride. Since metoclopramide was used for treatment of gastrointestinal disturbances, I was interested to see if it has some protective effects on reserpine-induced ulcers. I found that indeed it had. But I also noted some slight central activating effects. In order to understand this interaction with reserpine I went to study the literature about the mechanism of interaction with reserpine. And that was my debut in psychopharmacology.

You can imagine that there was not much to find in the literature at that time, since the very first papers about psychotropics started to appear only in the early 1960s. But my interest in these drugs and their mechanisms of action was awakened and to me it was suddenly evident that psychopharmacology was what to do next. But where? Who was strong in the field at that time? There was practically no university research in Europe. Most of the research was concentrated in the pharmaceutical industry. Geigy Laboratories in Basel was therefore the obvious choice because they were among the leaders in psychopharmacology and famous because of the discovery of imipramine.

Who was there?

The head of CNS Research was Dr Walter Theobald, who died in March 1995. He was the pharmacologist and essentially the 'biological' father of imipramine and the series of its analogues (desipramine, clomipramine, insidon, carbamazepine). He was the one who initiated the clinical studies with these drugs.

When I came to Geigy I intended to stay there only for a limited period of time, to learn about the backgrounds of psychotropics and then to go back to clinical practice. This period, however, never ended.

My first task was in the general screening laboratory. It was a very good start. Everything I did and had to do made sense to me. General screening combined all the techniques available at that time by means of which psychotropic properties could be identified. Among them, however, the one I credit with major importance was the general observation technique. I learned how to observe from the late Clara Morpurgo. I owe her most of my interest in psychopharmacology and my education in basic scientific principles. She was an exceptional personality, creative and pragmatic at the same time and a born scientist. Unfortunately she left Geigy about a year after I came, otherwise I would have probably progressed much more rapidly under her guidance. But so I had to learn everything by myself, by trials and errors and own experiences. There were no teaching facilities, no handbooks, not even monographs about psychotropics.

With Clara Morpurgo I worked first on the elaboration of a standardized, so-called drug-interaction test battery and operationalized observation technique in mice, which could be suitable for rapid and reliable recognition of various classes of centrally active compounds. The method was published in one of the issues of *Drug Research* in 1968. For a long time we have successfully used it as a routine procedure. Clara Morpurgo also encouraged me to start the development of animal models for testing psychotropics. Brain lesion-induced catalepsy in rats as a model of Parkinson's disease, conditioned hyperthermia as a somatic counterpart of anxiety, and several others that I have elaborated later on, were based on some principles that I have learned from her. These models were extremely useful, because they were not necessarily dependent on a preconceived hypothesis of the mechanism of action of a drug.

That's not the way drugs are found anymore.

No, all these screening techniques are more or less abandoned today and replaced by *in vitro* receptor binding assays or other molecular biology techniques. But at that time there was nothing else. We knew almost nothing about the functioning of the brain. Not even DA receptors in the brain were known at that time. All these discoveries came later. So the only instruments you had at your disposal were your eyes, your observation, your imagination, a search for analogies and extrapolations of what you saw in animals to clinical situations. It was a fantastic time. The observation and the search for analogy with clinical phenomenology were essential. There was an extraordinarily tight bond with the clinics. Nobody needs today to be medically trained to do research in psychopharmacology, but then – without that medical knowledge it was almost impossible to translate experimental findings to the clinical situation and vice versa.

How did clinical training count?

Well, we operated with simple and maybe very naive analogies from today's perspective. We thought, if you can produce convulsions in men, well by the same means you can produce convulsions in an animal. If you have a treatment against convulsions in men – and we went to the laboratory from the clinical observation – then any drug that you discover to have anticonvulsant effect in animals will have to exert the same effect in man. Cardiazol or electroshock convulsion were for instance models for petit-mal and grand-mal seizures as reserpine-induced depression was a model for testing antidepressant properties. There were also simple behavioural tests, like for instance the fighting mouse or the isolation-induced aggression as tests for anxiolytics. By testing and analysing a large number of drugs, by comparison to those already known to be active in the clinic, we elaborated a spectrum of activity that we supposed a new drug had to have. There was not much biochemistry. The interest in a compound was decided upon the spectrum of action in animals, upon quantitative or qualitative differences to a standard and assumptions about analogies. The fact that this was an efficient approach is illustrated by the number of major antidepressants that were developed during this period.

It was the only way to begin?

It was the only rational way to begin. It was an extraordinary way also because it was combined with so much learning about behaviour, about the mechanisms which control it and about CNS physiology. The investigating drugs were also a means to investigate the pathophysiology of brain functions. Geigy did not have a specialized CNS biochemistry unit, as was the case with Ciba. The importance of biochemistry increased only after the merger of the two.

Maprotiline was a Geigy drug or a Ciba drug?

This was almost a parallel discovery. I first worked on maprotiline in Geigy. The compound was synthesized by Dr H. Schröter and I have tested it (Delini-Stula, 1972). By intuition almost, because its particular biochemical profiles was unknown to us in Geigy, Dr Theobald proposed it for development. But I think Ciba had a priority in the patent application by about three months and Geigy had to abandon it. Anyway, after they merged it didn't matter who was the first.

An awful lot of people at that time operated by hunch. Brodie seems to have been a man who went on a hunch.

Absolutely. Why for instance did Dr Theobald selected Insidon for development – a drug which was unimpressive in the screening and did not even do much biochemically? I remember the discussions about that. An extraordinary simple philosophy was behind that – we have imipramine and we know what imipramine does. *Ergo*, we will look now for variations around the spectrum, a little more of this, a little less of that! Amazing, isn't it! So, Insidon impressed by its 'softness' as an antidepressant but it had more marked anti-aggressive properties.

Why did Ciba and Geigy merge? And what was the atmosphere at the time?

The atmosphere was very dramatic. Probably because it was the very first big merger of that kind. There were even suicides. The shocks produced today by mergers, economic crises, loss of jobs and functions are also dramatic, but I haven't heard about casualities of that kind. But, at that time the fact that you lose your job or position due to such an event was perceived as catastrophe by many people in Switzerland. Geigy staff probably suffered more than Ciba since the dominance of Ciba was obvious and their more authoritative management style was felt immediately. This was also the case in the CNS department headed by Professor Hugo Bein.

His is a very famous name.

Yes, he was a very famous name. He was also a very authoritative and sharp-minded person.

Tell me something more about the different management philosophies of the two companies?

Geigy was rather a family enterprise, where I felt there was a lot of respect for people's individualities. I am talking about what I have experienced; some may have seen it differently. Geigy was perhaps conservative and rigid, but rather human, at least I experienced it that way. Ciba was larger, with a stricter hierarchical order, and it was more impersonal. Anyway, the time in Ciba was quite different from the one I have spent in Geigy. Professor Bein left perhaps a year after the merger. After him none of the heads of the Biology Research Department were really CNS men having any psychiatric experience or background in the field. We in our CNS department managed somehow by ourselves.

The department was large and encompassed the CNS psychopharmacology group, which I was in charge of, and the CNS biochemistry group. Luckily, the collegues I had were all talented, dedicated and creative personalities. Retrospectively, it was the most productive period of my life, if you judge by the number of CNS compounds that were in the development between 1975–85. Ciba was among the first to have highly selective noradrenaline and 5-HT reuptake inhibitors as well as selective MAO-A inhibitors, even though the company never succeeded to introduce any of these into the market.

How were the 5-HT reuptake inhibitors discovered?

Their discovery is the best example of concept-guided development. It was based on the Carlsson's findings of differences in the potency of various tricyclics in inhibiting noradrenaline and 5-HT uptake and his hypothesis of the role of noradrenaline and 5-HT in the control of mood and drive – for example, that 5-HT might be more important for mood regulation than noradrenaline. The idea to look for a preferential or selective 5-HT uptake inhibitor as a better antidepressant was therefore almost obvious. So we put a lot of efforts into screening 5-HT-reuptake properties of drugs. Ciba had an excellent biochemistry group and, as I said, I consider myself lucky to have had the chance of having such good colleagues as for instance Laurent Maitre (who was also the head of the CNS department), Peter Waldmeier and Peter Baumann to name just a few. We collaborated intensely with each other and I still believe that this is important, because biochemistry alone, without integration of functional testing, cannot provide the necessary bridge to the clinic.

But it was a period where people were thinking about serotonergic and noradrenergic depressive subtype.

Yes, therefore drugs with selective 5-HT- or NA-uptake inhibiting properties were also considered as a means to identify possible subtypes of depression. We already had a highly selective NA-uptake inhibitor (oxaprotiline) in development (Delini-Stula *et al.*, 1982) and we thought it will be important to have its counterpart – for example, a selective 5-HT- one. Also other companies had started the same programmes in the early 1970s. But I believe that we were among the first to really have one, CGP 6085 (Waldmeier *et al.*, 1977). The drug went into human pharmacology testing, but was cancelled, last but not least because the decision-makers in the company did not share our confidence in this type of drug. Curiously enough, the company always insisted and asked for drugs which will not be me-too, but through all these years they never really had the courage to persist in developing a really novel drug.

Why, what went wrong?

Laurent Maitre and Peter Waldmeier may remember even better the tedious discussions and our fights for the novel projects and for each of the drugs we proposed for development. But, I believe the essential problem was that the research was mostly managed conservatively, by those who were unfamiliar with medicine in general and the CNS field in particular. There was nobody there who understood the complexity of psychiatric research, experimental as well as clinical. The eternal question was: 'What is the proof that you are right? Where are the facts?'. But, if you have a new concept how can you have the evidence without clinical experience? How can you have hard facts after early clinical trials ? How do you explain the pitfalls of bad study designs and a lack of statistical significance in a clinical trial or the importance of reproducible findings by experienced clinicians to those who believe that the only truth is $p < 0.05$? We were helplessly trapped in a circle of the most ridiculous types of reasonings. That's how, for instance, oxaprotiline, the most selective NA-uptake inhibitor, was killed, a drug which was certainly clinically efficient and very well tolerated, as it was recently demonstrated by a retrospective analysis of data. But, what I regret most was the fact that levoprotiline, the inactive enantiomer of oxaprotiline, was not pursued and properly clinically tested.

Now levoprotiline is an interesting story.

Levoprotiline was a unique means to test how correct the hypothesis of noradrenergic involvement in depression was or, more precisely, how important are presynaptic mechanisms for antidepressant properties. Biochemically, with respect to the effects on monoamine metabolism, the drug was inert (Waldmeier *et al.*, 1982). But it showed antidepressant properties and similar efficacy to oxaprotiline as well as tricyclics in several comparative clinical trials. We desperately argued for a rigorous placebo-controlled trial to prove its antidepressant effects, but never had it approved. You realize the importance of such confirmation – it might have been the breakthrough in our concepts about the depression and mechanisms of action of antidepressants. The frustration related to the levoprotiline story, with all the other frustrations due to the loss of so many promising compounds, was a final impetus for me to leave the company. Somehow I couldn't deal anymore with what in my opinion was a mismanagement of clinical development also.

I had started to increasingly involve myself in clinical research during the last five years in Ciba because, perhaps arrogantly, I thought I could influence it for the better. Nevertheless, of the almost 20 interesting and active CNS compounds in the portfolio, Ciba succeeded in bringing none of them out. The last development failure, as far as I know, is brofaromine, a selective MAO-A inhibitor, discovered in our screening in the early 1980s. This is a rather tragic and upsetting balance of accounts if you consider the excellence of CNS research in this company. Every new concept or finding of importance emerging from the basic CNS or clinical research was immediately implemented and further elaborated. We had a certain freedom in exploratory research which is practically non-existent now. Apart from benzodiazepine research, there was no other area where we were not actively engaged and at the front. From this point of view it was really a fantastic period.

You began to go back and train in the psychiatry?

Yes, because I wanted to follow and clinically test myself the drugs, which I thought are so precious for the further progress in the field. Essentially, I have never lost the contact with the clinic. In between I had sabbaticals at Psychiatric University Clinics in Basel and Zurich where I had the chance to work with late Paul Kielholz and Jules Angst, respectively.

What was Paul Kielholz like? He was a seminal figure in developments.

Yes, he was. Somehow his name and his personality fit very well together. You have never met him? He was impressive with his tall, fatherly figure and extraordinary charisma. The patients adored him; many feared him. It is difficult to say why it was so. When you talked to him you always had the feeling that he was able to see through you. He had this kind of slightly amusing smile as if saying – you know, everything is fine, don't take the things so seriously. That was also his attitude towards science and biological psychiatry. It's nice to have a bit of neurobiology, but don't take it too seriously. I don't think that he cared about beta- or alpha-receptor regulation concepts, or even really understood much of the biochemistry. He was down to earth and concerned with clinical practice all the time. But he was an authority and somehow he managed to put his mark on biological psychiatry, without – I ought to say – a truly scientific achievement.

Concepts like masked depression?

For instance. He put it forward because it thought it of practical importance for everyday clinical practice. He didn't like things which did not appear to have immediate clinical relevance. His classification systems were meant as a help and guidance to the practitioners. He didn't care about their scientific validation. His classification was very influential in Europe but he was also interested in concepts like target symptoms and he picked up on the idea of the MAOIs possibly causing suicide because they affected catecholamines.

Many of the things that he has postulated were designed to guide psychiatrists in their daily work. This was a didactic approach, based on his observations and his clinical intuition. But, there is no evidence that they are really correct.

No, there isn't, they were speculative concepts almost, but the idea of target symptoms and suicidality caught on despite the lack of evidence, which maybe says something about his powers of persuasion.

Yes, but also it reflected his cautious attitude. In clinical practice, the primary thing in his mind was not to harm and not to compromise anyone and not to compromise himself. So he didn't want therapeutic failures or problems or anything which might throw a shadow on the reputation of his clinic. For instance, his assumption that MAO inhibitors, or any kind of antidepressant, which lacks sedative properties would promote suicide was based more on intuition, but was accepted as a fact by almost everybody without ever any scientific evidence that this is true. This was the power of his personality and authority.

You also trained with Jules Angst?

Yes, I have spent some time in his clinics too. You can say that if there are two fundamentally different personalities then they are Paul Kielholz and Jules Angst. Kielholz didn't care about scientific precision or even maybe scientific truths, while Jules Angst was careful about every single scientific detail and believed only in facts. Paul Kielholz was a very social person and politically engaged. Jules Angst was rather withdrawn and exerting his influence at a different level. His contribution to psychiatry is remarkable, it will remain and will be referred to and quoted after a hundred years, which I doubt will be the case with many Paul Kielholz contributions. So you see the difference.

You came be in charge of research medically?

When in 1987, due to one of the reorganizations at Ciba, our Clinical Neuropsychopharmacology, that is, our Phase I/II, group was integrated in the Clinical Research and Development Department, I moved entirely to Clinical Research. Geographically it meant from Biology Research on the one side of the road to the Clinical Department on the other side of the road. But it was like being transferred to the other side of the ocean. There were profound differences in the hierarchical structures, management attitudes and styles between two departments. In the clinical Research, there was more rigidity, bureaucracy and, I am sorry to say, a lack of professionalism in the management of clinical studies. When during one of many restructurings of the Department the responsibility and authority of the heads of the groups was transferred to business-orientated managers without a medical background, I perceived that as a programmed disaster.

But did this affect CNS specially?

Perhaps CNS only, but I don't know exactly. Anyhow, CNS is the most difficult and complex research area. You don't have objective and well defined measures of mental states and their changes. Today the credibility is given to numbers, to 'hard' facts. But, can you explain a schizophrenic mind with numbers only? Medicine trains you more then any other science to operate with an interpretation of integrated observations, with 'soft' signs and a quick synthesis of personal experiences with given reality. I firmly believe that you will never be able to make a proper diagnosis of a mental disease only based on 'numbers'. This applies also to the understanding of the meaning of, let's say, Hamilton Scale scores. Can you justify the efficacy of a drug simply on the basis of a HAMD score? Well, you cannot develop a drug if you blindly consider the HAMD score difference as the only 'evidence' and, above all, without ever having experienced a depressed patient. You cannot do a good clinical trial if you don't have an understanding of clinical reality.

The introduction of Good Clinical Practice principles in Ciba at that time was certainly a must and none of us in clinical research has negated the importance of it. But somehow I think there must have been a big misunderstanding of what GCP means and of how it should have been implemented. Many of the control systems, which were imposed on us because of the lack of trust in our performance, ended up in increasingly rigid bureaucratic procedures and delays of decisions. They turned out to be rather counter-productive, inhibiting and demotivating. Well, I couldn't cope with that. I couldn't work for the lack of success. Luckily, when my decision to leave was almost ripe, I got the offer from Roche.

That's a bit like moving from AC Milan to Inter Milan, isn't it?

Not entirely. I was moving out of Basel. Roche opened a new International Clinical Research Centre on January 1 1990 in Strasbourg. On January 2 I was there in a positions of responsibility for the CNS research unit.

Why outside of Switzerland? Was the industry slowly leaving Switzerland?

I don't think this was the primary idea. I think the idea was to have a clinical research centre within the European community in order to be more flexible and to have easier access to experienced people from different countries. My task was supposed to be a building up of a research programme in schizophrenia – it was quite a challenging task for me. There is a lot of research and development in depression, justified, of course, but much less so in schizophrenia. I had felt that this is a field where a lot more research should be done. My project was related to one of the partial benzodiazepine agonists (bretazenil), which accidentally was shown to have some antipsychotic properties. The whole story about benzodiazepines and their antipsychotic potential has been a matter of debate over decades. So I felt there was something challenging to do and to learn about the benzodiazepines. All the methodological problems of clinical trials in schizophrenia also interested me.

Was Willy Haefely involved? He was one of the key people, who for some reason isn't known about so much?

Willy was a very good friend of mine and of course he was involved. He was the Head of CNS Research in the Biology Department in Roche. He was also another exceptional personality. I think there wouldn't have been any deep understanding of benzodiazepines without Willy Haefely. He was their father. An extraordinary mind. Very creative. If you have an image of a scientist as he should be then in my eyes it was very much Willy Haefely.

It's curious, if you read the books, people talk about Leo Sternbach but while he was involved in discovering chlordiazepoxide, Willy Haefely was the benzodiazepines.

I think I already said this. Essentially it's a very strange thing that there is a reference to the chemists who have synthesized a drug but hardly any to the biologist who discovered its potential. That there is reference to the chemist is perfectly all right. But the work done by the biologists, the astuteness of observations, the creative mind which sorts something meaningful out of the observations so that you can go further – nobody ever mentions that. The merit of the biologist who is sitting, observing and investigating the effects of the compounds and providing the conceptual framework for their development, as was the case with Willy Haefely, is rarely adequately praised. Now, whether he was right or wrong in some of his hypotheses that's a matter of debate, but I think this is irrelevant. Even the wrong concepts are stimulating. You go and find what is wrong and so it means further research and progress.

Anyway you entered the area with the issue of the partial agonists . . .

Yes, and the project went very well. But, unfortunately, two years afterwards Roche's interest in developing bretazenil for schizophrenia just faded and the project was abandoned generally. I have the impression that classical psychiatric indications are slowly losing their importance for big companies because I believe, they are not considered as very profitable. The development starts to be cumbersome and costly. The management sees only the difficulties and maybe perceives that at the moment in this area there is a kind of a steady-state. There is nothing conceptually really truly new. And maybe this is discouraging them from investing in this kind of research. Nowadays you have a very tedious and long road ahead of you if you want to develop another antidepressant, neuroleptic or tranquillizer. So there is a loss of interest in the classical CNS indications.

In a sense, then, we're at the end of an era, aren't we?

Well, yes, I would guess it is so. I don't know whether the extent of changes in the CNS field is as dramatic in other companies as the extent of change that I have perceived within the three big Swiss companies. Ciba-Geigy, a leader in antidepressants, abandoned research on antidepressants by 1986/87 or maybe even earlier. There was no further active research in antidepressants. In Roche the same thing is happening in the benzodiazepine field and in Sandoz, I guess, in neuroleptic research.

Why did Roche run with moclobemide when Ciba for instance didn't develop brofaromine?

The climate in Roche and the climate in Ciba were not identical. In Ciba the changes to 'business-orientated' research and development started very early, already in the mid-1980s. When I came to Roche in 1990, the structure and organization were different. But it doesn't mean that there were no difficulties in developing moclobemide. Nevertheless, personal authorities still counted. First of all, there was Mosé da Prada who discovered moclobemide's properties, then there was Willy Haefely and Roman Amrein, head of CNS Clinical Research. They were very strong and dedicated personalities who believed in the concept. In Roche, at that time, the opinion of such personalities was still respected.

But they had to cope with the legacy of the MAOIs?

Certainly. This had a big impact on the development and acceptance of the drug. The disbelief that a MAOI-type of drug, even if novel, will be accepted in USA, was probably decisive for the attitude of Ciba. I believe that unless there is the trust that you will have the USA market and have a sizeable profit, the big companies do not want to engage in the development of any drug. The costs of the development are just extraordinary and without that market the return-upon-investment is probably uninteresting. Roche certainly has the same attitude today, but to have the USA market was apparently not so decisive some years ago. The research succeeded with moclobemide really at the very last moment.

Has there been a problem in marketing moclobemide in that its the only RIMA?

This is of course unfortunate for the drug, because it is hard to argue about a drug class if you have a single compound only. From the scientific and research point of view every drug measures itself against another one. This helps to acquire a better knowledge, to improve and validate the concept, and to gain the confidence of the users. It is a pity that Roche has no follow-up development. What they intend to do I don't know.

Let's turn to the European College of Neuropsychopharmacology. Were you involved from the start?

Yes. The idea of founding the ECNP came from Per Bech and Carl Gottfries, who proposed this at the 25th Meeting of the Scandinavian Psychiatric Society. In 1985 they invited a group of representatives of other societies to Copenhagen where the proposal and the first outlines of the College were discussed. At that meeting the late Ole Rafaelsen proposed me as the member of the constitutional board, that is, the Executive Committee. That's how I came in. The idea about ECNP was enthusiastically accepted at that meeting. Also I have identified myself with it completely.

What did people hope to get from ECNP?

First of all I think there was a need to have a platform within Europe, a kind of forum of those people who have contributed here in Europe, in one way or the other, to the research in the field. There was CINP, of course, but CINP was not representative of Europe and not any longer what it was in the beginning. A kind of exclusive club where everybody knew everybody. The meetings are now huge–5000 persons or more and the activities not transparent any more. The second reason was the existence of ACNP, which is a very influential society and not only of scientific importance in giving direction to the research in the field. ACNP is representative of American opinion and politically important. In Europe there was no counterpart of the ACNP, and the CINP circle was not a proper platform to profile European biological psychiatry. So many of us felt that we needed a society where we can unify our experience and promote European standards and concepts. A society which will be a partner for discussion with our American colleagues.

There was also more and more an impression that European biological psychiatry was overwhelmed by American psychiatry. Of course, that's a development, but we should not forget that many of the 'American' ideas had been generated essentially in Europe. We are facing a very curious situation. You generate the fundamental things and they are taken overseas and all of a sudden you have to digest what they portray as their own creation. Isn't this a frustrating situation? I think all these motives were behind the idea of ECNP. There was also no association at European level, which would have been the one to give direction to young scientists, to give them the opportunity to profile themselves within Europe and compete with the Americans.

How did it happen that I was the first President-elect? After the meeting in Copenhagen we decided to organize the first ECNP constitutional meeting in Brussels which took place in 1987. At that meeting the general assembly elected C. Gottfries as a President, Per Bech as a Secretary and me as President-Elect, based on number of votes that the proposed candidates received. So that's how it happened. But at the following congress in Göthenburg somehow things went in a different direction and many decisions of the Brussels assembly were not respected. All of a sudden some other forces entered into play and nobody was prepared for that.

Other forces being . . .

It is a very delicate thing to talk about and people may think that what I say is because I was disappointed. This is really not the case. The procedure at the Göthenburg meeting was just irregular. There was a lot of manipulation behind the elections at that general assembly. Anyway a new Executive Committee was formed and another President elected. I understood that maybe what was wanted is a bigger and more influential name. I am not such a name for sure. A few of us who were initially in the Executive Committee couldn't however accept how the original idea of ECNP changed under the new presidency. We found that it turned out to be just another kind of society but not with the profile it was meant to have at the beginning. Maybe now the things will change again because there are new people in the Executive Committee.

It certainly hasn't become an ACNP-equivalent yet.

Definitely not. It doesn't have anything so distinctive as the ACNP has. It's just another society. Sometimes they have good meetings, sometimes bad meetings. But there is no specific attraction or motivation for any young person to think that it's a particular achievement to be elected a member of ECNP.

Where did the idea for a European Committee for standardization of clinical trials in Europe come from?

The idea came again from Per Bech. Initially we (Per, Jenny Wakelin and myself) were a sub-committee group of ECNP. But since we received no support for our activities from ECNP, in 1990 we decided to work independently. We wanted to find a way to promote standards of CNS clinical research in Europe in harmony with Good Clinical Practice requirements, European and FDA guidelines, but also considering the application of the newest scientific achievements. There wasn't any support for this kind of initiative in the ECNP. ECST is aimed to deal with clinical methodological problems generally. We felt that's what is really missing. The meetings that we have since 1991 in Strasbourg confirm this. I have proposed Strasbourg as the meeting place because I was there and I could really help to organize it. Those who participate in our meetings are quite enthusiastic about it, because our approach isn't academic but orientated towards practical solutions taking into account the newest findings.

It's one area that needs to go forward – the area of clinical trial designs and methods . . .

Definitely. I believe that there is a big gap between what the research can do and what can be proved in the clinic. A gap that is very difficult to bridge. The industry had a restrictive policy with respect to truly research-orientated trials but without industry you just can't do much.

One problem for ECNP is that at almost the same time the Association for European Psychiatry was formed and surely it would have always been hard to get two European organizations to start up at the same time. Another thing, as you said, is that the companies are beginning to leave mental health for the neurodegenerative areas.

I feel that we are facing almost evolution-like dynamics in the field. You had the time of big developments in psychiatry. Now we have a phase where we are as in a steady-state with our biological concepts. I don't think, with these kind of concepts that we have now, we can do much more than what we have done. Obviously you enter then in a phase of apparent decline. Perhaps the research will have to go again in the 'wrong' direction and then there's hope that there will be a turning point for something very new to emerge. But at the moment the pharmaceutical industry restricts developments and experiments. Even those who are big in CNS have limited their involvement. They support only those projects which appear to be the most profitable from the marketing point of view. There is more and more stringent selection as to who and what will be supported. The flourishing phase is certainly over. The new introductions nowdays are essentially drugs which are 10 or 12 years old or more.

Nobody works on animal models anymore. What are the implications?

Or very few and they are farther than ever from clinical reality. There are very few medically trained people in this kind of research today. Many learn about mental disorders from the DSM classifications and then believe they know what the diseases are like. They believe that if you have a drug which attacks receptor X, this will solve the problem of treatment, but that is naive. You can't progress without animal models from my point of view. But they need to have some construct validity and predictive value. You cannot really know what will happen in a living organism if you are only testing *in vitro* or in some isolated biological systems. This is so obvious. But creation and validation of conceptually novel models needs new drugs, clinical testing and decades of work.

You could argue that the only way now that we could actually find new antipsychotic agents or antidepressant agents would be by going down the neurodegenerative route because people will be trying to produce something completely different, which may co-incidentally . . .

Indeed, but you have to have the chance to test them and to go back to the models. On the other hand, because there are such restrictions now on the use of animals in research, you also have a problem. You have to justify every animal that you use so you just don't want to get into this trouble. But I really strongly believe that we will not be able to make any really new discoveries without a certain liberty of exploration, without preconceived hypothesis as to what you should find. With all the limitations imposed today by public opinion, authorities, rigid clinical development schemes and lack of resources, I am rather pessimistic about serendipity.

You were involved with AGNP, the German Society, before ECNP; what was it like?

I liked very much the AGNP because it was a small society. There were about 200 members, a number which was kept constant for years and years and among them were all the grand names of German-speaking psychiatrists. AGNP was influential because actively involved in political life, in taking the positions about actual issues and research activities via its working groups. It's a very active society but very transparent in the organization. What I liked about the society was that you could come and talk informally about your findings at the meetings. Everybody knew everybody. AGNP is a tradition, which maybe you also see in the BAP but hardly in any other societies, which are starting to be so huge and anonymous. AGNP as a platform for communication was very productive. From this point of view I like the kind of societies which really keep a certain standard in the membership and remain somehow modest.

The influence of industry on these things is mixed, isn't it. You've got to have the industry to produce the drugs and you've got to have the industry to support the various different societies

This is always a kind of partnership. The problem is that everything becomes so commercial, everything is business-orientated – there is no more real partnership just for the sake of the science. It's partnership just because there is buying and selling. Why was this different in the past? Because I believe that there was a period when the industry, science and the clinic lived in a system of mutual exchange and support without so much money directly involved. The clinic needs good drugs, but clinicians seem to be obliged to buy and promote every sort of rubbish because there is money involved. That's where there starts to be a problem.

Is what you're saying the industry needs clinical people to be independent and they're not?

I'm certainly for an independence of mind and objectivity. I am working for the industry but I want the freedom to be independent in my scientific opinions. If a drug does something which I think should be said that it does, I want it to be said. I never wanted to change my opinion just for the sake of the market sales. But it starts to be a problem that a lot of things are presented in a way which suits the marketing, but not scientific objectivity. That's where I think some people may be selling themselves.

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