

THE FOUNDING OF THE CINP & THE DISCOVERY OF CLOZAPINE HANNS HIPPIUS

There are two people at the moment who I particularly associate with an interest in History of Psychopharmacology -Tom Ban and yourself. Why are you interested?

Both of us - Tom Ban in Hungary and me in Germany - joined the field of psychiatry in the 1950s. We joined at a time that has since justly been called the "psychopharmacological turning point in psychiatric therapeutics". Therefore, as young psychiatrists we were involved in the early development of clinical psychopharmacology and took part in the discovery of new therapeutic drugs.

Now - almost forty years later - it is fascinating for us as participating witnesses of modern psychopharmacology from the beginning to document, to summarize and to analyze this history. Tom is particularly interested in this.

I am also interested in history - but the reaction I get from many in the profession is that history is bunk - Henry Ford's view. The field is moving forward, you only need to know what's current. How do you explain this?

I think the position of Henry Ford is not acceptable in our profession. Each psychiatrist has to be interested in history because in our everyday practical work we are occupied with biographies, with the histories of individual human beings.

Besides for a German psychiatrist, there exists a very serious and special reason to be engaged in the history of our field - the development and situation of psychiatry in my country during the Nazi period. In that time, German psychiatrists were responsible for the most excessive and cruel misuse of psychiatry. How was it possible that German psychiatrists tolerated and some of them even supported actively the killing of almost 100,000 psychiatric patients? This is up to now one of the most important problems for historical research in psychiatry.

Finally there are some personal roots and reasons for my interest in history. As a boy at school I was for a long time irresolute if I should study history or medicine. Later working in clinical psychiatry, I had the privilege to work in two places with outstanding psychiatric traditions - in Berlin from 1952 to 1970 and in Munich since 1971. For the past twenty years I have worked in the hospital where Emil Kraepelin, Alois Alzheimer and many other excellent psychiatrists were active as both clinicians and scientists. In such an atmosphere under the influence of this "genius loci" you must be interested in the history of psychiatry. In the library and in the record-office of the Munich hospital I discovered a lot of interesting documents. For example, there were the unpublished memoirs of Emil Kraepelin - now edited and published in German and English. I've got exciting letters from Wilhelm Wundt to Kraepelin or a private letter of Sigmund Freud to a patient with the recommendation to continue in treatment in Munich, because treatment in Vienna with Freud himself, with inflation as it was in the early 1920s would be too expensive. I also found documents on the mental state of King Ludwig II of Bavaria, who died in 1886 together with the psychiatrists Bernard von Gudden, one of the predecessors of Kraepelin in the Chair of Psychiatry at the University of Munich.

From 1900 - 1950, world psychiatry really was German psychiatry. The leading concepts and the leading people were German. As of 1950, there was this watershed

and in a sense no one seemed to replace the generation of Kurt Schneider. That's the way it seems to me, am I wrong?

I am not sure that it is justified to say that psychiatry from 1900 to 1950 was German psychiatry. It was owing to the efforts of French psychiatrists at the end of the 18th century that psychiatry had been established as a clinical discipline within medicine. At the same time, important influences also came from Great Britain in the field of the practical care of psychiatric patients. In Germany psychiatry developed in the first half of the 19th century on two separate fronts. Up to the middle of the century the first professors of psychiatry at the University in Germany were more engaged in philosophical aspects of mental illnesses than in the practical care of mental patients. These psychiatrists (Psychiker) created the basis for psychopathology and psychology, for anthropological aspects of our discipline and even for psychoanalysis.

More or less independent of these developments in the first half of the 19th century, in all parts of Germany, psychiatric hospitals were established. The medical doctors (sornaliker) working in these institutions became the pioneers of the practical care of mental patients. The relations and the exchanges between these two groups of psychiatrists were not very good - sometimes there were even pugnacious arguments.

This unsatisfactory situation changed in the course of the second half of the 19th century by establishing hospitals and chairs for psychiatry in all German universities. A key person for this development was Wilhelm Griesinger. And in connection with this evolution, German psychiatry - or it would be better to say psychiatry in the German speaking countries (Switzerland, Austria and Germany) - got an increasing role in psychiatry as science.

But the hegemony, as you put it, did not last up to 1950. I think it was only up to the 1920s or early 1930s. It was finished with the emigration of an enormous number of German speaking, especially Jewish psychiatrists, from Germany and later Austria, into other countries. In connection with this pitiable development, the standard of scientific psychiatry inside Germany sank remarkably and international attention on it decreased. The reputation of German psychiatry collapsed entirely in connection with political developments and the misuse of psychiatry during the Nazi time. This is also the reason for the fact that the reception of the scientific achievement of some German psychiatrists who worked and published inside Germany after 1933, for example Karl Bonhoeffer, Kurt Schneider, Ernst Kretschmer, Karl Leonhard, happened with more or less delay after the war.

The belated recognition of Jaspers' work has another origin. Karl Jaspers only worked in psychiatry for six years, from 1909 to 1915, at the psychiatric hospital of the University of Heidelberg. He left clinical psychiatry very early and had already by the age of 38 been appointed to the position of full professor of philosophy at the University of Heidelberg. Because his wife was Jewish, he was forced in 1937 to leave his outstanding chair of philosophy. After reinstatement in his former position in 1945, he moved in 1948 to a chair of philosophy at the University of Basel. For these reasons, Karl Jaspers was very often classified as a pure philosopher and his fundamental and famous book *Allgemeine Psychopathologie - General Psychopathology* - first published in 1912, for a long time did not find an entrance in psychiatry - with some exceptions such as Germany, Austria, Switzerland of course but for example Japan too.

If you talk about a watershed around 1950, I think this year marks a point of time for the start of the reintegration of German into international psychiatry. The situation of scientific

psychiatry inside Germany during the first years after the war was a peculiar one. At the University hospitals research was only oriented on the one side on psychopathology and on the other psychoanalysis. The philosophy of Husserl and Heidegger influenced the interpretation of psychopathological phenomena. This was so-called anthropological psychiatry. Immediately after the war almost all prominent psychiatrists were engaged in this while the younger ones were involved in the reimport of psychoanalysis and for them this had priority.

For biological research or even for therapeutic research at all there was little or no interest. This situation changed dramatically in the 1950s with the introduction of the neuroleptics. At this time several young psychiatrists began very soon to investigate the therapeutic effects of the new drugs. Doing this these young psychiatrists became increasingly enthusiastically engaged in the this field. But in the early 1950s, the heads of university departments, the full professors of psychiatry in Germany, had decided that therapeutic research could only be a "side-effect" of basis science in psychiatry. In the German tradition, since the last century through to Karl Jaspers and Kurt Schneider, "real" science could be psychopathological research only!. This situation is by the way the background for a German pioneer book on the new therapeutic drugs: the monograph on "Psychopharmacologie und Psychopathologie" published by Wolfgang de Boor in 1956. As a pupil of Kurt Schneider, he trained in psychiatry immediately after the war at the psychiatric hospital in Heidelberg. In his book De Boor reviewed the effects of psychotropic drugs firstly from the point of view of experimental psychology; he had much less interest in their role as therapeutic agents.

That tradition in a sense goes right back to Kraepelin who coined the term pharmacopsychology.

Yes, that is right. More than one hundred years ago, in 1892, Emil Kraepelin had published his classical monograph "Über die Beeinflussung einfacher psychischer Vorgänge durch einige Arzneimittel". Therefore it is justified to call Kraepelin one of the founders of experimental psychopathology.

In a sense, that's the one area of psychopharmacology that, in recent years, we have missed out on - the use of drugs to test cognitive function. Perhaps with the eclipse of LSD this whole area atrophied.

I agree with you but we should distinguish between drug-induced experimental psychology (in the sense of Kraepelin) and drug-induced experimental psychopathology in the sense of Moreau de Tours which had the aim of provoking a "model psychosis". This second kind of experimental psychology had in Germany a tradition up to the present time. For example K Behringer has investigated the psychotropic effects of mescaline and H Leuner has written on the basis of his experiments with LSD a monograph "Die experimentelle Psychose". Later Leuner tried to transfer his experiences with the application of LSD under experimental conditions into a special kind of psychotherapy - so-called psycholytic therapy. This therapy does not now play a role.

From my point of view for further scientific progress, we do not need this kind of experimental psychology with hallucinogens and related drugs. Instead of this purely experimental approach we should intensify again the global but more precise psychopathological investigations of therapeutic drugs o the whole - that means including drugs used in internal medicine.

How much do you think the War also influenced things by making the outside world hostile to German ideas. Reading back through some of the archives of the British

Journal of Psychiatry at annual meetings, just after World War I and after World War II, you heard statements being made in public meetings, "well the War has proved we cannot believe anything the Germans say". Do you think this kind of reaction delayed the acceptance of the ideas of Jaspers and Schneider?

Not very markedly. On the contrary - it was an unexpected and surprising experience for me as a young assistant to be welcomed in a very friendly way as a participant at international psychiatric congresses in the 1950s - Paris in 1955, Zurich in 1957 and Rome in 1958. German emigrants such as Willy Mayer-Gross from the UK, Lothar Kalinowsky and Fritz Freyhan from the US, Heinz Lehmann from Canada and Hans Hoff from Vienna who was back in Austria after his emigration time in Iraq.

Mayer-Gross and Kalinowsky later very strongly influenced my development in clinical psychiatry and research during my training in Berlin. When Mayer-Gross was informed that I had studied chemistry besides medicine, he stimulated me to do with this background of knowledge in biochemical and neurophysiological research into investigations on psychotropic drugs. In our correspondence, he had suggested already in the early 1960s that I should investigate serotonin in mental patients. Kalinowsky invited me to be the co-author with P Hoch and him in writing the textbook on Somatic Treatments in Psychiatry. I was responsible for all chapters on drug-treatment.

Now to the other part of your question. I cannot explain conclusively what the reason was for the long delay in the reception of the ideas of Jaspers and Schneider in the US and the UK. Is it not the general problem of the increasing influence and expansion of the English language in all branches of medicine, including psychiatry, with the consequence that the concepts and ideas of authors that need to be translated into English have a delayed reception?

Comparing the situation in the USA and the UK relative to the reception of German contributions to psychiatry in the 20th century, the UK had a different - if you want a better - situation. For example by the medium of Mayer-Gross and his classical textbook with co-authors Martin Roth and Eliot Slater and through the influence of Erwin Stengel, the contributions of German psychiatry were integrated unobtrusively in English psychiatry. In contrast to the UK, in the USA for example, Emil Kraepelin was not very well known until 1970 and the name of Alzheimer completely unknown until ten years ago. Now the situation in the USA has changed drastically with the result of DSM-III, DSM-IV and the so-called "Neo-Kraepelinism" and Alzheimer has advanced to a term of colloquial language.

I have not been aware of it in this manner. I'm sure you know the name Mayer-Gross? Mayer-Gross was an emigrant and I think he has influenced very strongly the development of psychiatry in Britain. He was a pupil of the so-called Heidelberg School and he brought with him what he had learned in Heidelberg with Jaspers about psychopathology ..

I think the reciprocal influences in psychiatry between our two countries in the last four decades were stronger than we will admit. For example, William Sargant's work on ECT was noted by the book of Hoch and Kalinowsky. And the Leonhard concept of classification and the course of the endogenous psychoses - mediated by Frank Fish - was for some time better known in the UK than in the western part of Germany. Finally the fruitful and successful development of social psychiatry in Germany after the war was owing to the many stimulations of British psychiatry.

You were at the 1955 Saint Anne meeting, and in Towards CINP you mention that it was the first of the large international meetings but also that one of the odd things about it for you it was that it was the first time for you to meet some people from Germany. Is that where you met Wolfgang de Boor?

You have to take into consideration that I have worked in this time in Berlin which was a very isolated situation. During the first ten years after the war travelling and attending scientific congresses - even inside Germany - was almost not possible. In these years German psychiatrists were not allowed to attend international meetings. They were not invited and not accepted as speakers. Therefore in 1950, with the exception of K Conrad, the professor of psychiatry in the Saar, which at this time was under the French Government, no German psychiatrist was allowed to attend the First World Congress of Psychiatry in Paris. In the following years the situation improved at first with regard to neurological congresses - for example the World Congress of Neurology in Lisbon in 1953. But the first important international psychiatric meeting with several German participants was the International Colloquium on Chlorpromazine and Neuroleptic Drugs in Psychiatric Treatment in Paris, in October of 1955.

By chance, I had the opportunity to attend this 3-day congress with many possibilities to meet for the first time psychiatric colleagues from Germany such as Wolfgang de Boor from Cologne, H Kranz from Mayence, Fritz Flugel and Dietmar Bente from Erlangen as well as psychiatrists from many other countries - Delay, Deniker, and Pichot from France, Rumke from the Netherlands, Hoff from Austria, Mayer-Gross from the UK, Delgado from Peru, Overholzer, Denber, and Freyhan from the USA, Lehmann from Canada and Barahona-Fernandes from Portugal.

For me, the very interesting scientific experience of the Paris Meeting was the differences between the conceptions of the few German psychiatrists - De Boor, Kranz and Selback - and the scientific approach of the majority of psychiatrists coming from other countries. For the German psychiatrists, the drug therapy of psychotic diseases was only an instrument for research. The overwhelming majority of psychiatrists from all other countries (including those who came originally from the German psychiatric tradition such as Mayer-Gross, Hoff, Lehmann and Freyhan) saw the enormous importance of chlorpromazine and other neuroleptics in the area of therapeutic efficacy. This experience was decisive for my own orientation to research since 1955 - my efforts I thought should be directed closely to psychiatric therapy.

Why is that?

The influence of philosophy on psychiatry has a long tradition in Germany. I have already referred to the situation of psychiatry in Germany during the romanticism early in the 19th Century. And immediately after World War II psychiatrists as scientists were again inclined to be engaged more with sophisticated philosophical problems than with such pragmatic and ordinary questions as therapy!

I do not want to be misunderstood: Psychiatry as a part of medicine has the function to import philosophical and anthropological ideas to all other disciplines of medicine. Psychiatry is the ideological seismograph of medicine, reflecting many facets of the predominant "Zeitgeist" - but psychiatry has to fulfil this function without neglecting its original duty: the care and therapy of patients!

I think several psychiatrists as Mayer-Gross - originally Germans but forced by the Nazis to leave Germany - emigrated to countries as UK with a long tradition of very pragmatic orientated psychiatry. The emigres became through their fate representatives of a very creative integration of two different psychiatric traditions. In their new homeland, they were proofed against too much philosophical speculations and were immune from the neglect of the care and treatment of their patients.

So how did you escape that?

I have studied both medicine and chemistry. After finishing my studies, I first work in an institute for immunology and biochemistry - then I switched to psychiatry. In my first position in a department for psychiatry and neurology I was responsible for the laboratory only, not for patients. But this changed. I got increasing interested in clinical work. In this field I had the choice between neurology and psychiatry. Initially I was inclined more to neurology. Finally my ambivalence between neurology and psychiatry was solved by the introduction of first therapeutic psychotropic drugs in psychiatry. This became decisive for my professional life. I switched definitely to psychiatry with the aim to work also in laboratories (EEG, clinical chemistry). My clinical training was directed from the beginning to therapeutic problems and my interest in research was in the field of biological psychiatry. At this time I read extensively the classical psychiatric literature in German. And of course I studied Jaspers - but I had only very little time to read Heidegger and all the other authors who were obligatory at this time for a young psychiatrist in Germany if he was interested in an academic career

Who introduced chlorpromazine to Germany?

In Germany chlorpromazine was already introduced in five university hospitals and in several state hospitals by 1953. The background for this early availability of chlorpromazine was the fact that since the end of the 40s, the first contacts between the French and German pharmaceutical industry (Rhone-Poulenc and Bayer) grew up. Because of this, information on the spectacular therapeutic results in French psychiatric hospitals came to the Bayer Company and then to the directors of the psychiatric hospitals. Surprisingly the resonance on this information was small. But in five university hospitals - independently from each other - younger assistants were stimulated to investigate chlorpromazine as a therapeutic agent. This was D Bente in Erlangen, Schmitt in Heidelberg, M P Engelmeier in Munster, K Heinrich in Mainz and J Hiob and me in Berlin.

In some places the first therapeutic trials with chlorpromazine were carried out without support by the chairman of the departments - in single hospitals even against the recommendations and orders of the chairman. Only Prof. Fritz Flugel, the chairman of department at the University of Erlangen actively promoted early on his assistants Bente and Itil in their research with chlorpromazine.

In Berlin, J Hiob was a pioneer with the early clinical investigations of chlorpromazine. He was an experienced clinician already trained in internal medicine. I came from the biochemistry laboratory and was a beginner in psychiatry. We both decided we should start a chlorpromazine trial in a single chronic patients. We had both read the early papers of our French colleagues and were so impressed that we ask the people of the Bayer Company, if we could have material for a therapeutic trial. We received the material but the director of our hospital hesitated to allow us go ahead. We regretted this order because we knew that we were one of the first places outside France in a position to investigate chlorpromazine. Because of the hold-up, I began with animal experiments and investigated the influence of chlorpromazine on the EEG of rabbits. Nice results, but not very useful! Hiob on the other hand had no interest in a switch over to animal experiments. He insisted on carrying out

therapeutic investigations. Finally our head of department agreed but told us to go ahead, but it would not be successful because all drugs which have been used since the beginning of the century, barbiturates etc., had not been effective. And in addition "therapy is not science!".

In spite of this not very encouraging comment, Hiob proposed to try chlorpromazine with a special patient. It was a female chronic schizophrenic patient with a paranoid - hallucinatory symptomatology. I remember exactly the visit with our Professor two weeks later. He said to us "please, look she improves completely independently of therapy! It was very good that I have not encouraged you to treat this patient with chlorpromazine. This is a typical incalculable spontaneous improvement. She has now much less hallucinations than two weeks ago. And I have saved you from a misinterpretation". Hiob hesitated several seconds and then he stuttered "Oh yes, oh no, oh yes - but we have treated her for two weeks with chlorpromazine". That was a peculiar situation. Our Professor of psychiatry was a little bit angry about all of this. But finally he permitted us to go ahead with further investigations.

What were your first impressions of this drug?

Over-whelming. Hiob and I had read the papers which came from the first meetings in France, Hiob was familiar with French and he said we have to use it. The Bayer company had a connection to Rhone-Poulenc and therefore we could get chlorpromazine for animal experiments and for clinical trials. We informed our Head of Department and he said - do it by all means but it will not be successful because all drugs which have been used since the beginning of the century, barbiturates and so on, are not effective and of course therapy is not science.

Hiob said we should do it in a special patient - a chronic patient with a chronic paranoid hallucinatory schizophrenia. I remember exactly the visit with our Professor, two weeks, later. He said to us "please look she improves completely independently of therapy, it's very good that I have not encouraged you to treat this patient with chlorpromazine - she is much better than two weeks ago. She has much less hallucinations". Hiob said "ah yes we have treated her for two weeks!" That was a very funny situation. Our professor was a little angry. But I have to say, then he has allowed us do more clinical experiments. It was completely overwhelming. On the other side, Hiob and I together we have read the literature about reserpine and one year later we made the first investigation with reserpine.

And did it work?

Yes I think it worked. But reserpine was only one drug. Many more came from chlorpromazine because their synthesis was very simple and we were interested to investigate connections between the chemical structure and the special profile of drugs and their actions. Reserpine was the only one of its kind and therefore there were no possibilities for this kind of work. Because of this interest we investigated many different tricyclic neuroleptics and because of this, we had a very early opportunity to look at imipramine but I have to say we have not registered that imipramine was an antidepressant. We thought it was a weak neuroleptic. It was Roland Kuhn, from Switzerland, or his nurses anyway that found that out.

I have heard people say this. Clearly once he came round, he did a great deal to push the idea but as I have heard it, it was very much the case that he was an existentialist by training and really didn't expect a drug to work and it took some time with the research team, the nursing staff and the industry saying to him, look don't you think something is happening before he really agreed.

I think all of us in the middle of Europe at this time, three years after the beginning of chlorpromazine, had been given this biochemical structure, very closely related chlorpromazine. We had all investigated this new drug by Geigy on this aspect of whether it had a neuroleptic profile and all we had found was that it was a weak neuroleptic - even in high doses up to 1000 mg. At 1000 mg, it began to resemble chlorpromazine a little bit more. But in this Swiss hospital I think they were very well trained male nurses and they had noticed that it had an antidepressant effect.

I think that this kind of discovery is not so rare. It is not seldom that the nurses or the people on the wards pick some of these things up first. I ask my nurses for side effects. Very often I get the first signs and the first information from the nurses. I think that's okay. I know Kuhn from 1956/57. I met him in this year because I was invited by Geigy to Zurich in 1957 because of my special interest and therefore I met Kuhn.

Were you at his talk, the lecture that he gave at the World Psychiatric Association in Zurich in 1957?

Yes, I was at that but also in this case the Head of the Department of Research, from Basel, was interested in the work and he invited me to come to Basel and to talk in a very small group about chemical structure and clinical effectiveness. And this was the first time I had met Kuhn. At that time he was much more engaged in anthropological psychiatry. That was his main research and it was only by chance that this drug was investigated in his Department.

Can I move you back to the 1955 meeting. What was the atmosphere at that like? Was it clear to all of you that this was a new era or not?

Oh I think yes. On the one side for the younger people, of course, because we were already identified with this. After having the experience with chlorpromazine we were convinced that a new era had begun and we were very glad that at an international meeting, prominent psychiatrists outside Germany, had the same convincing experience. But inside Germany, our teachers had said that if you want to do real research you can't do therapy. You have to do philosophical or biochemical basic research and therefore I think for many people, the meeting in 1955 was a great influence. Seeing Delay, Mayer-Gross, Hoff and Delgado and all the famous men who I had known only from the literature. They were all there at this meeting and because this was a three or four day meeting, it was possible to talk with them. I think there was a stimulating atmosphere.

Linford Rees was at that meeting and presented the only randomised controlled trials at the meeting - it does seem to have been a British thing, this idea of lets randomise...

I think for methodology the development in Great Britain was a big influence for the whole world. And at this time another German who was eminent in Britain was the psychologist, Hans Eysenck and he made contact with German academics very early after the War. In this way Great Britain either through clinicians like Linford Rees, or on the other side Eysenck as a psychologist, methodology came back to Germany.

Let me chase you a bit further and get into Mark Twain country.

The Mark Twain effect you should read in the excellent English of Mark Twain or Michael Shepherd. If you go into the history of psychopharmacology or in other fields you will find

that some people remember better and better with increasing age things which have never happened. For instance, I was an editor on the first booklet on the Founding Members of the CINP and I had a very critical comments from some people and I had to say that we know you were very involved but you were never a founding member.

This seems to have particularly applied to the 1957 meetings. Who was responsible for the 57 meeting.

In May..that was I think the psychopharmacologist Garattini. Garattini at this time was a young assistant of Trabucchi and he stimulated Trabucchi to arrange a more basic science orientated symposium. There was at this time already enough information through pharmacological institutes and hospitals which were doing therapeutic research in Europe and throughout the world ... Garattini, at that time was I think about my age and he stimulated his Chairman of Department, Trabucchi, who invited pharmacologists and basic scientists especially. For the basic scientists it was, I think, a very important meeting. The clinicians were not so involved in this meeting but I was impressed. At this time, I was responsible for the laboratory at this time and I worked in the hospital half of my time and half in the lab. The Hungarian psychiatrist, Stefan Szabo, who came from Hungary in 1956 and had discovered the hallucinogenic effect of dimethyltryptamine in my laboratory in Berlin, Stefan Szabo and I therefore decided even though we had not much money that we had to go to Milan. At that meeting I again met Wolfgang de Boor.

The meeting was stimulated by Garattini and in the course of it the idea for a CINP came up. This came I think from Radouco-Thomas, a pharmacologist who came from Romania and was working in Geneva, and also de Boor. So I think Garattini was responsible for getting the meeting together, at which de Boor and Radouco-Thomas came up with the idea of a CINP.

Why did de Boor get involved in getting the CINP going and then slip out of it so early on?

He has written the book Pharmacopsychologie and Psychopathologie - he was not so interested in therapy. And therefore what was done was a contribution to develop psychopathology - he was a real Schneiderian; Schneider, for instance, was not interested in therapy, he was more interested in classification and descriptive psychopathology. This was the same as de Boor. He left, therefore, very early, when things took a different turn. De Boor became a big star very early on in his career and it was a tragedy that he left the mainstream so early.

What was the chain of events from the Milan meeting to the actual founding of the CINP.

I have written a little bit that Rothlin, as President of the International Pharmacology Association, came to this meeting and said very strongly and quite extraordinarily that it was not possible, that it would not be allowed to found a special association for psychopharmacology. It was only allowed to have a section in the International Association of Pharmacology. I was surprised then that Rothlin, at this time he was the main pharmacologist in Sandoz, came to the World Congress of Psychiatry meeting in Zurich. He had invited some people to the meeting and surprisingly one of them was me. I think the reason was that I had talked with him in the Milan meeting on famous painters. He was a specialist in this area. Later on we had very many talks about this. But the invitation was still surprising. I was the youngest of this small group and Rothlin had me invited as a delegate

for Germany together with Professor Flugel from Erlangen and Rothlin then became the first President

Which was very surprising surely.

Yes, it was surprising. In 58, for the Rome meeting, Rothlin was the first President and because with the founding of the Association, it was not possible to have a President-Elect, Rothlin was therefore the President for two terms. During the Milan meeting, we were angry with Rothlin, the younger people, de Boor was angry and the rest of us were angry but I think it was a good decision.

I think that it was necessary to have very good scientists as founding members and not only young assistants. If only young assistants had founded this then I don't know if it would have developed such a resonance so quickly. For instance, many distinguished scientists came to CINP meetings. Rothlin had made a very good equilibration in the founding between clinicians and pharmacologists. I think at that time I was angry but looking back I think it was a very good because Radouco-Thomas as a pharmacologist or De Boor as a clinician never had such a resonance as a figure of international prestige as Rothlin.

There were some problems though for a few years - there were clashes of personality almost it seems for the first 2 or 3 years with people finding they weren't listed on the membership anymore.

That happens at any time. Questions of personality. The influences on every scientific body are not only science, there are some other influences too. For me the foundation of the CINP gave me my best scientific contacts which were with people who came later on from the United States, especially with Fritz Freyhan, who was an emigrant who came from Berlin. I have often visited him and he put me in contact with Joel Elkes and Seymour Kety. Kety and Elkes were later on in the clinical part of the National Institute.

Somewhere around this early period, was it because of this discontent, a German society for psychopharmacology began? Why did you begin so early? You and the Czech's were the first to begin national societies, which in a sense seems odd against the background of a German tradition of not being interested in therapy.

I think that was the initiative of Bente, he was a very productive and a little bit of a baroque type. At the time he was an assistant at Nuremberg. We convinced Professor Scheid, who was the Chairman in Cologne, who was not initially convinced but later on became convinced and he became one of the founding members of the Deutsche Arbeitsgemeinschaft. But already by this time de Boor had said that he was no longer interested and he didn't get involved.

The core group was the senior assistants of these four hospitals who had done the early work in this field. I think Bente was one of the first who has made investigations with the EEG and phenothiazines along with Turan Itil, who came from Turkey to Erlangen and became a co-worker of Bente. But Bente died. I think the influence of Bente was very central, especially with the pharmaco-EEG. My contribution was more in biochemistry - the influence on enzymes and so on and the comparison of chemical structures. We developed, together with the pharmaceutical industry, very early on a phenothiazine, which was more effective than chlorpromazine, piperazine, but because of patent regulations it was restricted to Germany. This was developed in Berlin together with a small pharmaceutical company in Germany. I think that was one of the earliest and best developments from chlorpromazine but it has not had any resonance in the world at large.

How has the Germany society gone? Is it still functioning with all these other societies ECNP and CINP. Does it still actually function as a national society?

Yes. At first they were very informal sessions. The first session I think was immediately after the 57 meeting in Milan - it was between the two meetings. The five directors of the hospitals with their five assistants were invited by the company Bayer to a meeting. Their pharmacologist Wirth, who attended the Milan meeting, was not very experienced in this field but I think he was convinced in the 57 May meeting in Milan that this will be an area for future development. Therefore, after this meeting, ten of us were invited to Leverkusen.

At this moment, of course, we didn't have a special psychopharmacology association - and this was before we knew what was going to happen in September in Zurich. So we said that we will have regular meetings. There were informal meetings at Erlangen near Nuremberg and therefore these became the so called Nuremberger symposium. The first years were annual meetings and now we have three annual meetings of the Deutsche Arbeitsgemeinschaft für Psychopharmacologie. Because we were already founded, after 57, we have made enquiries of the CINP who said they planned in the future national, local, advisory committees and therefore, our group became, by chance, the first local advisory committee for the CINP.

We were an informal group at this time. In Germany, we were termed the Funfer Club - that was the five people under the umbrella of our directors. But we decided it was not possible to publish under the name Funfer Club. So to give us a name, we called ourselves the Deutsche Arbeitsgemeinschaft für Neuropsychopharmacologie, the AGNP. The official registration of this legally was later but in practice we have arranged from 57 this first meeting in Leverkusen. In 58, 59, and 60, there were annual meetings in Nuremberg.

At first we were forty people. From year to year it was increasing and in the mid-60s, Bente, who was the leading person in our group, suggested that the CINP meetings were a point of contact for people in the Western world but that we should arrange our Nuremberger symposia to be a meeting place for psychopharmacologists from the Eastern countries and therefore Czechoslovakians, and delegates from Poland and Yugoslavia came to our meetings from very early on. In the 60s, Bente, who very often had big ideas, suggested that our Deutsche Arbeitsgemeinschaft must be a central European Arbeitsgemeinschaft. We had two meetings, one in Czechoslovakia and later on one in Yugoslavia, but we came back to Nuremberg and since the end of the 60s the meetings have only been in Nuremberg.

In recent years the British and US groups have almost become neuroscience societies rather than clinical psychopharmacology societies. Have you had the same problem?

A little bit yes. But on the other side I think we need the contact with the basic scientists and there must be a compromise. Sometimes the meetings are more in the basic direction or have good contributions from the basic sciences. A problem with the central Europe meetings was that the number of clinical studies increased enormously but the standards didn't increase in the same manner. But I think up till now the Deutsche Arbeitsgemeinschaft has had both clinical and basic sciences at each meeting. The presidency alternates between psychologists, pharmacologists and clinicians and the aim has been to bring people together.

But we have in our country two associations. One is for biological psychiatry and one is for neuropsychopharmacology. We don't have two meetings in the same year. They alternate.

This year it is biological psychiatry and next year it is AGNP because the topics are over-lapping.

There are clinicians who would say, at least in the US and the UK, that perhaps a biological psychiatry society is better because while neuroscience is clearly needed, a lot of what is now happening within the neurosciences is not necessarily clinically relevant.

I think it is necessary that the clinicians have some information about what is going on in molecular biology. Some of my younger assistants say they don't understand... But I'm convinced - a good example is clozapine. Clozapine acts on the D-1 receptor

Let me ask you about the early days of clozapine. How did it get introduced first.

Our group discussed the question of the connection between extrapyramidal symptoms and clinical effectiveness. On the one side of the argument was Paul Janssen and in Germany a prominent scientist, Haase, who said there is no clinical effect without extrapyramidal side-effects. Haase introduced the so-called hand-writing test. If a patient was treated with chlorpromazine or with reserpine, the early neuroleptic drugs, they had to write a nursery rhyme such as Jack and Jill went up the Hill, before treatment and then every day. The idea was to see that the writing becomes smaller and smaller as a part of the micrographia that you find in Parkinson's disease.

So there was a controversy between Janssen and some people, like Bente, and me. Bente was convinced that the patients must have extrapyramidal symptoms up to the highest degree, up to akinesia. In contrast, in Berlin we have tried to show, and we have investigated, if it is possible that it is not necessary to have akinesia. So we have used low doses and we had very simple studies and we have observed that it is possible. There are some patients without any extrapyramidal symptoms who do very well on neuroleptics.

Because of this we have searched for drugs which have less extrapyramidal effects and higher clinical effectiveness. The first step in this direction was Perazen, which is a drug which has been used in Germany until now, which had extra-pyramidal effects but less than chlorpromazine and with a better quality of effectiveness. Then we have searched for a long time for other drugs without extrapyramidal effects and I think the first we came up with was clozapine.

When did you come across it?

The first publication was 66 at a CINP Congress, which was a very small announcement that we have compared five different although similar structures and looked at which are effective and which have less extrapyramidal effects - we wrote *less* at this time rather than none. Later on we have specially investigated clozapine, because in this relation it was the most prospective drug..

But how did you get hold of it first. Who actually ...

From the chemical structure. We had contacts with the Swiss-German pharmaceutical industry and, for instance, we had been able to say to them in the case of Perazen that they could expect that it will be more effective because it had a special side chain which should strengthen its activity. That was the first step. With all these drugs it was speculation on the basis of the chemical structure.

At this time, in the chemical and pharmacological journals, you could find a great number of chemical structures published. So we have looked closely in the journals and at this time, there was a pharmacologist in the Wander company, a German company, published chemical structures of drugs, including clozapine. We made contacts. Stille was the pharmacologist; he had written that clozapine was unique in a pharmacological sense too. Therefore it was of the highest interest to investigators.

We got it. Our first experience with it was interesting and stimulating. Some Austrian investigators had it too and they published an enthusiastic paper. Angst did the first double blind trial and saw the same result. In Germany, we were a little bit behind with our methodology. From this moment, both the Swiss authors and our group, we began concentrating our investigations on clozapine but at this moment there were two developments. Wander was bought by Sandoz. It lost its independence and became a part of Sandoz. And some months after this there came the information from Finland about agranulocytosis.

That was quite early.

Sandoz had come already to the decision that this was a terrible drug and now that they had bought all of Wander that they would not continue with its development. I think that is one thing I am a little bit proud of. I travelled to Basel and I argued with Sandoz "you must continue". The answer from them was "but we don't believe it is effective because Janssen's ideas about neuroleptics. We know there is no extra-pyramidal side effects and therefore we will draw back". They only agreed because we were able to say because of our early investigations with chlorpromazine, perazen and other drugs that it was not unique in producing agranulocytosis. This happens with all these drugs, with the same frequency and it is not only a danger with clozapine. So we were allowed to continue with clozapine for almost twenty years, until Herbert Meltzer re-discovered it, which I am very glad about.

Now why did he re-discover it. He said he had one patient with tardive dyskinesia who he gave clozapine to because she wouldn't respond to anything else.

We have published this in the 60s but it was not registered. We had it in Germany and our experience was increasing but the publications were going down and then by chance Herb Meltzer... I know Herb Meltzer from some biochemical investigations in my early career. Already, in 1957 in the Zurich congress, I had published investigations on the influence of chlorpromazine and reserpine and other drugs on enzymes. The most interesting finding was that the creatine phosphokinase was influenced.

Herb read this paper and he was very active in this field. I had published only three or four pieces but astonishingly, and this was surprising for me, Herb Meltzer has given the original citation. He said that the first reports of this were by Hippus, Kahn and a man from the Phillipines, he was a student in my laboratory, Bengtson, who later on he became the Minister of Health in the Phillipines. I was surprised because we had a very often the experience that our publications are not very widely known.

With the Americans in particular, they've a reputation of claiming that they thought of something first.

Meltzer wrote to me and asked what the reason was that I had not continued with this work, that it was a very early and stimulating development. He said he was working on it now. And from this time on we have been in good contact about creatine phosphokinase. Later on he read the old papers and publications on clozapine. At the first meeting between American and European investigators, he invited me along. He said you have discovered clozapine

and we have to arrange a meeting. This is very nice experience about Her Meltzer that he has given the citation. That was the clozapine story.

You must have been awfully disappointed then that the agranulocytosis problems led to it being withdrawn from general release.

Yes. And we didn't understand the reason because I have done in my laboratory very early investigations on agranulocytosis with other drugs and it was evident to me that all chemical drugs with this structure will have agranulocytosis. It was not a unique property of clozapine.

The other thing was that I had, for 15 years, a bet with Paul Janssen. He said there will be never a drug without extra- pyramidal effects and as a result he has developed drugs from haloperidol to droperidol, drugs whose effective amount has become lower and lower and he has done this on the basis of ability to produce extrapyramidal symptoms. That was from our point of view the wrong way. We said you have to go the other way and from this point of view the most interesting drug was clozapine.

So why did it take so long for the field to come around. Why did the dopamine hypothesis gain such credence.

The prestige of Paul Janssen and Arvid Carlsson yes. After the resolution of this problem I was glad to see the development of Risperdal but I don't believe that risperidone is far enough in the right direction. The standard up to now is clozapine. Risperidone I think it is better than droperidol and so on ... but the problem with akathisia and with tardive dyskinesia must be solved.

Another way to read the clozapine story, which is something that the industry I guess have been unhappy with, is that they moved on a fairly coherent path from chlorpromazine through to remoxipride getting purer and purer agents and now we get a dirty drug again being better than the pure compounds. Does this say something about the nature of the illness? In a sense, its a problem for the industry because how do you make the correct dirty drug - its easier to purify drugs.

On the one side, from the basic sciences we have made great advances and have been able to produce drugs that are more and more selective. And on the other side the decision about which drugs should go in clinical trials should not only be taken by basic scientists. I think it must be more as it was in the pioneer time, when the pharmacologists and the clinicians were working together more.

In the 50s, I had very strong contacts and very frequent contacts with the chemists, for instance, in Ciba, who at this time had and ingenious chemist who speculated on chemical structure and effectiveness, Wilhelm. The clinicians were very active and were interested to have contact with basic scientists. For the pharmacologists and chemists, it was a new field and they learned very early they had to talk to the clinicians. In the first years, Paul Janssen was wonderful discussant for this. You know the story, Janssen has developed opiate related drugs and he has seen in his animals extrapyramidal symptoms and he said "I have to show this to the clinicians" and this led very early on to the development of the butyrophenones.

But after his quick successes, and it was tremendous what he has done in the early years, he had his dogma and he had as a discussion partner, the scientists in Germany, for instance, Haase and they have written a book together Haase and Janssen and the book

was written on the dogma that extrapyramidal effectiveness and clinical effectiveness belong together necessarily. It is interesting to consider what has happened since then.

Apart from clozapine nothing has really happened for almost 30 years. We've got some variations on a theme but no new themes.

I think though in between we have developed many things. In the development of neuroleptics, I think the most important years were between 1952 until the end of the 60s. Later on there was the same development with the antidepressants, for instance. Now they have come back to the monoamine oxidase inhibitors and there is the special development with the SSRIs.

We have lost some drugs - there is a connection here with clozapine. At the end of the 60s and the beginning of the 70s in most European countries, the pharmaceutical industry was very irritated that the public were being informed about the dangers of drugs. Sandoz was concerned that information about this dangerous drug would appear in the newspapers and that that would be a disadvantage and this was one reason to withdraw clozapine. This was prevented but with the only development original to Germany, nomifensine, we also had problems. Nomifensine up till now has no substitute. Hoechst produced it after hesitating to go into the field of psychotropic drugs. They developed it through very good chemical and pharmacological research and later on very good clinical research. It had a dopaminergic presynaptic mechanism.

Then there was news in the newspapers about I think it was only four patients, who a thrombocyte problem with nomifensine. Almost immediately nomifensine was withdrawn from the market.

Too quickly?

In my opinion too quickly. And I think the development with clozapine was in real danger of being stopped completely until its re-discovery in the United States - it couldn't be stopped now even though the risks are known. But with nomifensine there is no successor drug - and this line of development was completely stopped. It was withdrawn too early.

I think the problem is not that there is a dangerous side effect - we should be prepared to do anything to make the risk from dangerous side effects minimal. The problem is not the agranulocytosis, for instance, but death by agranulocytosis. Sandoz does this exactly in the United States - they have the drug monitored in a manner that if it is handled in an appropriate manner, death should be prevented. I see this with other drugs - every year a handful of cases of agranulocytosis but the patients survive and I think that's possible.

You've touched on an issue there which is an issue you've seen develop and its hit its peak maybe with the question of prozac in the US. With prozac, and with valium before it, but especially with prozac psychotropic drugs have entered a public domaine. They've become issues of controversy ...

In comparison to the US I think in Germany the development is much slower than in the United States and the United Kingdom. Lilly are surprised about this; they had hoped that it will be the same as in the United States.

Why do you think it has been so big there?

In the United States at this time they had only a few antidepressants. Sometimes I think, we, in Germany, have too many antidepressants and therefore the introduction of prozac even with the strong advertising activity by Lilly led to it being used but not as widely. Fluvoxamine

was already introduced in Germany before fluoxetine came on the market and given that fluvoxamine was there already, fluoxetine from my point of view, doesn't represent a further development. I think it will never be such a big product as it is in the United States.

Another problem, which I think is an unsolved problem up till now, is our approach which has been my approach also, which is that we have said it is only justified to use psychotropic drugs in real patients with illnesses. With the SSRIs it may be possible, all the advertising suggests that it possible to go over the boundaries of illnesses - to go into normal persons - if you are a little bit unlucky, take prozac. I think this is a very important general problem - is it is justified to use medical drugs in the field in which on the one side alcohol is used to feel better and on the other there are the addicts. I'm not sure what will happen in twenty years if one part of the population goes to drink whisky and the other go to take prozac. Since I have worked in this field, which is almost forty years now, one of my maxims has been to use such drugs only in patients who are ill and now this boundary is fluctuating and in this field the SSRIs play an important role.

Talking about clozapine, nomifensine and prozac and just how these drugs get out into the popular culture, raises the whole question of how the public assess risk and benefit. This must be something that you've had to think about.

I think the fate of nomifensine is an example in this time of how in the public and in the newspapers there can be such a movement against the pharmaceutical industry that the decision to withdraw the drug becomes understandable.

You said that at that time in Germany the pharmaceutical industry was looked on with a certain amount of suspicion, can I pursue that theme by asking a question. The pharmaceutical industry really began in Germany and Switzerland and it's been possible in those countries for over a hundred years now to have a respectable career within the industry in a way that in the US and the UK it hasn't been. In the US and UK, if one moved, as a clinician or as a research scientist, over to the industry you were thought as not being a respectable scientist. So its curious to hear that even in Germany the industry developed problems during the early 80s, what was happening?

I think that there was a general anti-natural sciences movement in Germany. This developed since 68 and the student revolution and later on it was with the ecological movement. For instance in the last two weeks, there was information from the World Congress of Social Psychiatry in many newspapers but on the CINP congress not a word. I regret a little bit that in Germany we have another polarisation, which is the polarisation between social psychiatry and biological psychiatry and that is not a good development. In the United States, the basis for the development of social psychiatry was the introduction of psychotropic drugs.

But in the UK it's almost been the opposite in that the centres of excellence for social psychiatry have always been somewhat anti-drugs. Aubrey Lewis at the first CINP meeting said that if we had to choose between the industrial rehabilitation units we have, and these new drugs, we would choose the industrial rehabilitation units and in the UK, psychopharmacology has happened outside the main scientific centres.

I think in Britain, nevertheless, they were much more pragmatic. For instance, Michael Shepherd took many aggressive positions about various things but on the other side in his daily work he was much more pragmatic than comparable people in Germany. I remember his attacks against lithium and its use by psychiatrists - he was almost killing Mogens Schou but on the other hand later on he used it. It was the same with Aubrey Lewis. I think that what happened in the Maudsley at this time influenced Germany. But in Germany, in

contrast to this, the polarisation is not only in the discussion, but it extends to daily practice too.

In the US, there was polarisation to the extent that the analysts would not prescribe drugs. There would be one doctor in the hospital who was termed the druggist, but the therapist wouldn't prescribe. Did polarisation go that far in Germany?

Yes and more. If there was a psycho-analyst as the head of the hospital, then he will not allow any drug therapy to be prescribed. In the United States, there was a certain pragmatism so that at least one doctor could prescribe and the first publications about the combination of psychotherapy and drug therapy were published in the United States. In our country its not possible. The doctors with a biological basis, if they do behavioural therapy, in combination with drug therapy for instance, they are attacked about this and told that what they do is not real behavioural therapy because they use drugs. I think the polarisation is greater and we take more intolerant positions.

Is it a case of having principles and sticking to them too much?

I believe that in many things, the German people are more abiding by principles than people in other parts of the world. It is a disadvantage of the Germans.

Let me take you back. Why did you go on to do medicine and why did you choose psychiatry?

I don't come from a medical family. My father was a school teacher in chemistry and physics and I was the only boy and his interest was that I should study medicine and chemistry. He was very upset when in the school my interest was in biology and on the other side I liked to be involved in subjects to do with human contacts. This I think explains my movement into medicine and later on my switching between a little bit of history, a little bit of chemistry. I think I stayed in psychiatry because I was caught up in the development of psychopharmacology - that was fascinating. Up to 52, I was active in immunology and sometimes in the last years I have tried to keep up with what is happening there and tomorrow we will hear the presentation of Brian Leonard on this area. I regret that the development of immunological research in psychiatry came so late. But I am very fascinated with what happens there and I have a small group which is now active in immunology research - so this is my heritage from the early 50's.

One of the other intriguing things about Europe in particular, which I guess you don't find in the US so much, is that in the different European countries or regions different drugs get prescribed and there are also different nosological entities - such as vegetative dystonia in Germany and Middle Europe. George Beaumont mentioned that some time back, when he was working for Geigy, they were saying that opipramol was marvellous for vegetative dystonia, go and find out what the market would be like in the UK but there was no-one with it in the UK.

Vegetative dystonia is only found in small places in Germany. In university hospitals, the term is not used, it is not an indication.

Not now but in the late 1960s? Is one of the things that's happening a case of the use of drugs leading to industry friendly classification systems like DSM III and IV which bring with them Anglo-American cultural imperialism in psychiatry?

No I don't believe that. I think that the patients have not changed but the classifications have changed tremendously especially in the United States. At this time vegetative symptoma-

tology was a little bit neglected. Vegetative dystonia was a pathophysiological concept, a German ideology. I'm convinced that many states, which had the name vegetative dystonia now fall more under the concept of newer endocrinological pathophysiologicals and we should have a look at them. I think the term vegetative dystonia will never come back but on the other side, DSM IV, what is the somatoform disorders? I think it is very good that we have an in-between concept like this. We did not have it in ICD-9. So there may be a little bit of a revival of what twenty years ago was called vegetative dystonia - not as a special entity but as a syndrome.

Could we turn the cultural imperialism on its head and say that US psychiatry has become very Kraepelinian. You could argue that the drugs, which were introduced in two broad groups - the antipsychotics and the antidepressants - seemed to cement the Kraepelinian formulation in place up till now anyway.

What I accept from the imperialism in the United States in the diagnostic field is that they have established the multi-axial diagnostic system and I think it is better to have multi-axial diagnostic classification than only a mono-axial system directed at disease entities. I think it is a misinterpretation of Kraepelin to say that DSM III and IV was neo-Kraepelinian. Kraepelin only up to 1910 has done his research in terms of separate entities. Later on in his later years he came more and more to have a look at syndromes too.

In Germany, there was a very famous controversy between Hoche, who produced a classification on the basis of syndromes, and Kraepelin who wanted to establish entities analogous to the entities in internal medicine - that was in 1904-1905. Kraepelin never accepted that he was more and more influenced by the thinking of Hoche, who was something of an enemy for him. Hoche has played a notorious role because he made a publication with a lawyer which was the basis of a book immediately after the World War I which was used later on by the Nazis as a basis to kill psychiatric patients. Hoche is, therefore, a very difficult figure in the history of psychiatry but his concept of symptomatology is a little bit more convincing for me than the very strong entity based approach of Kraepelin.

Kraepelin in the end accepted on the one side the influence of Hoche and in his last year he accepted that the syndrome of the patients should first be described, together with the course of the illness. I would like, if I had the opportunity to have a DSM V, then I would have a syndrome axis, a personality axis, an axis for the course of the illness and an axis for social surroundings. These would be descriptive axes and there should be a distinction from the aetiological axis. What I teach my students is that if Kraepelin had lived twenty years more that he would have developed a much better classification - in the direction of the DSM III but a better classification. From this background I think it is possible to have drugs directed against special courses of illnesses.

Special courses of illness?

In schizophrenia, twenty years ago we had schizophrenia and dopamine, depression and noradrenaline, 5HT and anxiety and acetylcholine and Alzheimer's ... In schizophrenia research was only done with dopamine. They have not investigated other systems. If you look at the course of schizophrenia, you will find dopamine abnormalities but very early on you will find that the noradrenaline system is involved too. For a long time noradrenaline was reserved only for depression research. Therefore, I think what we see in the course of an illness is that many systems are involved and that there is an interaction between the systems, and I believe we will never get such pure entities as we have in internal medicine. And if you think about it in internal medicine, this model only applies to the infectious diseases.

We will have more complex syndromes. For instance, it is possible that the biological basis of courses and the biological basis of symptoms may be completely separate. If you look at my training in psychiatry, in the beginning we were taught on Kraepelinian principles and therefore we were confined to schizophrenia and affective disorders. What have we in between. Schizo-affective disorder and what does this mean? - it means that we have to move away from these dual concepts. For instance, I know many patients who have obsessive compulsive syndromes who have a phasic course too and I treat these patients with lithium. Lithium in my opinion is a drug which is only directed to the course and not to the symptoms. The classical neuroleptics, antidepressants, or benzodiazepines are not directed to illnesses, they are directed to special conditions or syndromes.

So if the major entities break down what will the rational basis for giving drugs to people be other than giving it to them on an empirical kind of basis and seeing if this drug works for that person.

The revival of the old concept of target symptoms of Fritz Freyhan.

Tell me him and why he was important.

He was an emigrant in 1939 from Berlin and he has had the same kind of development as Heinz Lehmann. They both come from Berlin and they were both prominent early on. Freyhan worked very early with Seymour Kety and made investigations on the blood flow of the brain. Freyhan was a clinician and Kety was a pharmacologist. These publications made him well known. At this time then there was the introduction of chlorpromazine and Freyhan was one of the first investigators of these new drugs in the United States. Freyhan in the States and Lehmann in Canada.

One of his influences was that very early on he came back to Europe and came to German universities and stimulated younger people to go into psychiatry to do research in the field. From this time I had very good contact with him. His basic contribution was that he has described very precisely - because he knew all the old German literature, he knew Kraepelin, he knew Kurt Schneider, in contrast to his American colleagues, that was an advantage Lehmann had too - these two younger American psychiatrists had the whole background of German traditional literature - anyway Freyhan described the concept of target symptoms.

He said we need a double-entry system. You know "if I'm a salesman I have two pages in my books - on the one side you have all the ?????, you have calculation on the one side". This term had been introduced earlier in psychiatry as regards the orientation of schizophrenic patients. You have the orientation on the one side in their own paranoiac word and on the other side the orientation in reality. They are orientated with two dimensions which are different. Now Freyhan has said we have the same for the use of drugs - on the one side there is a diagnostic page and on the other we should put the target symptoms. He introduced the term of target symptoms and the idea of a use of drugs on the basis of target symptoms. That was very early on. This was interesting because the first drugs, such as chlorpromazine, were very often used in many conditions for instance in mania. But this idea was very often forgotten in the development because if you now ask a psychiatrist what is your indication for drugs, he says I use this in schizophrenia and this in affective disorders, but Freyhan has very early said, no, that is not the entity it is the target symptoms which are the basis for the use of drugs.

What were the target symptoms for the antidepressants.

The target symptom for the antidepressants is depressive mood alone. Freyhan was a good friend of Kielholz and they had some exchanges about this. Kielholz developed the idea that the combination of two or three target symptoms should be basis for the use of particular antidepressants. Depressives with excitement should take amitriptyline. If you have a depressive mood with retarded motility, then you should take imipramine. Therefore the idea was not only single target symptoms but constellations of some kind.

Has that held up. It hasn't really ...

Its in between I think. I think it will be found more and more and I think it's important. Freyhan was putting forward these ideas at the end of the 50s. Kielholz developed the idea of combinations of symptoms in the 60s and the 70s... For instance in Britain up to ten years ago, all anxiety syndromes were treated with benzodiazepines. Now you treat panic attacks with monoamine oxidase inhibitors and I think all these observations suggest our concepts are changing from decade to decade to entities to target symptoms to target symptom constellations, which is my concept of a syndrome. And if you add syndromes together with the course of the illness we go back to the late Kraepelin. And I think that this is the direction it will go in, on the one side from the psychopathology and from the clinical point of view and on the other side you have to look at the progress of what happens in basic research, with all the 5HT and the other receptors.

So you've still got hope for the future. We haven't come to the end of the road.

No. Especially where the development of drugs for the course of illnesses is concerned. That means for basic courses independent of symptomatology - schizo-affective, unipolar depressions, bipolar depressions, and even for phasic anxiety syndromes - lithium may be worth looking at in these conditions..

Carbamazepine, does that have a place there as well.

Yes. Lithium and carbamazepine belong together. That is fascinating - from the point of view of chemical constitution, carbamazepine is very close to many of the psychotropic drugs and neuroleptics but it was developed in epilepsy, later found to be useful in trigeminal attacks and as a third position that it has an influence on mood. Now common to mood disorder, epilepsy and trigeminal attacks, indeed characteristic of them, is their course. And therefore I think that there is no by accident that a drug developed for conditions with attacks, epileptic or trigeminal attacks, is now influencing the course of an illness.

The other point is that the special profile of clozapine was not discovered in the early investigations with clozapine. That was done by the Americans. They have found that clozapine is effective, as we have discovered with no extrapyramidal effects and a very good anti-psychotic effect, but the Americans have also discovered that it is effective against therapy resistant schizophrenia. And there is much discussion now about whether it is effective against negative symptomatology. The best drug against negative symptomatology, in my experience, nomifensine.

Ahha! There are other drugs which are somewhat like nomifensine such as pemoline and some of the psycho-stimulants. Because of the dopamine hypothesis, everybody has assumed that you cannot use dopamine agonists in schizophrenia but actually the literature is contradictory. The literature says that 1/3 of people with schizophrenia do well with dopamine agonists.

I have done some investigations in chronic schizophrenia. Our first investigations of the metabolites of dopamine we did in acute schizophrenics and then we investigated a group of

patients in a state hospital to look at what was the effect on the dopamine system after 10 years of the illness and there was nothing with dopamine only with noradrenaline. Therefore we suggested that in the beginning of schizophrenia the dopamine system may be involved but if you look at it longer and longer you see that other systems are too and therefore you may need dopamine stimulants and noradrenaline stimulants - nomifensine is a good example of this kind of drug. These drugs are needed for the defects in the system when the illness becomes chronic. These are interesting points but in a sense the effects of nomifensine and other stimulants on negative symptomatology is understandable but what is the reason for clozapine being effective - that needs to be investigated.

In the meantime you will keep on going to CINP meetings

Yes except there is one problem with CINP Congresses which is that every four years, like this year in Washington, they coincide with the World Cup. I was the President of the meeting, in 1974, in Paris, and I had a meeting with the Committee exactly at the time at which the final was being played between Holland and Germany. I proposed, together with Paul Janssen, that we should have a delay of the meeting but that was a problem Deniker. Deniker said "we are here in Paris not for soccer, we are here for a CINP meeting". My point of view was that I was the Chairman so I had to Chair - but Paul Janssen left.