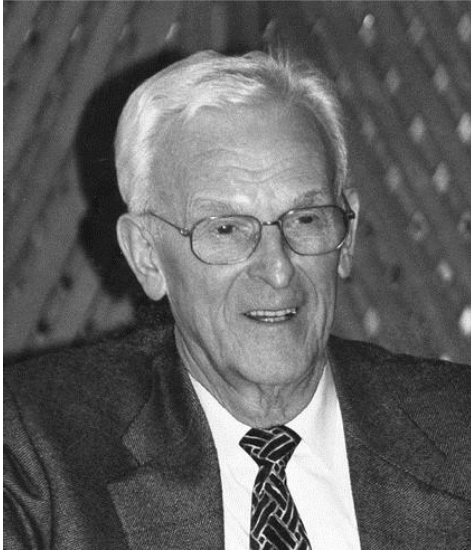


## Recollections of Hanns Hippus (1925-2021) by Hans-Jürgen Möller



Hanns Hippus passed away peacefully surrounded by his family on August 21, 2021, at the age of 96. We mourn the loss of a great man who was a founding member (1957) and President of the International College of Neuropsychopharmacology (CINP) from 1972 to 1974. Hanns Hippus was for many years Full Professor of Psychiatry Medical Director (1971-1994) of the Department of Psychiatry and Psychotherapy of the Ludwig Maximilian University Munich (LMU). He was an outstanding physician and scientist who shaped the field of psychiatry and especially psychopharmacology with his extraordinary mind and exemplary commitment, not only in Germany, but also worldwide.

I got my first impressions of Hanns Hippus, when I was working, since 1971, as clinical and research assistant at the Max-Planck-Institute of Psychiatry in Munich. He had taken over the chair of the huge Psychiatric Department of the LMU, the place where Kraepelin and Alzheimer used to work at the beginning of the 20th century, and - as he told me many, many years later - he was very proud about his position. Together with my colleagues from the Max-Planck Institute I observed how he transformed this traditional university hospital more and more into a modern research institute focussing on psychopharmacology and biological psychiatry/neuroscience. Due to this change the Psychiatric University Hospital came much closer to the research fields of the Max Planck Institute of Psychiatry. Somewhat frequent formal and much more often informal interactions between the assistants of the two institutions began. However, Hanns Hippus paid careful attention to preserve the autarky and identity of the University Department. He did not want that his department could be seen as an annex of the at that time much more famous Max-Planck-Institute of Psychiatry. Thus, also invitations of Max Planck collaborators for official presentations in the lecture hall of his department were seldom and he interpreted these as somewhat very exclusive. For example I got my first invitation not earlier than after I had finished my “habilitation,” an academic step (Dr. med.habil.) which in the tradition of the German university culture opens the gate to become university professor.

When he had retired in 1994 as chairman of the Psychiatric University Department of the Ludwig Maximilian University of Munich, I had the privilege to become his successor. Over the years I developed a close collegial relationship and friendship with him, in which he gave me a lot of information about the history of his academic life and

his personal ideas on several key issues of psychiatry and psychopharmacology. Given the fact that I myself was never a student or assistant of him - I received my education and training at the Max Planck Institute of Psychiatry, where I also made the first relevant steps of my scientific career - I was even more keen to use the chance to learn from this famous and all over highly respected scientist about his current and former hypotheses, views, activities and experiences related to our field. Each talk with him was for me full of inspirations and I experienced a lot from his expertise as the former chairman of this huge institution. Under many aspects he became my adviser and coach and I could profit from his knowledge, experience and wisdom in many fields, not only related to research and clinical issues, but also related to social and even political networking. In the late phase of his life, despite of his advanced age he was still full of vitality and intellect and his interest in the activities of his former department was still great. Meanwhile my successor Peter Falkai had taken over the chair of the department after my retirement in 2012. We both kept a close relationship to Hanns Hippus. Among others I used to have monthly phone talks with him. Unsurprisingly to those who knew his strong personality and positive attitude, he endured the increasing physical limitations of his final years without complaints.

According to his personal report, Hanns Hippus was born on April 18, 1925, in Mühlhausen in Thuringia, Germany. He studied medicine and chemistry at the universities of Freiburg in Breisgau, Marburg an der Lahn and at the Free University of Berlin. In 1950, he received his doctorate in medicine (Dr. med.) from the Free University (FU) of Berlin and subsequently became an assistant at the Institute for Experimental Therapy "Emil von Behring" in Marburg an der Lahn. His interest in neurobiochemical processes of mental diseases grew out of his chemistry studies, with which he had complemented his medical studies. Psychiatry and neurology became the focus of his clinical work, first as a research assistant and later as a senior physician in the Department of Psychiatry of the Free University (FU) West- Berlin. After his "habilitation" in psychiatry and neurology (1963), he became Full Professor of psychiatry and Chair of the Psychiatric Department II of the Free University Berlin from 1968 to 1970. From 1971 to 1994 he was Full Professor of psychiatry at the Ludwig Maximilian University Munich (LMU) and Chair of the Psychiatric University Hospital of the LMU.

Between 1972 and 1974 he served as President of the German Society for Psychiatry and Neurology (DGPN). He was a founding member (1957) of the International College of Neuropsychopharmacology (CINP), where he served as president from 1972 to 1974. He was also a founding member of the Association of European Psychiatrists (AEP), now the European Psychiatric Association (EPA), in 1983. He was a member of the prestigious German Academy of Sciences (Leopoldina). He was an honorary member of many psychiatric/psychopharmacological societies and received numerous other honours, including the Wilhelm Griesinger Medal of the German Society of Psychiatry, Neurology and Psychotherapy (DGPPN) and the Pioneer Award of CINP.

In our personal conversations Hanns Hippus repetitiously declared to me, that from the beginning of his academic career he has been mainly interested in

psychopharmacology and in association with this in neuroscience. Thus, when he 1969 became chairman of the Psychiatric Department of the Ludwig -Maximilian-University he tried to establish a research situation fitting to these interests, in which he saw part of the future of modern psychiatry. He established among others a large neurobiochemical laboratory under the direction of Norbert Matussek, who worked before at the MPIP. Based on this, Hanns Hippus and his co-workers made important contributions to the biochemical and immunological, and later on - corresponding to the new developments in the field - also to the molecular-biological and psychiatric-genetic research in psychiatry. In addition, he initiated further important developments in the field of psychiatry at a very early stage: For example, he promoted new research directions in his department such as electrophysiology and brain imaging (with CCT, SPECT and MRT). I observed from my outside perspective, when I worked at the Max-Planck Institute of Psychiatry in Munich and later on as professor of psychiatry at the Technical University Munich that with all these Hanns Hippus had an impressive influence on the development of psychiatry in Germany in general in that time. He conveyed psychopharmacotherapy and neuroscience research as central areas of psychiatry at a time, when most psychiatric university departments in Germany were still primarily oriented towards descriptive psychopathology. His influence in this regard can be seen, among others in the increasing number of psychiatrists with this scientific specialization who were appointed to chairs of psychiatry in Germany, most of them were former co-workers of him like Otto Benkert (Mainz), Helmut Beckmann (Würzburg), Eckart Rütger (Göttingen), Helmfried Klein (Regensburg), Dieter Naber (Hamburg), Florian Holsboer (Freiburg, later on Max Planck Institute of Psychiatry Munich) Franz Müller-Spahn (Basel). That so many of them took over highest academic positions was from my viewpoint not only the result of a very successful research institution and clinical department, but also the result of the excellent networking qualities of Hanns Hippus. When he tried to convince a university faculty to take one of his colleagues he mostly could hope on a positive response.

He reported to me that his key interest in clinical psychopharmacology was mirrored already early in several articles related to phenothiazines and reserpine. He carefully described in these papers effects of these drugs and searched among others for strategies to avoid extrapyramidal motor side effects of neuroleptics.

Due to his friendship to the pharmacologist Stille (working at the Swiss company Wander) he acquired knowledge of Clozapine, which did not produce catalepsy in animals and therefore at the first stage of its development was wrongly not considered by the company to be an effective antipsychotic. However, EEG results in animals gave hints for an antipsychotic activity and thus clinical trials started in Germany. The first publication appeared in 1966 at the 5th CINP Congress. But between 1966 and 1971 there was only little prove of the antipsychotic efficacy of this compound, fitting somewhat to the hypothesis of the German psychiatrist H.-J. Haase that for an antipsychotic EPMS side effects are necessary. However, more and more publications appeared about the antipsychotic efficacy of Clozapine, and to the satisfaction of Hanns Hippus, the hypothesis of Haase was challenged with this first “atypical antipsychotic.” This was also

in contrast to the position of P. Janssen (the director of Janssen Pharmaceuticals), who at that time focussed on the development of selective strong dopamine D2 antagonists, while clozapine has a very complex pharmacological profile with only a weak antidopaminergic mechanism. After I had started my work in psychiatry in 1971, I could experience that more and more results on the antipsychotic efficacy and the unique clinical profile of Clozapine - no extrapyramidal side effects, efficacy in negative symptoms, efficacy in treatment resistant schizophrenia - were published and that clozapine, licensed 1972 in Germany, reached an important place in clinical psychiatry. However, in 1976 Sandoz (the company which has bought Wander) wanted to withdraw Clozapine because of the risk of agranulocytosis. I admired at that time, how Hanns Hippus with his enormous reputation could convince the representatives of Sandoz, to allow - in agreement with the German drug authority BGA - treatment with Clozapine under certain restrictions. After a delay of some years, Clozapine found attention in the USA and was licensed there 1990. Clozapine became the starting point for the development of other atypical antipsychotics which are currently in use for the treatment of psychiatric disorders. I could derive from many lectures of Hanns Hippus and personal talks with him, how proud he was about his important contribution to the development of Clozapine. Personally, he had the impression that the second-generation antipsychotics, developed later - following somewhat but not fully the pharmacological model of clozapine (among others they were D2-5HT2 antagonists) - were not on the same level of clinical exclusivity.

Additionally, to his interest into neuroleptics, especially Clozapine as the model of an atypical antipsychotic, he was interested in the field of antidepressants. Already beginning in the early time of the tricyclic antidepressants and later on he initiated and carried out research with the tricyclic antidepressants Imipramine, Nortriptyline, Amitriptyline, Lofepamine as well as with MAO-Inhibitors, especially Jatrosome. Together with other colleagues, especially P. Kielholz (Basel), he developed initiatives for a better diagnosis and treatment of depression under outpatient conditions, especially by general practitioners. Thus, the first generation of antidepressants became in widespread clinical use. I remember well, how he was involved in these initiatives, and how he later on convinced me to take part in these initiatives. Representatives of his Department of Psychiatry in Munich, especially his co-worker, the chief of the psychopharmacological laboratory, Norbert Matussek, at that time were convinced, that the most relevant pharmacological mechanism for an antidepressant effect, is a noradrenergic one (based on noradrenaline reuptake inhibition). I remember the time, when in the eighties of the last century pharmaceutical companies started to develop selective serotonin reuptake inhibitors (SSRIs) as antidepressants, that some representatives of the Psychiatric University Department Munich, like especially Norbert Matussek, followed in this position by Helmut Beckmann, did not want to believe the data of sufficient antidepressive activity of SSRI compounds like fluvoxamine, fluoxetine and others. Helmut Beckmann, when he became chair of the Psychiatric Department Würzburg, did not allow the prescription of the SSRIs. Apparently, the theoretical position concerning the pharmacology of antidepressive mechanisms was for Matussek and Beckmann more important than the growing clinical data on the efficacy of the

SSRSs. I had many controversies with both colleagues about this issue already in the beginning of the time of the SSRIs development and later on, when I was chairman of the Psychiatric University Department Bonn (1988-1994), where I was supported by my deputy chair at the Psychiatric University Department Bonn Siegfried Kasper (the later chair of the Psychiatric University Department Vienna), in the position that the SSRIs are a clinically meaningful development under consideration of efficacy and tolerability. I do not remember that I had discussions on that with Hanns Hippus. I believe that he was not so much driven by such theoretical positions mentioned above, but more by clinical experience and insofar open for the new developments. I remember also from other debates that Hanns Hippus always gave clinical experience and wisdom the priority against theoretical hypotheses and dogmas, which impressed my very much. Maybe that this was a consequence of the Clozapine history.

With respect to his great interest in the clinical evaluation of drugs and their side effects Hanns Hippus developed - early after the introduction of the psychoactive medications - together with Bente et al. the first structured documentation system (AMP) which allowed among others the standardized evaluation of symptoms and unwanted effects under psychopharmacological treatment. This was developed further in cooperation with Jules Angst (Zürich) to the AMDP system, which is still in use in Germany and German speaking countries and also accessible in an English translation. He also organised the documentation of all undesired side effects of psychoactive compounds in drug surveillance projects in German psychiatric hospitals as well as for outpatient treatment in Germany. Furthermore, together with Jules Angst, Hanns Hippus organised the first consensus conferences for the psychopharmacological treatment of psychiatric disorders in a time, in which evidence-based guidelines were not yet available. Although he helped to develop all these important aspects of methodology in clinical psychopharmacology, he was always convinced that a very important part, if not the most important part, of drug evaluation is clinical experience and he trusted most in his own clinical experience. He always stated that the clinical observation of an experienced psychiatrist is the most important step in the development of a psychoactive compound, referring among others to the detection of the antidepressive effect of Imipramine due to the excellent clinical observations by the Swiss psychiatrist Roland Kuhn, and probably having in mind also his careful clinical observations of the unique clinical profile of Clozapine. For me, as a young researcher - having been trained in the Max-Planck Institute of Psychiatry in Munich especially in clinical trial methodology and standardized observation procedures - this position was always somewhat shocking I remember a quite familiar psychiatric symposium, where he stated openly, that for him the observations of a well trained and experienced psychiatrist would be much more relevant than several RCTs according to the modern trial methodology performed by me. Although this statement was shocking at that time for me, I tried to understand more and more in the following years his personal view, especially when the time of the very huge multi-center RCTs with often irrelevant results came, and even more in the starting and still ongoing phase of evidence-based medicine (EBM) and evidence-based treatment guidelines. He was, as further on attacked by the representatives of the modern evidence-based medicine,

really a senior representative of the so-called eminence-based medicine, full of the charisma of an extremely experienced clinical psychopharmacologist/psychiatrist. Sometimes, seduced by his wisdom and experience, I doubt whether the EBM is really bringing us sufficiently forward or in contrary kills by its bureaucratic attitudes all kinds of creativity and scientific imagination.

Of course, I could have mentioned many other issues, but here is not the place to expand the description much more. Therefore, finally only few sentences to his role in the context of CINP.

Hanns Hippus was a founding member of the CINP, which started 1957 during the 2<sup>nd</sup> World Congress of Psychiatry in Zürich. From this time on he attended all CINP Congresses. As a member of the Local Organisation Committee, he organised in 1962 the CINP Congress in Munich. As CINP president he was responsible for the CINP Congress in Paris, 1974. In 1988, he organised together with his co-workers another CINP Congress in Munich. He discussed very often with me the importance of such a powerful and international society of psychopharmacology like CINP and convinced me, especially when I had become his successor, to get involved as much as possible for CINP, which I did following his advice. He was extremely pleased, when I many years later was elected to become CINP president.

After his retirement in 1994, he focussed with great commitment on taking care of his large family (4 children, 5 grandchildren), to which he felt retrospectively that he had not always been able to devote enough time during the professional phase of his life. His wife's dementia overshadowed many years of this phase of his life to a considerable extent. For me it was admirable how Hanns Hippus under these conditions lovingly cared for his wife, first at home and later in a nursing home. One could regretfully observe how much he, who always loved to be among people, was thus closed off from the outside world and how much of his strength this task demanded. Nevertheless, when he himself became increasingly in need of care due to old age, he decided to bring his wife home and live with her in the house with the help of caregivers until her death. I always remember with pleasure the phone call when he told me full of joy: "I have brought Waltraud home again." This act of special humanity made a particularly deep impression on me.

I will remember Hanns Hippus as a great personality and a highly honoured colleague and friend.