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Life in movement as a scientist

Manfred Göthert

Childhood and Adolescence

On 12 December 1939, i. e., three and a half months after the beginning of World War II, I was born in Braunschweig (Germany). My father, Dr. rer. nat., Rudolf Göthert, was a physicist specialized in aerodynamics and my mother, Luise Göthert, was a housewife. A characteristic feature of my childhood was that, due to the war and the first five post war years, we had to move frequently to other towns or villages, leading to considerable inconvenience and various kinds of obstacles. This highly influenced the development of my character with respect to properties which play a significant role for successful research. In particular this also strengthened my ability to adapt to crucial changes of conditions – a favourable property when taking into account that a scientist at a German university has, as a rule, no chance to get a permanent position at the university at which he started his career: he has to apply and to compete with further applicants for professorship at another university. In view of the unusual importance of my childhood for my life as an adult scientist, I had to reserve adequate space for this period.

In 1941, my father took over a position in a research facility for novel types of airplanes in Gotha, Thüringen, where I experienced the end of the war, when the town was occupied by the U. S. Army. I remember cartridges lying on the ground. The older boys removed the gunpowder and set it on fire. Fortunately there was no major accident in our street.

Very soon after the end of the war, there was a rumour that the Western Allied Forces were going to take over three sectors of Berlin in exchange to the area of Thüringen and territories in the East of Germany. One evening, two American officers stood in front of our apartment door and asked my father whether he was Rudolf Göthert what he acknowledged. In response, they stated that he had to accompany them to a secret place in the Gotha area from where he would be transported to Paris. At Paris, the German scientists whose expertise was of interest for the Western Allies

would be offered positions in Western countries. My father asked for the promise that his family would be brought to relatives in Western parts of Germany before the occupation of Gotha by the Russian army. This promise was given by the officers. Two or three days later, an American truck stopped in front of our house and my mother was given thirty minutes to grab a few pieces of our belongings before the departure to Mesmerode, a village close to Hannover where relatives of my mother lived.

During that transport, we sat on a bench of the loading space in the back of the truck under a canvas cover, which normally was partly open. After a few hours we had to pass a Russian control station which had already been established as a result of the agreement between the Western Allies and Russian Forces. The relationship between them had already cooled down and the Russians considered the area of Thüringen as their own sphere of occupation. Therefore, they believed to be entitled to control whatever and whoever was leaving this area. Before arriving at the control station the canvas cover was completely closed. I was very urgently asked to be absolutely quiet in order not to give a hint at the „freight" of the truck, in particular not to let the Russians identify the latter as Germans leaving the Russian Zone. The Americans denied to be controlled. The situation was full of tension but finally the Russians let us pass. Late in the evening of the same day, we arrived in Mesmerode, where we got in touch by mail with my father in Paris soon afterwards. In the meantime, he had signed a 5-year contract of employment in France. Since the onset of this period was a few months ahead, he joined us for a certain time in Mesmerode, but after a few weeks his project started in a formerly German research facility in the area of lake „Bodensee" – a part of occupation administered by France („French Zone"). The destruction of German towns during the war and the necessity to accommodate many refugees from the former East German, now Polish, part of Europe resulted in severe shortage of housing space. This space was controlled by the political authorities and, accordingly, we had to live in one room in a rather small house.

In springtime of 1946 I had started my term as a schoolboy at the small primary school of Mesmerode. About four to five months after my first school day, my mother and I followed my father and moved to Zech, a suburb of Lindau. The school of Zech consisted of two classrooms. The first one was for boys and girls of the first four forms of the German primary school system. The second one was for children at the age of more than ten years, who attended the three-tofour-year period of the lowest level of the German secondary school system – the latter consisting of three stages of complexity. The teacher, who in 1946 to 1947 was simultaneously in charge of children of the first four forms, managed this system perfectly and we learned a lot.

When the main part of my father's French project started, my parents decided that he should first go to France alone whereas my mother and I returned to Mesmerode for a few months. Afterwards, we again spent another few-month period in Zech. Finally, we joined my father in France after he had found an apartment in a two-family house close to the airport of Marseille, where the German group of scientists worked.

I remember the first school day in Rognac (France), a village close to Marseille, when I, together with two boys from another German family, stood with the back to a wall of the schoolyard. The French pupils, while trying to get in contact with us, formed a half circle around us with teachers behind. It was a sensation that, in 1947,

Germans were again present in the village of Rognac, i. e., slightly more than two years after the end of German occupation of this area. From the second day onward, we were no longer considered as attraction, but we were involved in playing with our classmates. We learned French within extremely short time.

One feature of the disputable pedagogic background of a competitive system between the pupils was that we had to sit at the rank order of our abilities, the weakest boy on the left hand seat of the last row and the best one in the first row on the right hand side. In the course of the next two years, we, the German boys, experienced express move from one class to the next higher one with seats starting in the back and ending on the right hand side of the first row. In July 1949, this elite-favouring system ended for me with one of the book prizes which the best pupils got at the celebration of the end of the school year. When thinking about this experience later as an adolescent and adult, it became clear to me how much my attitude towards Europe was influenced by these two years. In fact, my parents and I myself did not experience discrimination but only friendship. As already stated above, I described these early phases of my life in more detail than usual because they played a crucial role in the development of my personality as a „German European".

Taken together, I am convinced that, nowadays, I would have been a case for a school psychologist after having „oscillated" between schools at Mesmerode and Zech twice within the short time of one year and three months, followed by another two-year period at a school in a country whose language I could not speak at the beginning of that term. However, I did not suffer from psychological disorder, but this experience turned out to be a good exercise for quick adaptation to new conditions, such as the necessity in Germany to move to another University as a prerequisite for a successful university career as a professor.

Much earlier in my biography than relevant in my professional life, I did already benefit of this ability to get along with a new situation. In 1949, my father's French employer – due to financial reasons – gave up the project in which he was involved. Based on this, the decision was to return to Germany. From September of that year onward we lived for about six months in one room of an apartment of one of my father's sisters in Hildesheim. There I was a pupil for the last half year of the fourth form of the primary school.

An initial major problem associated with my return to Germany was that I had forgotten German orthography in the two-year-period in France. On the first day at school in Hildesheim, a dictate was written which was not longer than three quarters of a DIN A5 page. Next day, it was returned with shocking 42 mistakes marked by red ink. For instance, the German (and English) „so" was „seaux" in my version. The only German book which I had read in those two years was about the adventures and fate of Simplicius Simplicissimus – a naive male individual from his childhood up to his life as an adult in Germany's Thirty-Year War (1618–1648). The author of the book – certainly not a typical piece of literature for an eight-year old boy – was Hans Jakob Christoffel von Grimmelshausen who lived in the seventeenth century. The cover picture of that book, a person riding on horseback, had attracted my interest. Everyday exercises with my mother had helped to overcome my German orthographic deficit within few months.

In March 1950, we moved to my birth town Braunschweig, where, one month later, I began the 9-year term of a high school as one of 45 boys in one class of the Martino-Katharineum. That school has a long tradition – it will celebrate its 600th anniversary in 2014 – with many famous personalities who attended it, such as the the mathematician Carl Friedrich Gauss (1777–1855), the composer Louis Spohr (1784–1859) and August Heinrich Hoffmann von Fallersleben (1798–1874), the poet of the „Deutschlandlied" (the third stanza is the German national anthem).

Many school buildings including that of my school had been destroyed during World War II and many teachers had been fatal victims or they had been seriously wounded, with permanent limitations of their professional abilities. As a consequence, the number of pupils per classroom had to be drastically increased (see above) and we shared one school building with another high school until reconstruction of our building. Thus, we had, at a given week, lessons in the morning, while the other school used the rooms in the afternoon and evening. In the following week, the order was reversed, etc..

After the third year at high school, my marks went down in parallel to puberty: I did not do homework and I paid attention in the lessons only at a minimum to avoid failure of the move to the next form. However, in the last three years at high school I became interested in the subjects of teaching, leading to immediate clear-cut improvement of my marks.

Study of Medicine

In April 1959, I started to study medicine at the University of Hamburg where I also passed the first examination, the so-called „Vorphysikum", after two semesters. For the third, fourth and fifth semester, I changed to the University of Freiburg. There, I got fascinated by two professors, namely Albrecht Fleckenstein, a physiologist, and Helmut Holzer, a biochemist. They were quite different characters. Fleckenstein was impulsive and ingenious in simplifying the subjects and he was a champion in rhetoric. Holzer was a very controlled personality with less didactic and rhetoric abilities than Fleckenstein, but the contents of his lectures were excellent as well. These lectures made me think for the first time to spend a certain time of my professional life in an institute of one of these disciplines, preferentially physiology.

After the second examination, the „Physikum", covering the subjects of physiology, biochemistry and anatomy, I moved to Innsbruck for the beginning of the clinical part of studies. Admittedly, I shared the habit of many German medical students to preferentially hike and ski in the surrounding mountains in addition to attending the lectures. In Innsbruck, I fell in love with my fellow student Irmgard Karin („Inka") Scheibler, whom I had already met in Hamburg and Freiburg as one of many colleagues and whom I married later (see below).

Together, we continued our clinical studies for one semester in Wien and four further ones in Göttingen. The differences in mentality of our academic teachers and of the atmosphere of the respective towns and universities were high, although the quality of the lectures was, on the average of all disciplines, similar. Hamburg and

Wien, towns with far more than one million inhabitants, and their universities were characterized by anonymity and virtual absence of students' life, for which the atmosphere in Freiburg and Göttingen was ideal. The professors in Innsbruck were very flexible as far as their lectures were concerned. The first lectures in the morning ended at about eleven a. m. (suitable for beginning activities in sports mentioned above) and they started again at about six (until ten) p. m. Taken together, there was certainly no drawback that we studied at five universities. In contrast, the ability to adapt to new situations was further increased.

Within clinical sciences, I was fascinated by the fact that surgery can be performed on the open heart. Accordingly, I was interested to carry out investigations on a topic in this field as a basis for my doctoral thesis. In Göttingen, the head of the clinic for heart surgery, Josef Koncz, was an inspiring example of a dedicated medical doctor. Before I could contact him, I heard from another student that a professor of surgery, Wilhelm Marggraf – obviously in cooperation with the clinic of cardiac surgery – was looking for a student, who could analyze pathophysiological mechanisms underlying certain changes in electrolyte and acid-base metabolism during and after heart surgery. Thus, by deciding to carry out those experiments, Marggraf became my promoter. I could finish the thesis before the final medical examination in Göttingen and I started my work as a physician with the title M. D. („Dr. med."), as did my friend Inka.

Professional activities as pharmacologist and toxicologist

This main section contains a selection of background information about the general scientific „atmosphere" in the three institutes in which I worked as a pharmacologist and toxicologist taking the metamorphosis of my viewpoint into account – my first step as a postdoc up to the end of my career as the director of the institute. It will be evident from the selection of the contents that in Hamburg the focus of my activities was in experimental work and the development of my research projects. My teaching load was restricted to more or less voluntary lectures in special topics of pharmacology.

As professor of biochemical neuropharmacology in Essen I had no direct responsibility for the whole institute implicating that I could still spend the largest part of my time working in my scientific projects. My teaching activities considerably increased to a level comprising lectures for all students in the first clinical semester of medicine and seminars in small groups of students in courses of pharmacology. I was very fond of teaching and my students liked my activities in this very important part of my profession. I will not further come back to teaching in this autobiography. Due to the increasing need to share my time in research with that in other activities, I did not describe here so many details of the progress in my scientific work in Essen and Bonn as I did for my time in Hamburg. More information on the research projects supplementing that given here is available in the following section (synopsis of topics).

As professor of pharmacology and toxicology in Bonn and director of the institute I was involved in many additional special activities related to my professional

expertise as a pharmacologist or as a member of the medical faculty. Thus, I was simultaneously president of the Deutsche Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie (DGPT), dean of the medical faculty, vice president of the International Society for Serotonin Research, Managing Editor of Naunyn Schmiedeberg's Archives of Pharmacology – all this in addition to my duties as academic teacher and the head of the institute of pharmacology. This work load made it difficult for me to keep up with my favourite activity as a researcher. However, it was my urgent wish (and I was successful) not to end mainly in bureaucracy. From 2003 onward a short period was left until 2006 in which I could concentrate again on my scientific activities.

Hamburg (1967–1978)

In the interval between clinical studies and education as pharmacologist, I spent only about one and a half year in clinical medicine, at hospitals in Bad Lippspringe and in Wedel. The most remarkable event in that time was that I married my fiancé Inka Scheibler.

I started in pharmacology at the respective institute of the medical faculty of the University of Hamburg, aiming at getting more expertise in drug therapy for specialization in internal medicine. There was no central theme as a scientific label of the institute. I was an illusionist in generally believing university professors to be experts with high reputation in their scientific discipline and university institutes to be facilities with some excellence. However, I had to get used to unequivocally negative statements by many faculty members and former students about pharmacology research and teaching at Hamburg University. Those statements supported my rapidly increasing readiness to revise illusionary prejudice and they did not discourage me and my colleague, Achim Schmoldt. His profound capabilities in analytical chemistry were ideal prerequisites for his career as forensic toxicologist. He became one of my closest friends.

The head of the institute, Günther Malorny, had asked me to start my professional activities in research on certain aspects of carbon monoxide toxicology which, admittedly, was not in the focus of toxicology research in those days. This request was combined with the option to change after a certain time into a laboratory in which investigations on drugs relevant in clinical therapy were carried out. My work on CO was accompanied by predictions of some of my new colleagues that I would share the fate of my predecessors to fail as a scientist by wasting my time without having the chance to publish any data. In fact, I had to go back at least three years in order to find a paper on carbon monoxide originating from that laboratory. Taking this into account, I came back to early lessons of my life as a schoolboy which had taught me to overcome serious problems by fighting, in this case by daring to develop an own scientific topic and to work as much as possible. This enabled me to write two original papers on the distribution of carbon monoxide between blood and tissues in the first year (e. g., reference [1]). Malorny believed the CO partial pressure in tissue to be of interest in view of putative additional effects of CO in tissue underlying the

psychological effects (described in a further paper to which I contributed). The paper appeared when I was mainly working in pharmacology, as did two further ones devoted to the toxicity at increased atmospheric pressure. My input into those two studies was high since I was critically involved in the experiments which were based on my prediction/calculation (according to the law of mass action) of a lower COHb level at increased pressure.

According to my agreement with MALORNY, I changed into the laboratory of HANS-FRIEDRICH BENTHE, who worked on cardiovascular pharmacology. He was an excellent teacher and I expected his standard in research to be similarly high. However, he wasted his scientific capabilities by not consequently trying to provide evidence for new working hypotheses emerging from interesting new results. Furthermore, I was disappointed that he did not systematically publish his findings. With respect to application of new methods, I had to be an autodidact. The lack of instructions also was the reason for my ignorance of the high importance of the last (besides the first) authorship reserved for the head of the working group in a multi-authored original paper. This became particularly evident in a highly cited paper [2] based on cooperation with GÜNTER ENGEL, a scientist at SANDOZ (Basel) and his co-workers. My group had contributed fifty percent of the results and I had written the first draft of the manuscript. Based on this, it was suggested that ENGEL should be the first and I the last author, yet I insisted on the second position of the list of authors. Finally and paradoxically my student HILLENBRANDT became the last author – another aspect of my ignorance: I believed the last position in the rank order of authors to be appropriate in his case since I assumed the last author to be that with the least contribution to the paper. Thus, due to my own fault, this important paper was largely ascribed to ENGEL's group, although we had contributed at least equally to that study which provided the first classification of presynaptic 5-HT autoreceptors as 5-HT_{1B} [2]. This had already been my working hypothesis in an analogous study (experiments mainly carried out 8 years before) with own serotonin release results (and binding data from the literature) – a study published 3 years earlier [3].

The deficiency in being taught in the basics of science was at least partly compensated by ULLRICH TRENDELENBURG (the director of the institute of pharmacology at the University of Würzburg). He was managing editor of NAUNYN-SCHMIEDEBERG's Archives of Pharmacology (the oldest still existing journal of pharmacology) in those days. His comments on my first manuscripts, which I had submitted to him for consideration as original papers in that journal, were shocking for me. The more I had thought about his points of criticism, the more did I get depressed about his apparently negative opinion on the contents of my manuscripts. In Hamburg where publication of a paper was a seldom event, nobody knew how carefully TRENDELENBURG read manuscripts, aiming at identifying weak points that could help the author to improve his paper. I almost overlooked the last and important sentences in which he stated that he believed the manuscript to be very interesting and, after appropriate revision, it would be acceptable for publication. TRENDELENBURG believed in my abilities and fostered my career.

Within the field of pharmacological science my main interest was focussed on general anaesthetics and on auxiliary drugs used in clinical anaesthesia, in particular

neuro-muscular blocking drugs at the skeletal muscle endplate. I decided that my habilitation thesis should be based on experiments with those classes of drugs. In more detail, my thesis comprised effects of those drugs on catecholamine release in the adrenal medulla and the role of modified catecholamine release in the development of cardiovascular side effects of those compounds.

After having criticized certain properties of my direct supervisor, Hans-Friedrich Benthe (see above), I now would like to state that he was very fair in supporting my research. He carefully read the draft of my thesis and made some relevant suggestions for improvement. As the official peer reviewer appointed by the faculty he endorsed my habilitation for which I got qualified at the age of 31, on 1st December 1971. My thesis was printed in a series of monographs entitled „Anaesthesiology and Resuscitation" [4]. In my case, habilitation comprised conferment of the venia legendi in pharmacology and toxicology (i. e., permission to teach this science at the university level). The title „Professor" was conferred to me in 1976.

My wife and I could celebrate an additional private event in December 1971, namely the baptism of our twin sons, Joachim and Wolfram, who were born in April 1971. In this context, I would like to mention that our family became complete when our third son, Martin, was born in March 1975.

After habilitation I continued to work on adrenal medullary effects of anaesthetics, extended by experiments in vivo [5] and by studies of effects of general anaesthetics (prototype: halothane [6]) on sympathetic nerve terminals. Subsequently, these terminals of the isolated rabbit heart were used as a biochemical model for the identification of the site of action of anaesthetics, ethanol and other alcohols. My group consisted of myself, students working for their doctoral thesis, and above all, Gisela Thielicke, who was the best technician of the institute. <G. T. started her carrier as technician – MTA – in Frankfurt in the laboratory Hans-Joachim Schümann. She must have been an excellent, almost mythically qualified technician. She additionally drew the diagrams, photographed them and made slides for all co-workers of the institute of pharmacology. She left Frankfurt about 1959, a few months before I started working with Schümann, to go to Hamburg.>*

The availability of multiple methods of stimulation of noradrenaline release was the basis for the identification of the site and mechanism of action underlying the acute effects of anaesthetics, ethanol and other alcohols. In detail, release was stimulated by, e. g., electrical impulses delivered to the postganglionic nerves, by increasing the K^+ concentration (leading to membrane depolarisation), by tyramine (release independent of Ca^{2+} ions) and by nicotinic receptor agonists and serotonin (acting at nicotinic acetylcholine receptors and 5-HT_3 receptors, respectively). It was found in the experiments with prototypic compounds – ethanol [7], halothane [6] and pentobarbital [8] – that only the nicotinic agonist- or serotonin-induced release was inhibited by the drugs at clinically relevant (or non-lethal in the case of ethanol) concentrations. The degree of inhibition of the three prototypic drugs and further anaesthetics and alcohol correlated with their hydrophobic property, suggesting that the neuronal mechanism underlying the acute action of these drugs is based on their interaction

* Ergänzende Erläuterungen von Athineos Philippou in < >

with hydrophobic regions of the nicotinic and 5-HT_3 receptors, respectively, i. e., two ligand-gated ion channels identified in this model.

By inducing a conformational change of the receptor protein structure, they mediate a decrease in function underlying their acute depressant effect on the CNS.

The selectivity of action of halothane at nicotinic and 5-HT_3 receptors observed in the sympathetic nerve terminals of the isolated rabbit heart is shared in another neuronal model system, namely the catecholamine-secreting cells of the perfused bovine adrenal [9]. Interestingly, the catecholamine release induced by activation of G-protein-coupled receptors such as histamine and muscarinic acetylcholine receptors was not affected by halothane. Thus, we were the first to identify the nicotinic and the 5-HT_3 receptor, two ligand-gated ion channels as sites of action of ethanol and general anaesthetics. These conclusions were drawn from biochemical results at about one decade earlier than by electrophysiologists from their data. My biochemical models obviously were unknown systems used by an unknown author, who published so far unknown results – a typical constellation for not being cited in the relevant literature. I was very disappointed by this outcome of my experimental investigations. However, on the other hand, it was Klaus Starke who pointed in a TIPS article [10] at their importance. He identified my publications as progress beyond the hypothesis of Overton and Meyer, who had speculated lipid constituents of the cell membrane to be sites of action of general anaesthetics and alcohols [references in 11].

My first attempt failed to identify an analogous model of a central nervous cell system. Desensitization of nicotinic receptors and 5-HT receptors on noradrenaline, dopamine or serotonin nerve terminals, in superfused cerebral slices appeared to be too fast as to be applicable for stimulation of release of radioactively labelled neurotransmitter in response to addition of a nicotinic or 5-HT_3 receptor agonist. I had learned the technique of superfused brain slices as a guest in the laboratory of Klaus Starke in Essen.

We decided to apply this method of analysis of transmitter release in superfused brain slices to another scientific problem which had fascinated me, namely the identification of presynaptic receptors. In this field, Erich Muscholl, Klaus Starke and Salomon Langer were pioneers, who identified presynaptic receptors on noradrenergic axon terminals [12–14]. My aim was to extend this concept to presynaptic receptors on serotoninergic neurones.

My interest in the serotonin system was triggered by Hans-Georg Baumgarten, a neuroanatomist working in Hamburg. He had developed selective serotonin neurotoxins [15] and had approached me because he needed confirmation of his results by serotonin concentrations in the respective tissues. He had learned that I had established the method of Bertler and co-workers to measure tissue catecholamine concentrations and that I was about to extend this method to serotonin determination. I promised to help him as far as I could and I was „infected“ by his fascination of the importance of this neurotransmitter. However, the serotonin and presynaptic receptor stories, which started in Hamburg, were mainly written in Essen and later in Bonn.

In 1982, Hasso Scholz became full professor of pharmacology and head of the institute. Under his directorate, only little time elapsed until this institution had a high scientific reputation.

Essen (1978–1985)

I was very pleased to be appointed Professor of Biochemical Neuropharmacology as successor of Klaus Starke (who had moved to Freiburg) at the institute of pharmacology of the University of Essen. On the other hand, I was sad not to see my family from Monday to Friday of the week, because I had given up finding a home in Essen which was similar to the standard of our house and ground in Hamburg. In addition, I received signals that Essen would be only an intermediate, relatively short period of my career.

In the institute in Essen, the central research theme was devoted to neurotransmitter systems in the peripheral and central nervous system with emphasis on the sympathetic innervation of the cardiovascular system. In the focus of my activity was the identification of presynaptic 5-HT autoreceptors and various heteroreceptors on 5-HT axon terminals in the cerebral cortex. Both my group and that of Maurizio Raiteri were the first to identify presynaptic autoreceptors in the brain [references in 16, 17]. Further details of these investigations and of studies on open questions in other, e. g., noradrenergic, neuronal systems are included in the section „synopsis of my research activities" (see below).

In Essen I lost the feeling to be isolated from the scientific community, characteristic for my time in Hamburg. Hans-Joachim Schümann, the head of the institute, had significant contacts to Japanese and Portuguese pharmacologists. Of particular importance for me was the onset of long lasting friendships to pharmacologists in Porto, in particular my personal relationship to the head of the department of pharmacology of the University of Porto, Walter Osswald. He is a remarkable personality, who, after retirement from his successful career as a pharmacologist, became an equally highly estimated scientist in bioethics. Osswald had organized small, very efficient meetings on adrenergic mechanisms every two or three years. Serafim Guimaraes, his successor, maintained this tradition. I was a regular participant as an invited guest. Later, during my professional occupation in Bonn, Daniel Moura, a scientist at the department of pharmacology in Porto, spent half a year in my institute as a recipient of a Deutscher Akademischer Austauschdienst (DAAD) fellowship in order to get familiar with the radioligand binding technique.

Bonn (officially 1985–2006)

As full professor of pharmacology and toxicology and director of the institute in Bonn I was responsible for the organization of its administration as well as for teaching and research. My responsibility in academic matters was guided by the idea to generate an atmosphere of positive motivation with mutual respect, everybody recognizing his/her responsibility as a prerequisite for successful work. At important decisions I informed the other professors of the institute about my view and asked them for their opinion. The institute is one of the first institutes of pharmacology established in Germany. A chair of pharmacology had already been founded together with the University of Bonn in 1818, but an institute of pharmacology – justified to be named

after this discipline as an experimental biomedical science – was established by Carl Binz, who became head of the institute in 1868. He held this position until 1908. His high reputation as a researcher on e. g., malaria and the pharmacological properties of chinin was the reason why the army doctor, Emil von Behring, the first Nobel laureate in „physiology and medicine" in 1901, was commanded to work for a two-year period (1887–1888) in the institute of pharmacology in Bonn. My position as a director of the institute was associated with a change in the central topic of research from inflammation, arthrosis and antiphlogistic compounds to physiology and pharmacology of signal molecules, comprising neurotransmitters and the gas NO. Two professors, Karlfried Karzel and Dieter Abbo Kalbhen, represented the previous era, as did Jürgen Steinmeyer, who got qualified for habilitation. Heinz Bönisch, Kurt Racké, Ivar von Kügelgen and I, professors coming from other universities, were active in the new focus, as were Eberhard Schlicker, Klaus Fink, Gerhard Molderings, Martin Barann, Michael Brüss and Markus Kathmann. They got qualified as young researchers for habilitation. Schlicker, Fink and Molderings were appointed professors; in the case of Brüss, all scientific prerequisites for professorship had been fulfilled before he died much too early at the age of 45.

Among my scientific activities, I continued to work on several of the topics that were started in Hamburg or Essen. The institute did benefit from the move of Heinz Bönisch, a former co-worker of Ullrich Trendelenburg, from Würzburg to Bonn. He extended the pattern of methods available in the institute by modern cell biological and molecular biological techniques. We decided to cooperate on effects of general anaesthetics at ligand-gated ion channels – a scientific project which did benefit from such an extension of applicable methods.

A new field of interest was opened up by the „Sonderforschungsbereich 400" dealing with the molecular basis of neuropsychiatric disorders. This intensified our contacts to the department of human genetics headed by Peter Propping, who is an outstanding scientist in this field. In particular, we studied the biochemical effects of single nucleotide polymorphisms (SNPS), which can be involved in the pathogenesis of neuropsychiatric disorders and in the modification of transmitter receptor function.

Those activities were accompanied by efforts to extend cooperation with scientists in other countries. Scientific contacts between Polish and German pharmacologists, established 40 years ago, have played a particularly important role among my cooperative projects with our neighbours in Europe. In contrast to the violence initiated by the German attack towards Poland in 1939 and maintained until the end of the German occupation of Poland, a partnership characterized by good and peaceful neighbourhood has developed between the two states in the decades that followed the seventies of the 20th century. In this context I would like to point at the multiple honours which I received from various Polish institutions (see below: „Honours"). Furthermore, Polish pharmacologists did benefit from research in German institutes and vice versa. Accordingly, several Polish scientists worked as guests in my department in Bonn – above all, Barbara Malinowska from Bialystok as a recipient of a Humboldt fellowship and later head of a department of physiology and pathophysiology at the faculty of pharmacy of the Medical University of Bialystok. At

the end of my career, I worked in Malinowska's department for six months (split into several periods over three years; 2006–2009) as a Guest Professor and recipient of an Alexander von Humboldt Polish Honorary Research Fellowship. An official letter of intention to cooperate was signed by the Rector of the Medical University of Bialystok and by me as Dean of the Medical Faculty of the University of Bonn. This provided a strong basis for future common research projects.

My positive experience as a schoolboy in France motivated me as an adult scientist to search a French partner for a common research project. Such a cooperation was established by Michel Hamon, a French neurobiologist and pharmacologist. He assembled several European serotonin scientists – I was one of them – who successfully applied for financial support for a joined project in serotonin research within the framework of the European Community.

It was a highlight of my efforts for German-French cooperation that I was appointed the representative of the Rector of the University of Bonn for the cooperation with the Collège de France in Paris from 2002 to 2009. Furthermore, I had negotiated as the German partner with the French organizers of a joined meeting of the French and German pharmacological societies in Lille, 1993. At the banquet of that congress, the president of the French Pharmacological Society, Prof. Charles Advenier, gave his official talk in German language – a unique act of friendship which I gratefully appreciated.

The special role of scientists and organizations from Poland, France and Portugal mentioned so far as my partners in common projects, by no means diminishes, denies or excludes the significants of other European (e. g., British – I appreciated to become a member of their society in view of the important contributions of British scientists to serotonin research – Italian, Greek and Swiss), American, Japanese and Australian events, organizations and researchers in the progress of my scientific work. In this context I would like to specify multiple contacts with scientists working in the United States, e. g., at the occasion of several meetings under the auspices of the New York Academy of Sciences. I became a member of that organization in 1977 and I appreciated the privilege to participate in five of such meetings as an invited speaker. In addition, I organized – together with Donald Reis from New York and my co-worker Gerhard Molderings – a symposium in Bonn on imidazoline receptors and their endogenous ligends under the auspices of the New York Academy of Sciences in 1998 and to edit the corresponding volume of the „Annals" [18].

Main activities in which I was involved referred to sciences and academic self-administration are described in the following section „Other activities". I continued to work also after my official retirement as a guest in „my" former institute in Bonn and I continued to travel between Hamburg and Bonn until 2009. My family never moved to Bonn because my wife had an own medical practice as general practitioner in Hamburg. When taking all points into account, I would like to state that I did never regret to have stayed in Bonn and not to have accepted the professorship and directorate in pharmacology at the medical university in Lübeck – a decision which was not easy for me in 1988 in view of the much lower distance to Hamburg.

Finally, I would like to point at the analogies between renaissance and the present era. This refers, for instance, to the analogy in progress between the invention of book

printing by Johannes Gutenberg (about 1400–1468) in renaissance and the development of information technology in the past few decades. Another example is the progress in pharmacology brought about by Paracelsus (1493–1541) and the enormous increase in knowledge of drug treatment to which, in the course of the last about 100 years, many eminent scientists contributed. The analogies are evident in all sciences and numerous further examples could be given. I cannot resist the temptation to quote Ulrich von Hutten (1488–1523), a humanist and poet in renaissance, whose feelings I share as a member of the community of currently living pharmacologists: „Oh century, oh sciences, it is a lust to live!"

Synopsis of my research activities

This section provides a short overview over my main research topics within the framework of the science represented by the DGPT (German Society of Pharmacology and Toxicology) in its original form. Later, the DGPT consisted of three sections, namely „Experimental Pharmacology", „Clinical Pharmacology" and „Toxicology". The sections then became three largely autonomous societies, the DGPT being only a roof above them with a rather awkward name (hidden behind the „old" abbreviation DGPT, which is still valid): Deutsche Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie; (German Society for Experimental and Clinical Pharmacology and Toxicology).

When changing from one sub-discipline to another within my research topics in all three of them, I never lost the feeling to work in basically the same science. The main difference for me was that formerly I had to pay for membership in only one society, the DGPT, but nowadays, membership fees for three societies are necessary to cover the scope of my scientific interests and papers. Overlap between this section and the previous one could not be completely avoided; however, it was kept to a minimum.

Distribution of CO between blood and tissue, effects of low CO concentrations and toxicity of CO at elevated atmospheric pressure (from 1967 until 1970)

The project has been adequately described in the previous section on professional activities.

Cardiovascular effects of general anaesthetics and the role of the sympathetic nervous system in these effects (from 1969 until 1975)

This project is described in detail in the main section on professional activities.

Investigations into the site and mechanism of action of ethanol and general anaesthetics (from 1970 until 2004)

This project has been described in detail in the previous main section on professional activities. One important aspect has to be considered here, namely the investi-

gations into the site of mechanism of action of ethanol, which had been carried out so far only in peripheral biochemical models. The studies were extended to noradrenergic neurones in the brain as soon as it was shown that noradrenaline release can be induced by activation of exicitatory presynaptic NMDA receptors, which belong to the superfamily of ligand-gated ion channels. Simultaneously with the group of Lovinger, but indepently of them, we were the first to prove that the NMDA receptor is a major site of action of ethanol [19] and that hydrophobic interaction with the receptor is responsible for this effect. The latter conclusion could be derived from the correlation between the potency of several aliphatic alcohols and their hydrophobicity.

Identification, characterization and classification of 5-HT_3-receptors (1972–2011)

Simultaneously with the group of John Fozard (an excellent pharmacologist working in those days as a guest in the institute of pharmacology of the University of Mainz) we provided evidence that, in isolated rabbit hearts, 5-HT and other indolethylamines evoke noradrenaline release by activating a presynaptic 5-HT-receptor, which was originally named „M" and, later, renamed 5-HT_3. It is a ligand-gated ion channel. Since 1990 I closely cooperated with Heinz Bönisch (a pharmacologist who moved from Würzburg to Bonn in 1989) and with B. W. Urban (a neuroscientist working in experimental anaesthesiology). The [^{14}C]guanidinium influx technique and the patch clamp method in excised outside-out patches was used to measure 5-HT_3-receptor function in cultured native cells and in cells transfected with the cDNA of the mouse and human 5-HT_3-receptor.

Modulation of serotonin release in the brain via presynaptic auto- and heteroreceptors (from 1977 until 2011)

This project is described in detail in the previous main section on professional activities.

Modulation of noradrenaline release via presynaptic receptors in the peripheral and central nervous system (since 1977 until 2011)

In addition to experiments described in the previous section, we aimed at providing evidence that modification of Ca^{2+} influx via membrane potential-regulated Ca^{2+}channels plays a critical role in the chain of events leading to the inhibition or increase of noradrenaline (NA) release [20] by activation of presynaptic receptors (a_2-autoreceptors as well as muscarinic, angiotensin and opiate heteroreceptors). Evidence for this could be derived from experiments in which NA release was induced by short-term introduction of a low Ca^{2+}concentration into K^+-rich, Ca^{2+}-free perfusion/superfusion fluid as the only parameter changed. This Ca^{2+}-evoked, depolarization-promoted noradrenaline release was modulated via those receptors. This was not the case in the experiments in which the Ca^{2+}-evoked noradrenaline release was due to the Ca^{2+}-permeation across the cell membrane of the norad-

renergic axon terminals preloaded with the ionophore A23176:Ca^{2+}-inward translocation is brought about (independently of native Ca^{2+}channels) by the transmembrane movement of the ionophore with Ca^{2+} bound at the outside and set free at the inside of the cell membrane. In the case of -adrenoceptor mediated facilitation of noradrenaline release, we found the local renin-angiotensin system to be involved. This, however, could not yet be reproduced by other authors.
On the postganglionic sympathetic nerves of the pulmonary artery, we identified facilitatory ACTH-receptors; the increasing effect of stimulation of these receptors on noradrenaline release involves an activation of adenylyl cyclase.
As a link to our research in the field of 5-HT-receptors, we carried out experiments which aimed at identifying and characterizing presynaptic 5-HT-heteroreceptors on sympathetic nerve terminals in blood vessels of humans. In fact, we found such receptors which could be classified as $5\text{-}HT_{1D}$-receptors.

Effects of drugs with imidazoline structure and attempts to identify imidazoline receptors (from 1977 until 2011)

Discussion of this issue was very controversial, as evident in the proceedings of a meeting sponsored by the New York Academy of Sciences [18].

Identification of Ca^{2+}channels involved in Ca^{2+}influx into nerve terminals and effects of Ca^{2+}channel blockers and gabapentin on neurotransmitter release (from 1978 until 2011)

In a first systematic study, my group found that Ca^{2+}channel blockers such as verapamil and D600, known to block the L-type Ca^{2+}channel, have to be present at extremely high concentrations to induce an inhibition of action potential induced noradrenaline release in the heart. These data suggested that another, verapamil-resistant Ca^{2+}channel must be involved in noradrenaline release [21].
In human heart atria, it was proved by application of neurotoxins specifically blocking certain Ca^{2+}channels that Ca^{2+}influx into the sympathetic axon terminals exclusively occurs via N-type channels. Evidence could also be presented that mibefradil, a blocker of T- and N-type Ca^{2+}channels, at clinically relevant concentrations inhibits noradrenaline release by blocking N-type channels [22] and that this probably contributes to the beneficial cardiovascular effects of this drug (which, however, in the meantime was withdrawn from the market).
A further study with gabapentin aimed at investigating whether an inhibition of Ca^{2+}influx into glutamate nerve terminals contributes to the so far unclear mechanism of action of this anticonvulsant drug. In fact, it could be concluded from measurements of the K^+- induced increase in neocortical synaptosomal Ca^{2+} concentration and of neurotransmitter release under the influence of gabapentin that gabapentin reduces the depolarization-induced $[Ca^{2+}]i$ increase in glutamatergic nerve terminals by inhibiting P/Q-type Ca^{2+}channels. Decreased Ca^{2+}influx via those channels underlies the attenuation of K^+-evoked glutamate release and, as a consequence, decreased activation of excitatory AMPA-receptors, located on NA

neurones. Thus, gabapentin indirectly inhibits noradrenaline release [23]. These effects which occur at therapeutically relevant concentrations may be assumed to contribute to the therapeutic actions of gabapentin.

Glutamate receptors in the brain and their pharmacological properties (from 1988 until 2000)

We investigated where subcellularly the NMDA receptors mediating noradrenaline release are located and how the Mg^{2+} block of the receptor can be overcome. The Mg^{2+} block of the receptor can be removed by partial depolarization of the cell membrane by an elevated K^{+}concentration or veratridine [24].
In addition, activation of NMDA-receptors also induces dopamine, 5-HT and GABA release. In the context of a putative interaction of excitatory and inhibitory presynaptic receptors on the neurones mentioned, we demonstrated that presynaptic a_2-autoreceptors and cannabinoid-CB_1-heteroreceptors mediate an inhibition of the NMDA-evoked noradrenaline release and that analogous presynaptic 5-HT-autoreceptors modulate NMDA-evoked 5-HT release [25].

Pharmacological properties of naturally occurring genetic variants of human 5-HT receptors

These experiments were briefly outlined within the previous main section on professional activities.

Special activities

This section comprises various activities which partly are described in some detail in order to give interesting examples. In many cases, the activities are believed to be self-explanatory or no details are given for the sake of brevity.

Dean of the Medical Faculty (1998–2002)

In 1997, the Medical Faculty of the University of Bonn was evaluated by the „Wissenschaftsrat“ (Science Council). The duty of this institution, established in 1957, is to advise the federal and state authorities in matters of the German university system and of non-university research facilities. Furthermore the council evaluates those institutions. In case of the Bonn medical faculty, the outcome of this evaluation was disastrous. This was the condition under which I decided to accept election as Dean of the Faculty in 1998.
A major point of criticism by the Science Council was that research was not focussed on a limited number of central themes and that no laboratory space was reserved for particularly successful scientists. Important disciplines such as virology were not adequately established in the Medical Faculty; there was only a small group of virology in the Institute of Microbiology. Criticism also referred to seri-

ous problems of the preclinical institutes, such as the urgent need to renovate the interior of buildings which were erected in the 19th century. The desperate state of those buildings which housed the Institute of Biochemistry and one of the two Institutes of Physiology was a major obstacle against the need to find highly qualified successors for the key positions of a professor of biochemistry and a professor of physiology.
Taken together, the Medical Faculty on the whole and, above all, the preclinical institutions were endangered to be closed down. It became clear to me that the position of the Dean in the three-year period beginning 1998 would be associated with an unusual workload based on long-term strategic considerations. This was based on the rundown of the interior of some of the buildings, not only of the precinical research institutes but also of the clinics and the clinical research institutes in addition to the serious structural shortcomings addressed by the „Wissenschaftssrat".
The „Wissenschaftsrat" announced that the faculty would be re-evaluated in 2003. However, the „Wissenschaftsrat" did not visit Bonn again in that year because of the information, e. g., by my introductory talk at the 62nd „Fakultätentag" (see below) that all of the main obstacles addressed in 1997 could be removed.
My very first hour in office as Dean was devoted to the first step towards establishment of an Institute of Virology headed by an independent professor of virology. In order to know the opinion of the professor of microbiology, Klaus Schaal (whose focus in that science was bacteriology), on this matter, I had invited him for a discussion on the future of whole field of microbiology. As suspected, his suggestion was to further extend his influence beyond bacteriology to virology, taking his own competence in the latter field into account; in other words, to leave everything as it was. In response, I pointed at virology-specific methodical approaches and research topics (e. g., oncology). However, my attempt to modify his view was in vain. On the basis of the negative result of this conversation, my strategy was to proceed cautiously in this matter. I feared solidarity of a conservative majority of the professors of the faculty with a colleague whom they might believe to be a victim of my attempt to diminish the size of his „empire", which was granted to him in his initial negotiations with the University. In view of this danger I decided to bring this up as early as possible, but to wait for a favourable occasion.
In fact, I was successfully involved in paving the road towards a solution of this problem in my last year as Dean when – at the retirement of Hans Martin Seitz, professor of parasitology and director of the institute – discussion of the structure of the whole complex of the three related disciplines (implicating the necessity to secure competent clinical routine investigations in all three subdisciplines) could not be further postponed. The Commission of Structure and Personnel approved my suggestion to keep the triple of professorship, institute and directorate of parasitology because of a tradition of this scientific field in our faculty. In particular, this also included the Institute of Pharmacology where Carl Binz and Werner Schulemann, two of my predecessors, had been internationally highly estimated malaria specialists.
The solution of the problem of virology implicated a simple name of the corresponding institution, namely Institute of Virology in addition to an institute with the

focus in research on parasitology, generated by the merger of the former institutes of parasitology and microbiology and with the complicated name composed of a superordinate, an additional and a subordinate discipline. The name Institute of Medical Microbiology, Immunology and Parasitology, respectively, implicated that the director of the institute of microbiology had the feeling that at his retirement „his" institute also continued to exist in addition to the newly tailored institute of parasitology. This compromise made it possible to unite the pool of personnel of the former institute of microbiology with that of the much smaller one of the former institute of parasitology, thus making it possible to offer the successor of Seitz as a professor of parasitology additional positions of academic and non-academic coworkers than were available before. In addition, personnel became available for the negotiations with the new professor of virology. The top candidate for the directorate of the merged insitute parasitology and microbiology Achim Hörauf, who accepted the position, had a licence for all routine investigations associated with that position.

Another initial measure was to increase the efficiency of the work of the Dean and of the Faculty by decreasing the number of commissions. In particular, it was a drawback that different commissions existed for structure and personnel in spite of the vital interdependence between both. Therefore, I unified those responsibilities by establishing a strong Commission of Structure and Personnel.

As requested by the „Wissenschaftsrat", four central research themes of the faculty were defined: Neurosciences, Genetic Bases and Genetic Epidemiology of Human Diseases, Hepato-Gastroenterology and Diseases of the Cardiovascular System. In the four and a half years as dean, I strengthened research on these themes by reoccupation of fifteen positions of professors with respective focus of research, among them key professorships for biochemistry, physiology, pathology, molecular medicine and cardiac surgery.

My work as dean was highly supported by three vice deans, Peter Propping, Tilman Sauerbruch and Anke Rohde, for matters of finance, structure and teaching, respectively.

Another scientist whose advice I appreciated was Otmar Wiestler who was full professor of neuropathology in Bonn from 1992 until 2003, when he became president of the German Center of Cancer Research. His merits for the faculty cannot be overestimated but the reaction of the faculty to his initiatives often was inadequate. A special relationship between him, Propping and me had developed in many meetings in his first years in Bonn, when we elaborated initiatives to establish a „Sonderforschungsbereich" (SFB) and an internal system of financial support of scientific projects. In addition Wiestler's merit was to attract the money for the research platform LIFE AND BRAIN, which I supported against obstacles of the faculty. At the end of my term as dean I was pleased about a phone call by Wiestler in which he appreciated my efforts and achievements for the faculty.

Most helpful during my workload as dean was my secretary Renate Milz.

62. Medizinischer Fakultätentag der Bundesrepublik Deutschland, Bonn, 2001 (62nd Annual Meeting of Medical Faculties of the Federal Republik of Germany, Bonn, 2001)

Local Organizers: Anke Rohde and Manfred Göthert. Delegates of the faculties were, as a rule, the dean and/or a vice dean (in many cases vice dean for teaching matters). As the dean of the host faculty I gave the introductory talk in which I reported on research activities and new developments of the Medical Faculty in Bonn.

President of the DGPT (1997–1999)

For the first time I was approached to be available as a candidate to become successor of Hasso Scholz in 1989, but I could not take over this responsibility because I had to solve serious problems in the context of my move from Essen to Bonn. I suggested Helmut Greim to become the next president because this might remove the danger that the toxicologists could found a separate society. In fact, he was elected. I was elected president of the society for the three-year term from 1997 until 1999. Our society was considered important enough (more than 3000 members; the DGPT was one society composed of three sections in those days, not a roof for three societies) to be received for an one-hour inauguration visit by the Federal Minister of Health, Horst Seehofer. A highlight of my presidentship was that the DGPT was host of the IUPHAR congress in München in 1998, where I gave one of the introductory talks [26]. In the context of the organization of that meeting, I had to travel repeatedly to München as a member of the local organizing committee. The fate of the society is described in some detail in the previous main section containing the synopsis of activities.

President of EPHAR (2004–2006)

The establishment of the Federation of the European Pharmacological Societies (EPHAR) as an official partner of the International Union of Basic and Clinical Pharmacology (IUPHAR) filled a gap in the overall structure of pharmacological societies. As is understandable on the basis of my biography, I was very keen to contribute to its establishment. Later, as the President of EPHAR for the period 2004–2006, my concept comprised three points. (1) The EPHAR congresses should no longer take place at random time intervals but at constant ones of four years in the middle between two IUPHAR congresses; thus, an accumulation of three of such meetings as around 2000 should be avoided in the future. (2) The registration fee should be moderate enough to allow young scientists to participate. (3) Serotonin should come into play inasmuch as meetings of the Serotonin Club should be coupled as satellites to the EPHAR congresses at least as tight as they are to IUPHAR congresses. I was happy that this concept was accepted by the EPHAR Council and Executive Committee at the occasion of business meetings at the 15th IUPHAR Congress in Beijing (China) in 2006. Accordingly, the 2004, the 2008 and

the 2012 Serotonin Club Meetings in Porto (Portugal), Oxford (UK), and Montpellier (France), respectively, became the 1st, 2nd and 3rd Official Satellites of the 4th, 5th and 6th EPHAR congresses in Porto (Portugal), Manchester (UK) and Granada (Spain), respectively.

Vice President of the International Society of Serotonin Research (formerly Serotonin Club)

I was Vice President of this Society from 1994 to 1998. Normally, after having been vice president, my term as the president of that society would have started in 1998. However, I did not accept that position because of my enormous workload with many parallel activities.

Organization of symposia and congresses (1989–2014)

1989: „Serotonin and 5-HT2-Receptor-Blockade in the Cardiovascular System" (Symposium, Frankfurt, [27], organizer M. Göthert)
1989: „5-HT1A-Receptors in the Brain and Blood Pressure" (Symposium, Bonn, [18], organizers M. Göthert, N. Kolassa)
1990: „Vascular Neuroeffector Mechanisms" (Symposium in Bonn, Satellite of the 11th IUPHAR Congress; Amsterdam, 1990, [28], organizers: M. Göthert in cooperation with J. A. Bevan, W. Kuschinsky, R. A. Maxwell)
1998: 13th IUPHAR Congress (München, chairman of the program committee: F. Hofmann; local organizers: H. Greim, F. Hofmann, M. Göthert, R. Kretzschmar, A. Walland)
1998: „Imidazoline Receptors and Their Endogenous Ligands" (Symposium in Bonn; Satellite of the 13th IUPHAR Congress, München; 1998, organizers: M. Göthert, G. J. Molderings, D. J. Rice)
2003: German-Polish Symposium „Thirty years of cooperation between German and Polish pharmacologists". (Bialowiecza, Poland, 2003, organizers: B. Malinowska, E. Schlicker, M. Göthert, E. Przegalinski)
2004: 4th EPHAR Congress (Porto, Portugal; organizer and president A. Cuthbert, supported by M. Göthert and local organizers J. Goncalves and D. Moura)
2004: Symposium of the International Society of Serotonin Research (formerly Serotonin Club; Porto, 2004; Satellite of the EPHAR Congress in Porto; organizer of Satellite: M. Göthert; local organizers: J. Goncalves and D. Moura)
2014 Minisymposium „Four Decades of Cooperation of Polish and German Pharmacologists", scientific topic „Role of Cannabinoids in Cerebral and Cardiovascular Functions and Disorders" (to be held in Hannover, 2014, organizer: M. Göthert)

Editor of journals (1986–2014)

I was advisory editor and managing editor (in this function 1995–2002) of Naunyn-Schmiedeberg's Archives of Pharmacology, furthermore advisory editor of British Journal of Pharmacology, Fundamental and Clinical Pharmacology, Pharmacological Reports, Neurochemistry International, Drug Development Research.

Deutsche Forschungsgemeinschaft (DFG; German Research Council)

I was elected reviewer for pharmacology for two terms: 1996–1998; 2004–2007

„Institut für die Arzneimittelverordnung in der gesetzlichen Krankenversicherung" (1992–1996)

The „Gesundheitsstrukturgesetz" (Law for maintenance and improvement of structure of statutory health insurance) of December 1992 aimed at keeping the expenses for the Health System constant by, e. g., establishing long-term stable health insurance contributions. Among other points, a list of proprietary medicinal products which can be prescribed within the framework of statutory health insurance had to be introduced as of 1st January 1996. For the elaboration of such a positive list an „Institut für die Arzneimittelverordnung in der gesetzlichen Krankenversicherung" (Institute for the Prescription of Drugs within the Framework of Statutory Health Insurance) was founded in 1992. The members of this institute, among them myself, were appointed in a letter signed by Horst Seehofer who was Minister of Health in those days.
We had to meet at least once each month for one working day in Berlin over a period of three years. The draft of this list was finished in 1995. Elaboration within the deadline was a piece of hard work. As a result, small non-researching drug companies which had introduced drugs with unproven effects to the market were endangered by bankruptcy. Since lobbying was successful, the list was destroyed in front of a television camera – a frustrating experience for those who had invested so much work. In the meantime, further attempts to establish such a list have also failed. It is a scandal that, in Germany, it is not possible to make the work of medical doctors easier by rendering the drug market more transparent.

Scientific Advisory Board of the BfArM (1998–2004)

Important tasks of the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM; Federal Institute for Drugs and Medicinal Products) are, e. g., the approval of new proprietary drugs and the registration, evaluation, and defense against, the risks associated with drug therapy. It is a huge institution with about one thousand coworkers. After its establishment in 1995, it was originally located in Berlin but it

moved to Bonn in several steps from 1999 until 2001. This was a measure within the framework of the Berlin/Bonn Law as a compensation for the loss of the status of German capital, associated with the move of the parliament, the government and embassies to Berlin.
In this context it is interesting to note that there was a strong opposition in Bonn among politicians and other citizens, including many members of the Medical Faculty, against this loss of political influence. Furthermore, major unemployment was feared. In Bonn, every Thursday there was a demonstration in favour of Bonn as capital of Germany. In the beginning the whole market place was crowded but gradually the resistance against the decision of the parliament became evident by a decreasing number of participants, finally to less than twenty persons.
The advisory board met only twice per year. Information about BfArM's most important activities and events was given at the beginning of each session by the president of BfArM as a basis for the scientific discussions on the tasks in which the board was involved. In the new building of this institution in Bonn, excellent laboratories and a modern animal house are available – ideal conditions for scientific work, but not yet ideally used.

Drug Commission of German Medical Association („Arzneimittelkommission der deutschen Ärzteschaft"; „AKdÄ"; 1996–2005)

The duty of this commission – an expert committee of the German Medical Association – is to independently advise the association in scientific matters arising in the context of drug therapy. The members of the committee meet one per year for the main event and in addition there are several meetings dealing with specific problems within the framework of drug application. A newsletter named „Prescription of drugs in the medical practice (Arzneiverordnungen in der Praxis, AVP) is distributed among the German physicians and the members of the committee are expected to contribute to the latter when asked for written statements within the respective expertise.

Representative of the Rector of the University of Bonn for the cooperation with the Collège de France (Paris; 2002–2010)

The Collège de France is an elite institution which is involved in basic of natural and humane sciences. My duties were to act as a host for professors giving lectures on their special scientific fields and to travel to Paris for negotiations on the progress in cooperation. At the end of my involvement in this matter, an official document defining the aspects of various collaboration which, in a ceremony at the Collège, was signed in Paris by the Administrator of the Collège de France („Administrateur", a position which actually represents the function of a President) and by the Rector of the University of Bonn.

Honours

1975: Conferment of the Dr. Martini Prize (the oldest biomedical prize in Germany, conferred annually since 1883 to researchers at Hamburg hospitals; this prize has to be discriminated from the Martini-Prize for research in Clinical Pharmacology)
1997: Election as a member of the Polish Academy of Arts and Sciences
1998: Election as a member of the „Nationale Akademie der Wissenschaften Leopoldina" (German National Academy Leopoldina)
1999: Conferment of an honorary Medal by the Institute of Pharmacology of the Polish Academy of Sciences (chemical structure of serotonin on one side; conferred at the occasion of my 60th birthday)
2001: Conferment of honorary membership of the Polish Pharmacological Society
2002: Conferment of the Badge of Honour of the Medical Faculty of the University of Bonn (at the occasion of the end of my four-and-a-half-year term as Dean of the Medical Faculty)
2003: Conferment of the degree „Dr. honoris causa", Medical University, Bialystok, Poland
2004: Conferment of the degree „Dr. honoris causa", Silesian Medical Academy, Katowice, Poland
2006: Alexander von Humboldt Polish Honorary Research Fellowship
2006: First honorary EPHAR Lecture at the 37th Congress of the Portuguese Pharmacological Society, Porto, Portugal
2008: Honorary membership of the International Society for Serotonin Research (formerly Serotonin Club)
2009: Conferment of the Badge of Honour of the Medical Faculty of the University of Bonn (for a second time; at the occasion of my Retirement Symposium)
2010: Third Honorary Rapport Lecture at the 9th Meeting of the International Society for Serotonin Research (formerly Serotonin Club), Montreal, Canada
2010: Conferment of the EPHAR Standard in appreciation of services to EPHAR (at the occasion of the 20th anniversary of EPHAR)
2010: Honorary Lecture at the 17th International Congress of the Polish Pharmacological Society at Krynica Zdroj
2014: Conferment of the honorary membership of the Deutsche Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie

DEUTSCHE ZUSAMMENFASSUNG

Am 12. Dezember 1939 wurde ich, Manfred Göthert, als Sohn des Physikers (Arbeitsschwerpunkt Aerodynamik) Dr. rer. nat. Rudolf Göthert und seiner Ehefrau Luise, geb. Freise, in Braunschweig geboren. Bedingt durch den Zweiten Weltkrieg und die Nachkriegszeit, war meine Kindheit bis zum 10. Lebensjahr geprägt durch

häufige Umzüge mit Schulwechseln. In den ersten 1¼ Jahren nach der Einschulung im Jahr 1946 wechselte ich zwischen zwei Dorfschulen – eine in Mesmerode bei Hannover, die andere in Zech bei Lindau am Bodensee – zweimal hin und her, wobei jede einzelne Periode in den beiden Dörfern zwei bis fünf Monate lang war. Hierauf zogen wir für zwei Jahre nach Frankreich in die Nähe des Flughafens Marseille, wo mein Vater eine Arbeit in der Flugzeugentwicklung angenommen hatte (in Deutschland war Flugzeugforschung nach dem Krieg verboten) und ich die Grundschule von Rognac bei Marseille besuchte. Wir wurden von den Franzosen freundlich behandelt, was zweieinhalb Jahre nach dem Abzug der deutschen Besatzungstruppen nicht selbstverständlich war. Ein halbes Jahr nach der Rückkehr nach Deutschland und sechs Monaten Grundschule in Hildesheim schloss ich die Grundschulausbildung, trotz der vielen Umschulungen, in der Regelzeit nach der 4. Klasse ab. Im Gegensatz zu dieser unruhigen Grundschulzeit verbrachte ich die neun Jahre Oberschule bis zum Abitur auf dem Martino-Katharineum in Braunschweig.

Das Medizinstudium absolvierte ich an fünf Universitäten – Hamburg Freiburg, Innsbruck, Wien und Göttingen. Besonders beeindruckt war ich von zwei Professoren in Freiburg in den Fächern Physiologie und Biochemie, Albrecht Fleckenstein und Helmut Holzer, wodurch ich schon damals in Erwägung zog, nach dem Studium für eine begrenzte Zeit, in einem der beiden Fächer zu arbeiten. Im Jahr 1966 heiratete ich meine langjährige Studienfreundin Dr. med. Irmgard Karin Scheibler. Unsere Familie wurde vollständig durch die Geburt unserer drei Söhne.

Meine Tätigkeit als Pharmakologe begann ich am pharmakologischen Institut der Universität Hamburg. Mir war nicht bewusst, dass dieses Institut innerhalb der Fakultät und außerhalb in Fachkreisen keinen guten Ruf hatte. Meine erste Forschungstätigkeit war dem Giftgas Kohlenoxid (CO) gewidmet, wobei es mir gelang, in relativ kurzer Zeit als Co-Autor fünf Publikationen (davon vier federführend) zu veröffentlichen. Im Rahmen klinisch-therapeutisch bedeutsamer Arzneistoffe untersuchte ich zunächst die Nebenwirkungen von Inhalationsnarkotika und ihre Ursachen, besonders die ursächliche Bedeutung des sympathoadrenalen Systems. Ich habilitierte mich im Alter von 31 Jahren mit einer Arbeit aus diesem Bereich. Diese Untersuchungen waren Ausgangspunkt für die Entwicklung eines biochemischen Modells, in dem die Angriffspunkte von Allgemeinanaesthetika und Ethanol ermittelt werden konnten. Im Einzelnen handelte es sich um zwei ligand-gesteuerte Ionenkanäle, den nikotinischen Acetylcholin-Rezeptorkanal und den 5-HT_3-Rezeptorkanal.

Im Jahre 1978 wurde ich auf die C3-Professur für Biochemische Neuropharmakologie in Essen als Nachfolger von Klaus Starke berufen. Das zentrale Thema des Institutes unter Leitung von Hans-Joachim Schümann bestand in der Analyse von Neurotransmitter-Systemen im peripheren und zentralen Nervensystem. Im Mittelpunkt meines eigenen Forschungsprogramms stand die Identifizierung von präsynaptischen 5-HT-Autorezeptoren und präsynaptischen Heterorezeptoren an den Axonendigungen der 5-HT-Neurone im Großhirn. Außerdem bearbeitete ich offene Fragen zur Modulation der Transmitterfreisetzung aus Noradrenalin- und Dopamin-Neuronen.

Letzte Station meines offiziellen Berufslebens war die C4-Professur für Pharmakologie und Toxikologie am Institut für Pharmakologie und Toxikologie der Universität

Bonn, wo ich bis zu meiner Pensionierung im Jahr 2006 tätig war. Die Ablehnung des Rufs auf die C4-Stelle an der Medizinischen Universität von Lübeck habe ich nie bereut. In Bonn setzte ich meine Arbeit in mehreren in Hamburg und Essen begonnenen Forschungsprojekten fort. Zusätzlich beschäftigte ich mich im Rahmen des unter meiner Mitwirkung entstandenen Sonderforschungsbereichs (SFB) 400 mit biochemischen Auswirkungen von Einzelnukleotid-Polymorphismen (SNPs) auf 5-HT-Rezeptoren. Durch Änderung von deren Funktion können SNPs die Pathogenese neuropsychiatrischer Störungen und die pharmakologischen Eigenschaften von 5-HT-Rezeptoren modifizieren. In zunehmendem Maß übernahm ich arbeitsaufwendige Tätigkeiten, die im Zusammenhang mit meiner wissenschaftlichen Expertise und der akademischen Selbstverwaltung stehen: Dekan der Medizinischen Fakultät (4 ½ Jahre), Präsident der Deutschen Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie (DGPT; 3 Jahre), Präsident der Federation of European Pharmacological Societies (EPHAR, 2 Jahre), Vize-Präsident der Internationalen Gesellschaft für Serotonin-Forschung (4 Jahre), Herausgeber mehrerer Fachzeitschriften, Beteiligung an der Organisation von Symposien und Kongressen, u. a. IUPHAR-Kongress 1998, EPHAR-Kongress in Porto 2004, drei Satelliten-Symposien von IUPHAR- oder EPHAR-Kongressen 1990, 1998 und 2004, gewählter Fachgutachter für Pharmakologie bei der Deutschen Forschungsgemeinschaft (DFG), Mitarbeit in einem Institut für die Erarbeitung einer Arzneimittel-Positivliste. Vielfältige Ehrungen, u. a. Dr. Martini-Preis, gewähltes Mitglied der Polnischen Akademie der Künste und Wissenschaften und der Deutschen Nationalakademie der Wissenschaften Leopoldina, Dr. h. c. der medizinischen Universitäten Bialystok und Katowize, Polen, Ehrenmitgliedschaften in der Polnischen Pharmakologischen Gesellschaft, der DGPT und der Internationalen Gesellschaft für Serotoninforschung.

References

1 Göthert, M., F. Lutz, G. Malorny: Carbon monoxide partial pressure in tissue of different animals. Environ. Res. 1970, 3, 303–309.
2 Engel, G., M. Göthert, D. Hoyer, E. Schlicker, K. Hillenbrand: Identity of inhibitory presynaptic 5-hydroxytryptamine (5-HT) autoreceptors in the rat brain cortex with 5-HT1B binding sites. Naunyn Schmiedeberg's Arch. Pharmacol. 1986, 332, 1–7.
3 Göthert, M., E. Schlicker E: Autoreceptor-mediated inhibition of ^{3}H-5-hydroxytryptamine release from rat brain cortex slices by analogues of 5-hydroxytryptamine. Life Sci. 1983, 32, 1183–1191.
4 Göthert, M.: Die Sekretionsleistung des Nebennierenmarks unter dem Einfluß von Narkotica und Muskelrelaxantien. Springer Berlin Heidelberg New York 1972, 1–89.
5 Göthert, M., C. Dreyer: Inhibitory effect of halothane anaesthesia on catecholamine release from the adrenal medulla. Naunyn Schmiedeberg's Arch. Pharmacol. 1973, 277, 253–266.
6 Göthert, M.: Effects of halothane on the sympathetic nerve terminals of the rabbit heart. Differences in membrane actions of halothane and tetracaine. Naunyn Schmiedeberg's Arch. Pharmacol. 1974, 286, 125–143.
7 Göthert, M., G. Thielecke: Inhibition by ethanol of noradrenaline output from peripheral sympathetic nerves: possible interaction of ethanol with neuronal receptors. Eur. J. Pharmacol. 1976, 37, 321–328.
8 Göthert, M., J. M. Rieckesmann: Inhibition of noradrenaline release from sympathetic nerves by pentobarbital. Experientia 1978, 34, 282–284.

9 Göthert, M., W. Dorn, I. Loewenstein: Inhibition of catecholamine release from the adrenal medulla by halothane. Site and mechanism of action. Naunyn Schmiedeberg's Arch. Pharmacol. 1976, 294, 239–249
10 Starke, K: Selectivity of ethanol on ligand-gated ion channels. Trends Pharmacol. Sci. 1991, 12, 182.
11 Urban, B. W.: The Site of Anesthetic Action. In: J. Schüttler, H. Schwilden (Ed.): Modern Anesthetics, Handbook of Experimental Pharmacology, Springer-Verlag Berlin Heidelberg, 2008, 182, 1–30.
12 Fuder, H., E. Muscholl: Heteroreceptor-mediated modulation of noradrenaline and acetylcholine release from peripheral nerves. Rev. Physiol. Biochem. Pharmacol. 1995, 126, 265–412.
13 Starke, K.: Presynaptic receptors. Annu. Rev. Pharmacol. Toxicol. 1981, 21, 7–30.
14 Langer, S. Z.: 25 years since the discovery of presynaptic receptors: present knowledge and future perspectives. Trends Pharmacol. Sci. 1997, 18, 95–99.
15 Jacoby, J. H., L. D. Lytle: Serotonin Neurotoxins: Ann. N. Y. Acad. Sci. 1978, 305–702.
16 Starke K., M. Göthert, H. Kilbinger: Modulation of neurotransmitter release by presynaptic autoreceptors. Physiol. Rev. 1989, 69, 864–989.
17 Göthert, M., E. Schlicker: Regulation of 5-HT release in the CNS by presynaptic 5-HT autoreceptors and by 5-HT heteroreceptors. In: H. G. Baumgarten, M. Göthert (Ed.): Serotoninergic neurons and 5-HT receptors in the CNS. Springer Springer Berlin Heidelberg. 1997, 129, 307–350.
18 Göthert, M., G. J. Molderings, D. J. Reis (eds.): Imidazoline receptors and their endogenous ligands. Current concepts and therapeutic potential. Ann. N. Y. Acad. Sci. 1999, 881, 1–452.
19 Göthert, M., K. Fink: Inhibition of N-methyl-D-aspartate (NMDA)- and L-glutamate-induced noradrenaline and acetylcholine release in the rat brain by ethanol. Naunyn Schmiedeberg's Arch. Pharmacol. 1989, 340, 516–521.
20 Göthert, M.: Effects of presynaptic modulators on Ca2+-induced noradrenaline release from cardiac sympathetic nerves. Naunyn Schmiedeberg's Arch. Pharmacol. 1977, 300, 267–272.
21 Göthert, M., P. Nawroth, H. Neumeyer: Inhibitory effects of verapamil, prenylamine and D 600 on Ca2+-dependent noradrenaline release from the sympathetic nerves of isolated rabbit hearts. Naunyn Schmiedeberg's Arch. Pharmacol. 1979, 310, 11–19.
22 Molderings, G. J., J. Likungu, M. Göthert: N-Type calcium channels control sympathetic neurotransmission in human heart atrium. Circulation 2000, 101, 403–407.
23 Fink, K., W. Meder, D. J. Dooley, M. Göthert: Inhibition of neuronal Ca(2+) influx by gabapentin and subsequent reduction of neurotransmitter release from rat neocortical slices. Br. J. Pharmacol. 2000, 130, 900–906.
24 Fink, K., M. Göthert, E. Schlicker: Veratridine and other depolarizing agents counteract the inhibitory effect of Mg2+ ions on N-methyl-D-aspartate (NMDA)-induced noradrenaline release in vitro. Naunyn Schmiedeberg's Arch. Pharmacol. 1990, 342, 53–60.
25 Fink, K., C. Böing, M. Göthert: Presynaptic 5-HT autoreceptors modulate N-methyl-D-aspartate-evoked 5-hydroxytryptamine release in the guinea-pig brain cortex. Eur. J. Pharmacol. 1996, 300, 79–82.
26 Göthert, M.: Welcome by the president of the DGPT to the XIIIth international congress of pharmacology. Trends Pharmacol. Sci. 1998, 19, 1995–1996.
27 Göthert, M. (ed.): Serotonin and 5-HT2 receptor blockade in the cardiovascular system. Gustav Fischer Verlag, Stuttgart, New York, 1990.
28 Göthert, M., N. Kolassa (eds.): 5-HT1A receptors in the brain. A subtype of serotonin receptors involved in blood pressure reduction. J. Cardiovasc. Pharmacol. 1990, 15, S. 1–86.

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