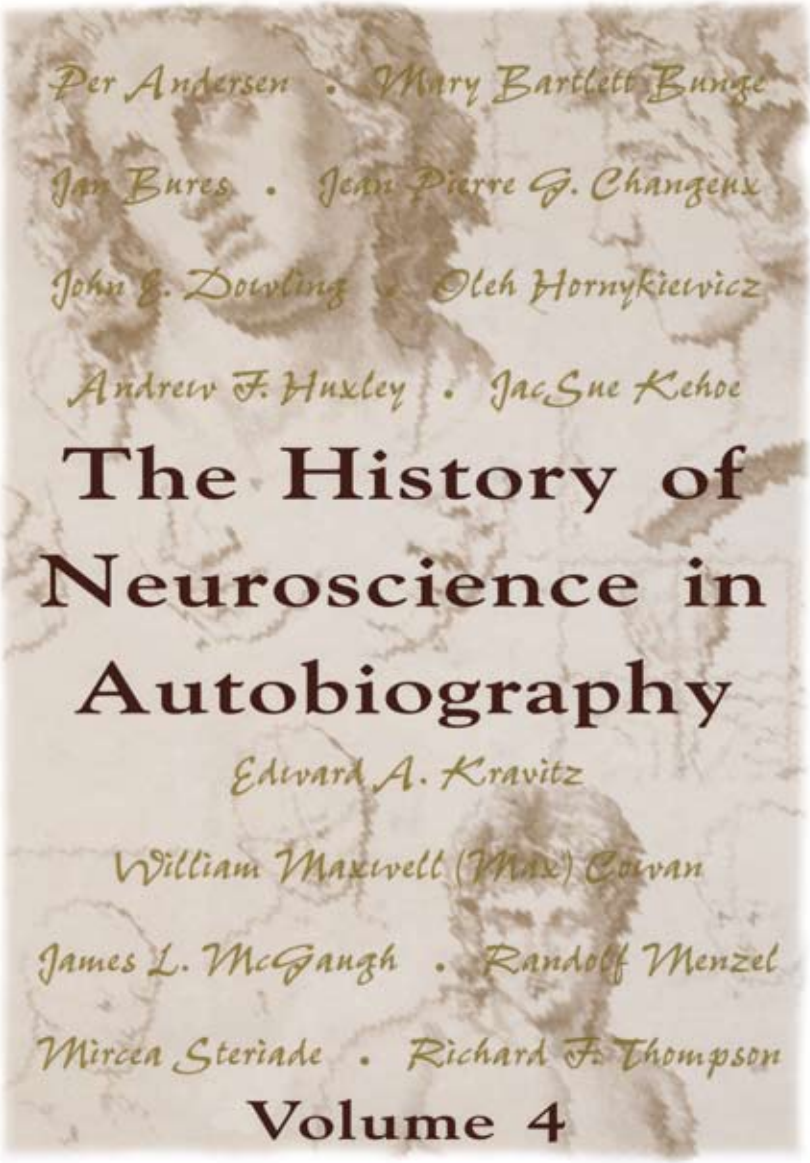
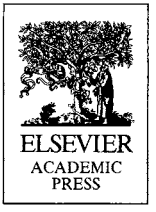




Edited by Larry R. Squire

# The History of Neuroscience in Autobiography

## VOLUME 4

Edited by Larry R. Squire

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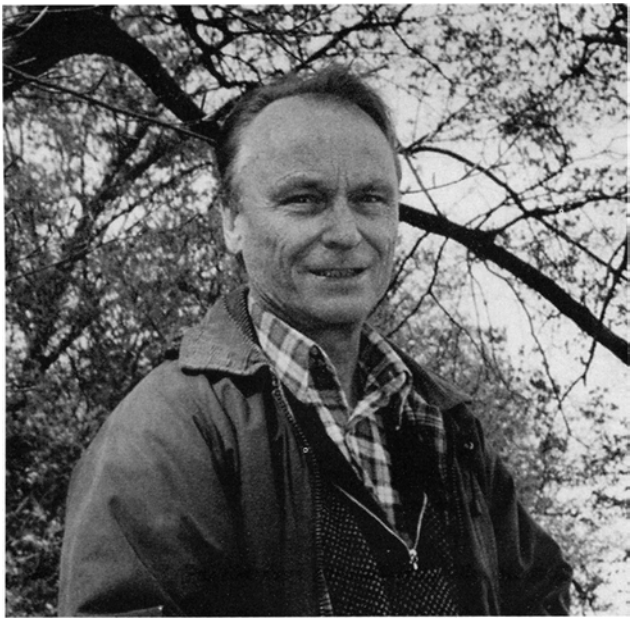

# *Randolf Menzel*

**BORN:**

Marienbad, Czech Republic/Germany
June 7, 1940

**EDUCATION:**

University Frankfurt/Main, Ph.D.

**APPOINTMENTS:**

University Frankfurt/Main (1967)
Technical University Darmstadt (1969)
Australian National University Canberra (1973)
Technical University Darmstadt (1974)
Free University Berlin (1976)

**HONORS AND AWARDS (SELECTED):**

Hörlein Price of the German Biology Society (1960)
Fellow of the Academy of Arts and Sciences (1991)
Leibniz Award of the German Research Council (1991)
President of the International Society of Neuroethology (1992)
Fellow of the Academy of Science, Berlin (1993)
Fellow of the Academy of Natural Sciences Leopoldina, Halle (1996)
Fellow of the Royal Norwegian Academy of Sciences (2000)
Körber Award of European Sciences (2002)

*Randolf Menzel pioneered the honeybee as a model system in neuroscience with respect to color vision, olfaction, learning, and memory. Combining levels of analysis from natural behavior to single neurons, he traced perceptual and cognitive capacities to their neural and cellular substrates. He established the first evidence for the role of the insect mushroom body in memory formation and characterized the cellular and neural correlates of different phases of memory.*

# Randolf Menzel

We carry our ancestors' genes within us; they define the surroundings in which body and spirit develop. The information genes contain is not directly available to us—not now, not in the foreseeable future—but certain genetic effects are reflected in our forefathers' life stories. Therefore, understanding ourselves implies remembering our ancestors' histories as well. We still don't know to what extent our ancestors' physical and mental characteristics are determined by the entirety of their genes, their life circumstances, and their experiences. We also know nothing about how combinations of genes from different lines of our ancestors, together with the particular experiences of these individuals, result in who they were, but occasionally, we discover surprising resemblances between their characters and life history and ours. This reminds us about the framework in which our physical and mental constitution develops.

## Some of My Ancestors

This choice is, of course, not objective, because written history about many forefathers is so severely limited that it is impossible to describe them, and one naturally looks for similarities to one's own biography and picks out the favorable features.

My father's family came from a small village (Fulnek) in Moravia, on the Czech/Polish border. The village was one of those areas in eastern Europe where Germans, Poles, and Czechs lived together for centuries. His mother's family line (the Schindler family in Brünn) crosses with that of Gregor Mendel. Brünn is well known because it is the town near the monastery where Gregor Mendel did his famous cross-breeding experiments with peas.

The Germans in this multicultural border region were mainly members of the upper class: teachers, lawyers, factory owners, and clergy. My father's family (architect and brickyard owner) was well-to-do until the political upheavals resulting from World War I occurred (collapse of the old Austrian Habsburg monarchy). After 1924 the region was divided up into Polish and Czech territory, and the Germans had to decide to adopt either Polish or Czech citizenship. My father, who was studying languages and philosophy at the Charles University in Prague at the time, voted for Czech, while everyone else in his family voted for Polish citizenship. Many personal and social sore spots were created by the break up of German–Austrian culture

in this area (as in many other multicultural areas in Czech, Polish, and Hungarian border regions); later (1939/1940), these wounds had devastating effects on political events.

After studies in philosophy, English and German philology in Prague and Vienna, my father completed his doctorate with a thesis on Heinrich von Kleist and worked as a secondary school teacher and director of a teacher-training college in Marienbad until 1944. The American army held him as a prisoner of war until 1948. Then he worked as a secondary school teacher in Gernsheim, a small town south of Frankfurt/Main, where the family had found a new home after being forced to leave western Sudetenland (the German settlement area of Behemian Lands: Bohemia and Moravia).

My mother's family line can be followed on the paternal side back over more than 10 generations to the early 16th century. They lived in the western Sudetenland; Marienbad, Plan, and Eger are the larger towns in this region. Her forefathers were farmers, millers, weavers, and other artisans. My mother's grandfather, Michl Urban, was a country doctor, local history buff, and poet. During his long life (1847–1936) he wrote numerous articles and pamphlets about rural medicine and the science of medicinal baths in the area around Marienbad and collected fairy tales, poems, folksy comedies, and historic studies about local towns, castles, and churches.

My mother's family line leads back to England and to the city of Graz in southern Austria. I want to dwell a bit on her grandfather, Robert von Lendenfeld (1858–1913), because he was a remarkable personality and the first scientist in the family tree.

He grew up in Graz and studied natural sciences at the university there. In 1881 he finished his doctorate on dragonfly flight under the supervision of F. E. Schultze, the zoologist who later headed the Zoological Institute and the Natural Sciences Museum of the Berlin University, and played a central role in developing evolutionary-biologically oriented animal taxonomy. For example, in 1936 Schultze edited the multivolume work *The Animal Kingdom* (*Das Tierreich*, published by Walter de Gruyter, Berlin).

R. von Lendenfeld left Europe immediately after receiving his doctorate (1881) and headed to Australia with his wife, whose dowry was important for this adventurous project. As a naturalist and mountaineer, he verified the glaciation of the Snowy Mountain area, determined the highest mountain in Australia, and gave his name to several mountain ridges in the Snowy Mountains. In the New Zealand Alps, several mountains were named by him or carry his name. For example, he was the first person to climb the second highest peak in New Zealand, the Hochstetter Dom. He wrote about his Australian and New Zealand expeditions in his book, *Australian Trip* (1892). This book is a gold mine of lively depictions of Australian flora and fauna, geology, landscape structures, and the way of life of the Australian settlers at the end of the 19th century. (My friend and colleague David Sandman, New South Wales University, Sydney, translated the book into English, but,

unfortunately, it has not yet been published.) von Lendenfeld's own work was on primitive marine animals, predominantly Porifers und Coelenterates, but he was also interested in deep-sea fish (in particular, the histology of their light-producing organs). In 1886 R. von Lendenfeld went to London to work on Porifers and rhizostomatic Meduses as Ray Lancaster's assistant at the British Museum. Via the universities of Innsbruck and Czernowitz, he arrived at the Charles University in Prague and in 1897 was named Head of its Zoology Institute. For several years around 1910 he was rector of this famous university, founded by Charles the Fifth as the first university north of the Alps. With his group, he worked on the Porifers from the Challenger and the Valdivia expeditions and the catch from the "Albatross," an American research ship. R. von Lendenfeld's many and mostly quite long books are full of spectacular, often multi-colored lithographies, which show the sponges' habits, histology, and, most importantly, their needles. Drawing morphological structures, for publications and as wall diagrams for use in teaching, was an important activity in his institute, and my grandfather, Ferdinand Urban, also drew lots of teaching materials and illustrated publications for his doctoral supervisor, who later became his father-in-law. In order to be able to mass produce high-quality drawings, he ran his institute in Prague with military precision and included his family and his many children in his work. Both the drawings and the stories about them and how they were produced were passed on through the generations and made a deep and lasting impression on me.

R. von Lendenfeld's work is relevant to neuroscience at a core level, namely, in connection with the question of how the nervous system, in its simplest form, developed during the course of evolution. In his early publications, still in Australia, he joined Ernst Haeckel in his belief that the Porifers (Spongae) belong to the Coelenterates. He soon corrected this and acknowledged the completely different histological organization as a much simpler parachymatic arrangement of various cell types. As early as 1885 (von Lendenfeld, 1885a,b) he described neuron-type and sensory cell-type cells that exist alongside contracting muscle cells and the various types of epithelial cells, with or without flagellas. Using Cajal's reduced silver impregnation method and vital dyes, he found individual, randomly distributed cells that were not bound in a network, which he designated "nerve" and "sensory" cells (von Lendenfeld, 1887). He attributed to these cells a stimulus-transmitting and a coordinating function for the sponge's contractions, which are caused by mechanical and chemical stimuli (Lendenfeld, 1889). For decades, this view was held to be wrong; people believed that the obvious muscle cell contractions and changes in shape of the whole sponge or its parts as a reaction to mechanical and chemical stimuli were achieved only by direct effects, even though von Lendefeld had already demonstrated that even stimuli in remote regions of the sponge can trigger responses and that curare can block this action. The standard work on invertebrates,

*Structure and Function in the Nervous Systems of Invertebrates*, by Bullock und Horridge (1969) names von Lendenfeld as the discoverer of nerve and sensory cells in the porifers (p. 450 ff.). A French group gave lasting support to von Lendenfelds interpretations from 1952 on (Tuzet and Pavans, 1953). However, the neural function of these cells and their sensory and coordinating effect are still unclear, since it was not possible to measure neural excitation and conduction directly (Lawn, 1982). In 1977, Bullock wrote: "We conclude that Porifera lack a true nervous system," and this perception is still accepted today. A true nervous system certainly cannot exist, because their tissue systems are inherently unstable (Pavans de Ceccatty, 1974). Is the earliest physiological preliminary stage of the nervous system a loose connection of neuroid cells that transports signals (transmitters; biogenic amines, acetylcholine, and peptides have been identified) by wandering? How can neuroid cells identify their destinations, and how are they excited by the sensory cells? Is it conceivable that an integrative system similar to that possessed by the sponges was used by some remote ancestor of the Metazoa? Such a structure would lend itself to the emergence of a true nervous system, one comparable to that found in the Coelenterates (Lawn 1982; Cavalier-Smith et al., 1996). In his writings, von Lendenfeld follows this line of argumentation.

R. von Lendenfeld was a remarkable character. In his youth he was extremely strong and fit; in his later years he was a massive and imposing figure, which helped to reinforce his authority. For example, when he was rector of the Charles University, the German-language university, and Czech students attacked his office, he successfully rescued the university's centuries-old official seal. He gave his lectures in English and kept in contact with his colleagues all over the world with research trips to marine research stations, especially on the Mediterranean.

Ferdinand Urban (1879–1951), his assistant and, later, his son-in-law, was working on marine and freshwater biology and preparing to succeed von Lendenfeld. However, even though Urban was, like his father-in-law, a strong, short-tempered personality, it was difficult to exist in his shadow. So after finishing his doctorate (on a collection of Californian calcium sponges, which Professor Heath from Stanford University had sent), he left research and became a secondary school teacher. In addition to his teaching job, he carried on his research privately for many years, working on the calcium sponges collected on the Valdivia expedition and the "Gauss" South Pole expedition and those Agassiz found during the Albatross expedition. In his early teaching years around 1910, he possessed the largest collection of calcium sponges in the world and was considered their foremost expert. During stays at marine research stations, foremostly the Stazione Zoologica di Napoli, which Anton Dohrn founded in 1872 (see autobiography of Brian B. Boycott in this series: Vol. 3, p. 38, 2001), he focused on sponge development and degeneration, using physiological experiments. Unfortunately,

these studies were never brought to an end and published because—severely overworked as he was—he began to lose sight in his left eye, his "microscope eye," and suffered from massive headaches. His lifelong relationship with zoology was full of longing, melancholy, and woe. His vast amount of material was given to the Naturkundemuseum in Berlin, where I was able to see it and read his notes. I have more to say about his books below.

My parents (Dr. Hans Menzel, 1903–1977; Dr. Helene Menzel, 1906–2002) were both philologists. My mother, whose strong influence on every living thing within reach was surely inherited from her father, stimulated and encouraged my early interests in identifying and observing flora and fauna. We made signs for the wild plants in our yard and caught insects, frogs, and reptiles to keep in a terrarium.

## Memes

My early childhood years were during the final phase of World War II. My earliest memories were happy ones of a large family (I was the fourth child; later, two more were born) in a nice house with a large yard on a river, the Eger, in the town of Eger (now Cheb, a city north of Marienbad in the Czech Republic). I was born in Marienbad in 1940. However, these few pleasant childhood memories were soon replaced by alarming and ominous events. Our father became a soldier in 1944 and then disappeared. We fled from the attacks by the American army and went to Plan, the village where our great-grandparents (Michel und Anna Urban) lived. Their house, a splendid Gothic building with walls three feet thick and primitive sanitary facilities, had a wondrous yard, where my grandfather (Ferdinand Urban) introduced me to all the plants and animals. When American planes set the village on fire, we watched from the edge of the forest. We saw the flames devastating the houses and hoped that "our" house wouldn't be destroyed. In fact, it suffered only minor damage. These flash memories from those days are from the last year of the war, as the American army came in from the west, occupying towns and stopping just outside of Prague. My mother, who had been begging at a farm, trying to get some goat's milk for us kids (we were hiding in the forest nearby), was spotted by a small military plane and shot at. She ran in zigzags like a crazed rabbit, avoiding the machine guns, as we watched from our hiding place. A German tank blew up a bridge and sank in the mud. Endless streams of refugees filled the village and endangered our survival: scared people coming from the east, trying to flee from the Russians. The local American military authorities converted the basement of the town hall into a prison, and soon I discovered my father's face at a window there. He was a prisoner of war. My mother's brother was murdered by Czechs, and my father's brother was murdered by Poles. In the fall of 1946, the American army withdrew westward and, according to the Potsdam Agreement for carving up Europe among the Allies, turned over the area

that became Czechoslovakia to the Russians. This meant that we had to flee westward immediately. My mother was able to get her four youngest children onto a cattle car in the last train leaving town. Our mother carried what little she could, and several days later, after an adventurous trip, we arrived in a refugees' camp near Nürnberg.

During this time something happened about which I heard only many years later and which instilled in me a deep appreciation for the international scientific community; I believe that this event had a decisive influence on my choice of work later in life.

Due to his poor health, my grandfather, Ferdinand Urban, would not have survived one of the customary mass transports during the Germans' expulsion from the Sudetenland. Furthermore, he was unable to leave behind his scientific library, a collection that he had inherited from his father-in-law, R. von Lendenfeld, and to which he had added countless volumes. My mother, who was working as a translator for the local American military administration, was able to make contact with a soldier who had studied marine biology in Berkeley and who was familiar with von Lendenfeld's and Urban's scientific publications. My grandfather's request was to give the books to Professor Heath in Palo Alto, the man who had given him the material for his doctoral project and after whom he had named the most beautiful calcium sponge in his collection. The military authorities, however, denied this request. So the soldier from Berkeley simply loaded the old man and his collection into a Jeep and drove him across the western border into safety, thus saving the old man's life and rescuing the library—thousands of reprints, zoological books from the final decades of the 19th century and the first half of the 20th century, and all of von Lendenfeld's and his own publications. In Urban's will, he stated that the library should be passed on to those descendants that studied biology. I inherited the collection many years later. I donated the materials to the library of the Senckenberg Museum in Frankfurt and was made a permanent member of this venerable museum—a great, unearned honor.

Amid the storms of the postwar period, survival was everything. We ended up living in a tiny hamlet in the Rhine region south of Frankfurt. I have memories of the incredible CARE packages from the United States and of my 14-year-old brother's black market dealings in all the surrounding towns in order to get such crucial items as matches, a bit of fuel for a cook stove, toothbrushes, and paper. My mother displayed unfailing strength, not only keeping us all alive, but making us inquisitive by keeping up a lively family life, having us perform plays, giving us religious instruction, and encouraging our imagination. All four of her sons later became scientists, and I attribute this to my mother's influence during these years. Schools were chaotic in the postwar era. I first went to a one-room school in which kids of all ages were taught by one teacher and then to a school quite far away (I had to walk, of course). I was in a class with 70 kids. Here the

teacher spent the first hour of every day caning pupils. These school years left behind a deep mistrust of the importance of teaching curriculum and lesson plans. As I look back, I would say that the most valuable experience was my time in the one-room school, because the teacher radiated satisfaction with his work and he had enough imagination to adequately deal with the impossible situation he was in. My life became a bit more normal when I entered the Gymnasium (college-preparatory secondary school) when I was 10. My father had returned and was teaching at a Gymnasium; we moved to a little house in Gernsheim, a town on the Rhine. Here we had the signs on the plants and the terrariums that I mentioned earlier.

An event that was crucial for my career choice was when, at 15, I received my deceased grandfather's microscope, a brass model from Leitz built in 1900 and kept in a polished wooden box. Ferdinand Urban had bought this microscope for 400 guilders, money earned from private tutoring during his second semester in Prague. He needed the microscope for his marine biology course in Triest. In his memoirs, he wrote: "... my precious, beautiful microscope, that has accompanied me throughout my life as a dear, true comrade. It was an exquisite instrument ... it widened my horizon and influenced my entire relationship to science." That microscope may have had magic powers, since the same miracle happened to me 55 years later and brought me into biology.

A few weeks after my first experiments with the miraculous microscope, the pond that I had built began to turn red. I poured pond water through a fine net and found the microscopic wonders of my pond: red globules that dyed the water. I also found plankton plants and plankton animals. My enthusiasm was roused, and from that moment on my plankton net and I visited every pond in the Rhine plain. During my final years at secondary school, I did systematic studies of pond ecology throughout the four seasons; I determined and drew hundreds of plankton algae, rotifers, copepods, phylopods, and ciliates. I was interested in the interrelationships between the physical and chemical parameters in ponds, those of the plankton, and their changes during the day and throughout the years. My observations and drawings culminated in a 256-page work with over 100 illustrations, written in 1960, the year I finished secondary school, and which won the prize for the best student biology report in all of Germany (Hörlein Prize of the German Biology Society). Thus, my choice was made for biology as my university major subject and my professional field.

My affinity for freshwater biology brought me into contact for the first time with a famous scientist and a research lab. Franz Ruttner, the famous limnologist, who for many years was Head of the Research Station in Lunz am See in Austria, was a college friend of my grandfather's. I visited the station when I was still a secondary school student, participated as a young college student in various summer courses there, and met Professor Ruttner. I will always remember this distinguished senior scientist's eyes agleam with

pride as he showed me "his" nanno-plankton (plankton organisms smaller than 5 μm) under the microscope and his readiness and generosity in giving a mere high school student a guided tour of his lab. This incident made a strong impression on me as to what the ideal scientist should be. I was an ardent admirer of the contemplative working atmosphere in the research station. Work out in the field, lab work, taxonomic and ecological studies, chemical-physical readings, and physiological experiments were combined with each other. Exhausting mountain hikes, taking samples from lakes and rivers, were compensated for with long nights at the microscope and in the library. Even as a first-year student, I got a pleasant glimpse of research work, and I met scholars who became my role models.

However, my course of studies at the University was a bit less attractive. I was studying biology, chemistry, and physics at the University of Frankfurt/Main. The zoology and botany courses consisted exclusively of making drawings. The lectures were mere obligatory rituals, and only a few of the excursions were at all interesting. However, physics and chemistry were different; there were enthralling lectures and interesting courses.

The situation in the Zoology Institute was especially adverse. The professor position was empty, and a retired professor, Professor Giersberg, gave lectures on classic zoological topics that were from prewar days. Almost no classes were offered in animal physiology. This was made worse by the fact that there was no real textbook for this field. It was only in 1963 that I read an animal physiology textbook: Prosser's *Comparative Animal Physiology* (1961). No classes were offered in ecology and behavioral biology, so I spent my first two college years studying physics, chemistry, and microbiology.

The course of studies in biology at a German university at this time was poorly structured. The only degrees offered were a doctorate or a secondary school teaching certificate. There were no directives about when one had to take which courses, and there were practically no exams during the course of studies. So we students put together our own degree programs; this gave us a great deal of academic freedom, but left us completely alone and often overwhelmed and a bit lost. Therefore, it was very fortunate for me, right away in first semester, to find friends with whom I have stayed in contact through the years, first as college pals and then as colleagues: Rüdiger Wehner and Günther Fleißner. We organized our own excursions (both Rüdiger and Günther are outstanding bird experts), attended the same lectures and courses, and had intense discussions about the topics covered in them.

Since five of the kids in my family were in college at the same time, I had to work during semester breaks. My skills in freshwater biology proved to be useful; I took a course at the University of Munich and became a qualified wastewater biologist. With this certification, I got a job with the Merck Pharmaceutical Company in my hometown, Gernsheim, where I did independent work in a small research lab on biological processes for the

company's waste. The job had many good features: its research relevance, the freedom to be able to plan my work myself, good pay, and the fact that I could work during semester breaks. In fact, I was even able to continue my work on the Rhine Valley ponds; I published my first scientific article on this topic (Menzel, 1968b). Nevertheless, this taste of life in the commercial sector convinced me that I didn't want to pursue a career in industry: there was no open discussion (which I had grown to value in the Institute in Lunz and at the university); the staff was not thrilled with its work; all results had to remain secret; and, most importantly, the factory that I worked in polluted the Rhine to such an extent that I was in a major moral quandary, wondering whether I should bring this out into the open. My bosses forbade me to publicize the pollution, threatening me with legal action. It's surely understandable that I generalized about my experiences with big industry and that, with my leftist political leanings of the time, I characterized them as typical for the capitalist system. These semester breaks working in industrial surroundings even dimmed my interest in limnology, and I became unsure whether I wanted to pursue a career in freshwater biology or ecology.

The deficiencies in the animal physiology degree program at the University of Frankfurt motivated my friend Günther Fleißner and me to study at the University of Tübingen for one semester. As luck would have it, we were able to participate in a lab course held by Werner Loher (who later became a professor at the University of California, Berkeley). Furthermore, I attended lectures by Franz Huber (on color changes in the animal kingdom). Meeting Franz Huber was pivotal for finding my new field of interest. Unlike the other zoology lectures that I had endured, Huber's classes sparkled, full of verve and zeal. They linked together morphological, physiological, behavioral, and neurobiological aspects, creating a convincing overall picture. And he was available for his students. At the end of the semester, in summer 1963, I asked him what he thought of the idea of studying the physiology of learning processes in the microscopically small, transparent rotifers (e.g., in *Asplanchna*); after all, their nerve cells are directly visible, and they can be bred easily. Without my really having noticed, this question combined my two main motivating interests in biology: limnology and learning mechanisms. Huber encouraged me in my basic notion of studying something so complicated as learning in such well-suited model organisms. He recommended Prosser (1961) and Kenneth Roeder (1963) as suitable textbooks, and then lent me (but only over the weekend) a huge pile of proofs: Bullock and Horridge's book. Before he dismissed me with the proofs, he asked something very simple, which was, for me, incredibly enlightening: Why should these animals in fact learn, seeing as they swim around in an unstructured and unlimited ocean, and can neither avoid nor seek anything? This little question opened my eyes to ethological-behavioral argumentation.

All of this happened before 1964, when Tauc und Kandel published the first cellular analyses of synaptic plasticity in the nervous system of

*Aplysia*, when intracellular recording was still quite rare in neuroscience, and before the successful single-cell analysis of invertebrate nervous systems had started. But things were evolving at a fast pace. Franz Huber prepared us for these new developments by reporting on the exciting developments going on in labs all over the world and by telling us what he was working on: the attempt to ascribe behavior to the function of individual nerve cells or small neuronal networks. I got a vague idea of what direction I wanted to go, but how could I combine this direction with my interests in the mechanisms of learning processes? Huber didn't want to get involved with such a project; he recommended Martin Lindauer, who had taken up the professorship for zoology in Frankfurt. So I returned to Frankfurt and began my doctoral work on color learning in bees (Menzel, 1967).

Lindauer himself showed me how to train bees; he talked about his professor, Karl von Frisch, and then left me to work almost completely on my own for two years. Since my friend Rüdiger Wehner had also just started working with bee-training experiments, we were able to help each other. I built a complicated spectral apparatus with a strong Xenon bulb to train the bees to monochromatic light. In Germany, this kind of bee training is only possible from mid-July (when there is little nectar available) through the end of October (if it hasn't already gotten too cold). During this period, there are no free weekends, and if the apparatus breaks down, you repair it at night. Alongside our experimental work, we had time to read and have discussions. The role models I found in my readings were Karl von Frisch (1965), Thorpe (1963), Lashley (1950), Thorndike (1932), Pavlov (1927), von Holst (1935), Tolman (1932), and Köhler (1921), a colorful mixture, representing conflicting schools within behavioral biology. I could understand how important it was to use objective and quantifiable criteria to record behavior; my own experimental work was an intensive effort in this direction, but I was disappointed that behavioral biology did not refer to the brain. The American learning psychologists caught my eye, but they were also the most disappointing because they thoroughly dismissed any connection to brain mechanisms. Ethologists, on the other hand, disappointed me because they ignored learning processes and instead developed such rather strange concepts as "release mechanism modified by experience" as the only possible explanation for learning, even though learning quite obviously consists of acquiring totally new skills. Despite being enthralled with Karl von Frisch and having devoured his book with unflagging interest, I couldn't quite understand why he concentrated exclusively on sensory mechanisms when successful decision-making during nectar search, dance communication, navigation, social coordination, and more is clearly the result of brain mechanisms.

These questions were discussed with Rüdiger Wehner, but there was no great interest in discussions in the Zoology Institute; in particular, no one was familiar with Parlow or the American psychologists. Therefore, it

was a great discovery to attend a seminar in the Psychology Institute which covered Hermann Ebbinghaus (reprinted 1964) and Müller and Pilzecker (1900). Vague perspectives appeared here: the correlation of behavioral tasks with neurological pathologies, comparative studies in animals and humans, and EEG recordings and retention measurements. A defining moment was when I read McGaugh's article on memory phases (1966). A new world opened up for me: so there were indeed possibilities to closely correlate strict behavioral events (retention) with mechanisms of brain function. After reading his article, and inspired by the early works by Agranoff, Davis, and Brink (1966), Flexner, Flexner, and Roberts (1966), and others, I knew what I wanted to do. I had a vague inkling that the task was to create a synthesis between the inconsistencies of the various behavioral biological schools of thought.

## Finding My Own Way

Since in the meantime (having completed my doctorate in 1967) I had a thorough knowledge of my experimental animal, it was clear to me that I wanted to continue to work with bees. Bees learn very quickly and have a good, long-lasting memory (Martin Lindauer had just reported that even after 5 months bees can remember the characteristics of nectar source); enough animals are available year-round, the experimental animals are genetically closely related (daughters of one queen); and they demonstrate complex behavior. I, meanwhile, knew how to work with them in the open, in order to pose questions and quantify their behavior. However, whether they were suitable for laboratory experimentation and for neurophysiological studies was still unclear. I gathered some hope from the fact that intracellular recordings of retinula cells of the bee eye had been successfully carried out (Naka: 1961, Autrum and von Zwehl, 1964). Even though I had not yet prepared a bee brain and had no experience with neurophysiological methods, I wanted to study the neuronal foundations of their behavior, particularly, behavior that plays a role in learning and memory formation.

I'd like to make a comment about my supervisor Martin Lindauer and the state of behavioral/neurobiological research in Germany in the 1960s. Lindauer had been Karl von Frisch's most important pupil, and he carried on Frisch's work on orientation and communication in bees. His scientific skills came to fruition in his work with bees and in personal discussions about specific problems in bee research. He was not an especially brilliant lecturer or a great organizer. His teaching was not top notch. However, in everything he did he transmitted a sense of pleasure in his research work; ongoing curiosity about the wondrous accomplishments of his experimental animal, the bee; and an ability to immerse himself in bee biology. Strict discipline in experiments, dedication during difficult and long projects, and a critical view of one's own data were exemplary traits that we learned from

him. In Germany at this time, the most influential zoologist was Hans-Jochen Autrum, Head of the Zoology Institute in Munich; Lindauer had worked there before going to Frankfurt. Autrum's pupils filled many professorships, broadening the influence and increasing the dominance of his field, sensory physiology. Lindauer was not part of this "inner circle," nor was Franz Huber. Although Lindauer himself never made the switch to neurophysiological studies, he prepared his pupils for them. For him, receptor and communication tasks in the bee were not exclusively carried out by receptors, but included brain processes. He began to think about learning and memory formation and, in doing so, distanced himself from two strong traditions which had been a firm basis for his previous work: sensory physiology from the behavioral-analytical point of view, and ethology (more in Tinbergen's sense than in Lorenz's). His discoveries in magnetic field orientation, communication, comb building, and bees' choice strategy got him thinking about the unknown processes in the bee brain that still needed to be investigated. His curiosity infected his pupils; many of his direct and indirect pupils became neuroscientists or spent at least part of their careers working in neurophysiology (Markl, Rathmayer, Wehner).

So the first thing I needed to do was to learn neurophysiology. Martin Lindauer helped me get a postdoc position and agreed that I should learn intracellular recording of retinula cells in the bee eye in Dietrich Burkhardt's lab; he was the second professor in the Institute. Back then (1967), capillary electrodes were pulled with homemade pullers and were filled by keeping them in water vapor for days. It was rare to get a successful recording. I began the journey down the thorny path of electrophysiology; in spite of many methodological improvements through the years, it is still a difficult discipline. Nowadays, we know that the bee brain is a difficult object for electrophysiologists, most likely because the neurons are especially thin, the mechanical stability of the brain is minimal, and the prepared brain is exceedingly sensitive to a lack of oxygen. Still, my fascination with these intracellular recordings has not faded, and to this day I spend time in the lab working on these recordings.

In the fall of 1967 I met Karl von Frisch. Martin Lindauer had a get together for his research group in Frisch's house on Lake Wolfgang in Austria, and von Frisch (who was then 81 years old) gave those of us who had just finished our doctorates an extra oral exam. I remember how startled I was by his question for me: Which bees move from blossom to blossom without ever flying? I first thought he was joking because I did not know very much about these strange little solitary bees that wait in flowers for big bees and clamp to their legs when they fly off to the next flower. So, I guess, Karl von Frisch did not get a good impression about my knowledge of general bee biology.

After the exam we told him about our experiments, and he encouraged us with tips that proved that he understood the underlying problem. I reported

that bees learn violet spectral light especially quickly, and that this effect cannot be due to a sensory mechanism, but rather must be based on an evaluation process made by the central nervous system. von Frisch had worked on a similar query with his pupils at a time when little was known about color vision in bees, and his results could not be correlated with mine. The inconsistencies interested him the most. Since my attempts to explain things relied on many details from the psychophysics of color vision, I feared the discussion would become a bit sticky. Nothing of the kind: von Frisch was exceptionally well informed, wanted to learn from me, and gave me numerous tips for further experimentation. He didn't want to follow my core argumentation, however, which was the differentiation between peripheral and central mechanisms of estimating color.

Another topic of our conversation concerned color vision in bees, and this discussion was even more controversial. Let me dwell on this topic because it can serve as an illustration for the conceptual shift in sensory physiology at this time. von Hess (1913) had shown that bees act like color-blind animals in their phototactical behavior, whereas von Frisch (1914) proved that bees do differentiate colors when they learn food cues. von Frisch maintained that his finding proved von Hess' assumption wrong. However, this assumes that both phototaxis and learning color differences make use of the same central color vision system. My theory (speculative back then, but in the meantime experimentally proven, see Menzel und Greggers, 1985) was that this is not the case, but rather that the bee has various central chromatic integration systems that are assigned to various behaviors. This way of thinking was alien to von Frisch, which told me that he, following the tradition of sensory physiology from the first half of the 20th century, equated perception with peripheral (mostly receptor) performance. This mindset was surely remarkably successful and had led to great discoveries by Karl von Frisch and his students (i.e., seeing UV light, seeing polarized light, odor perception, and differentiation between acoustic and vibratory mechanosensory perception). The limitations of this way of thinking seemed obvious to me, but I could not satisfy von Frisch; he could not accept the existence of central evaluating mechanisms as a basis for an explanation. He was right with that, of course, as long as nothing is known about these hypothetical central mechanisms. I took this as a challenge to work on exactly this problem and to search for these central mechanisms.

In the fall of 1969, I took a position as an Assistant in the Zoology Institute of the Technical University of Darmstadt, where Hubert Markl had just taken over as Director. I was able to form my own research group. I wanted to work in parallel on two topics: the search for the neuronal basis of learning and memory and color vision in bees. The experimental approach for the former was greatly helped along by my visit to the Max-Planck-Institute for Behavioral Physiology in Seewiesen in 1970. There I met a doctoral student of Dietrich Schneider's, Ekkehard Vareschi, who was studying odor

discrimination in the bee (Vareschi, 1971). He showed me the experiment that had been developed 20 years earlier by Masutaro Kuwabara (1957) in Karl von Frisch's lab: classical conditioning of the proboscis extension response (PER) in bees mounted in small tubes. I immediately saw that this was the experimental setup that I had been looking for. Even though I was familiar with Kuwabara's publications, I hadn't thought of using this paradigm for my studies. From that moment on, throughout my entire scientific life, this paradigm has accompanied me in my work and has made quintessential contributions to current knowledge of behavioral and neural mechanisms of appetitive olfactory learning and memory formation.

The PER paradigm has an interesting history. In the 1930s and 1940s Karl von Frisch's group studied bees' perception of food substances, especially sugar. He used Minnich's (1932) method; Minnich had noticed that hungry insects activate their mandibles when their tarsi or antennae are stimulated with sucrose solution. Hungry bees will extend their proboscis. One of von Frisch's students (Kantner) was determining the perceptual threshold for various sugars and believed that he had discovered an exceedingly high sensitivity; even a few sugar molecules per liter of water should be sufficient to release the response. von Frisch was skeptical and sent the student home (von Frisch, 1965, p. 533). In the 1950s, when Kuwabara joined his group, von Frisch told him about this peculiar experiment, and Kuwabara repeated the experiments. Kuwabara stimulated their antennae or front leg tarsi with a drop of sucrose solution. The bees' reflexes caused them to stick out their probosces. When he stimulated the sugar receptors on the tarsi, Kuwabara usually cut off the antennae, because that helped him achieve a more reliable reaction. But now, without antennae, the bees had lost their extremely high sensitivity to sugar. Kuwabara surmised that the bee perceives other stimuli (e.g., water vapor) simultaneously with the rewarding sugar stimulus and then associatively links the two. Kuwabara and Takeda (1956) then proceeded to prove that the antennae do indeed perceive the water vapor and that, after being repeatedly coupled with sugar stimulation, water vapor alone will trigger the PER. As a control, he stimulated the bees for the same number of trials with plain water. It was thus clearly a case of classical conditioning. Kuwabara was able to prove this quite convincingly when he used colored lights as the conditional stimulus and, after cutting off the antennae, stimulated only the sugar receptors on the tarsi (Kuwabara, 1957). Here he didn't use control groups, but he did test for color discriminatiation and at the end of the experiments carried out an extinction series. Conditioning to colored stimuli takes much longer than to water vapor or odors. It is noteworthy that Karl von Frisch (1965) cited work by Kuwabara and his colleagues only where it dealt with proofs of sensory capabilities and not regarding learning.

While my first two doctoral students (Jochen Erber und Thomas Masuhr) worked on learning and memory formation, I was searching for

ways to become acquainted with central vision physiology. My skills in intracellular recordings from photoreceptors in insect eyes were still limited, and my attempts to get recordings from visual neurons failed. Adrian Horridge invited me to spend a year at his institute at the Australian National University (ANU) in Canberra, where I learned electrophysiology from his doctoral student Simon Laughlin. My goal was to study the role the primary visual interneurons, the monopolar cells, in the bee lamina play in coding color stimuli. This proved to be technically overwhelmingly difficult then, and it still is (Menzel, 1974; de Souza et al., 1992), but in the intellectually stimulating atmosphere with Allan Snyder and Simon Laughlin I got a totally new perspective on visual physiology and also did some intensive work on photoreceptors in the bee eye. Allan Snyder, a brilliant theoretical physicist and an expert on the theory of optical wave guides, was establishing the new field of photoreceptor optics. In the shade of the eucalyptus trees on the ANU campus, we carried out our intellectual flights of fancy, recognizing the lateral filter principle in the fused rhadom, and searched for the receptor mechanisms for analyzing the e-vector of light. In these studies I measured the retinula cells' sensitivity to linear polarized light and found, to my great surprise, that only a few of the UV-sensitive cells had sensitivity to polarized light; all the other cells—even the UV-sensitive cells, which were seen more often—had miniscule sensitivity. I was, of course, familiar with von Frisch's explanation for the bees' ability to detect polarization patterns in daylight (see von Frisch's star filter model, 1967). My data were diametrically opposite to his model, which assumes that all visual cells in the bee ommatidium are sensitive to polarized light. How would von Frisch and how would my revered former supervisor Lindauer react to these findings and my interpretation? Did I have any chance at all to publish these results, and would I have any chance to do research in Germany in a situation like this? With great trepidation, I submitted my manuscript to the *Journal of Comparative Physiology*, and asked Autrum, the Editor, to pass it on to von Frisch for evaluation. von Frisch was enthusiastically supportive, and the article was immediately accepted for publication. A scientist's true greatness is shown not only in his discoveries, but in his ability to correct his opinions when faced with a new results.

In the pre-Internet era, with the erratic Australian postal service and without phone contact, I tried to keep in touch with my group in Darmstadt via a constant barrage of letters. At the same time I was substituting for Horridge in administrative matters in his Institute, because he was off in Oxford taking a sabbatical year. These multiple duties, ranging from the various research topics represented in the Institute to the unavoidable administrative tasks, added up to pose an enormous challenge. In addition, at age 32, I was living in an English-speaking country for the first time and had to rise to the challenge of communicating effectively in a foreign language. The defining event of my time in Australia was the zeal for theoretical

and experimental research that pervaded the group around Allan Snyder and Simon Laughlin. We came up with an experiment and did it the following day. If it didn't succeed, which happened often, of course, we looked for ways to simplify it. Theoretically picking apart a problem so tenaciously before setting up an experiment was a completely new experience for me.

I returned to Darmstadt as a professor in 1973. The German ambassador in Canberra swore me in as a professor, which was a good thing, because otherwise I would have ended up staying in Canberra (they had made me an offer). It wasn't very easy to adapt to the German zoology scene after my experience abroad. It was especially difficult for me, since my research work, especially on learning and memory formation, didn't fit into the narrow zoology curriculum taught at German universities. The ethologists didn't understand what I and many other young researchers were doing, and they decided who would get hired as behavioral biology professors in this small country. The neurophysiologists, under the powerful influence of Hans-Jochen Autrum, were exclusively sensory physiologists, and many professor positions had just been filled, directly or indirectly, with Autrum's pupils. During this phase, which was critical for my career, a new discipline was coming into existence, due to the initiative of Franz Huber, Ernst Florey, Hubert Markl, Werner Rathmayer, and Gerhardt Neuweiler; it aimed to study the neural basis of behavior, with emphasis on central mechanisms. The German Research Council (Deutsche Forschungsgemeinschaft) set up a nationally organized framework which provided intensive support to 20 research groups, with my small group included. For 15 years (1970–1985) the members of this program met regularly in stimulating sessions. Looking back, I have the impression that the most innovative neuroscience research in the zoological sector in Germany was carried out during this period. There was definitely a sense of making a fresh start. New methods in intracellular electrophysiology and new ways to dye neurons opened new perspectives. It was possible for the first time to correlate single-neuron analyses, foremostly in insects, with behavior. Our enthusiasm was boundless in 1970 when Zettler showed us an intracellularly marked neuron, one of the first intracellular markings worldwide. The unique neuron concept, the command neuron concept, and the identified neuron concept were all discussed intensively. Franz Huber was the central figure in this circle. His group at the Max-Planck-Institute for Behavioral Biology in Seewiesen set the standards, and he established the upbeat tone of our discussions. We were also quite sure that neuroscientists working on the insect nervous system were far ahead of those working on mammalian brains. Within the small brains of our insects, with their rich behavioral repertoire, we were able to point out individual neurons and describe their intracellularly recorded activity during almost normal behavior. Therefore, we thought, it should be possible to understand—from its individual elements—the function of natural neuronal networks in the context of biologically relevant sensory and

motor processes. Each newly identified neuron was greeted with glee and seen as another stepping-stone along the way to achieving our goal. Today, many of us are still following this path, albeit with a more realistic attitude regarding our high hopes in those early years, but we are still convinced that neuronal networks can only be understood on the basis of neurons' individuality, their singular conformations and connectivities, their physiological attributes, and their specific forms of ontogenetic and experience-dependent plasticity.

Meanwhile, it was 1976, and I was busy establishing my group at the Free University of Berlin (FU). I was still blissfully unaware of the problems I would be facing in this enormous university (about 60,000 students during the 1980s and 1990s). I had decided to go to Berlin, and not to Princeton (where I would have succeeded Vincent Detier) or to the university in Hamburg. Perhaps my decision would have turned out differently if I had known that the FU students hardly ever came to lectures (and were encouraged in this behavior by other professors); that they were carrying out massive student strikes at the university, trying to get rid of exams; and that serious research on an international level was hard to find. During these years of turmoil on all levels of academic life at the FU, and violent encounters between political extremes, I fled every summer to the Marine Biological Laboratory (MBL) in Woods Hole, MA, to teach the course on "Neural Systems and Behavior" that had been founded by Alan Gelperin and Ron Hoy. The enthusiasm of the American students and the collegiality among the lecturers reminded me of a long-lost academic way of life, which was only reestablished at the FU in the mid-1980s.

In the rest of this autobiography I'll talk about some research projects that I've worked on over the years. First, however, I would like to comment on a central activity in Germany universities: teaching. The teaching load for professors at German universities is considerably higher than for our colleagues in the United States. Required teaching is normally 90–120 academic hours per semester, and if lab courses and seminars are involved, that number can be much higher. This workload, combined with numerous oral exams and supervisory duties for Diploma and Master's theses, is enormous and greatly reduces the time available for research during the semester. A crucial prerequisite for work at a university is therefore the willingness to teach ever-new generations of students. In my early years at the Technical University in Darmstadt, I taught general zoology, taxonomy, morphology, physiology, behavior, and ecology, with some of the disciplines being rather remote from my own areas of research. Later, in Berlin, I was able to concentrate my teaching on animal physiology and behavior. Satisfaction with teaching comes when the teacher is successful in conveying to the students the intellectual journey that he made while preparing the lecture, presenting valuable material such that it expands the insights and captures the interest of those listening to the finished product. The communicative process

involved is hugely suspenseful and risky. When boredom and disinterest have taken over the lecture hall, everything is lost; I have bitter memories of this from some semesters in the late 1970s. Luckily, the student generation changed in the early 1980s, and university teaching returned to its normal, rewarding state.

## Research

### *Color Vision*

The first step in understanding color vision in any animal is to relate the spectral properties of the various receptor types in the eye with color perception. Bees were the first animals for which the spectral properties of receptors, as measured by intracellular recordings, allowed one to interpret basic characteristics of color perception (Autrum and von Zwehl, 1964; Daumer, 1956; von Helversen, 1972). My first contribution to this field was the proof that all three of the spectral receptor types are present in the ommatidium and play a role in the function of the fused rhabdom (Menzel and Blakers, 1975). This structure is designed to keep the narrow spectral sensitivity functions of each individual receptor, although it provides a high quantum yield (Menzel and Snyder, 1975). Assigning the functional receptor types to their respective morphological types led to the development of a wiring diagram of the peripheral visual neuropils of the bee brain, and this was, at least partially, verified with intracellular recordings of the primary visual interneurons. As is also the case in other color vision systems, further neuronal processing occurs in chromatically antagonistic neurons (Kien and Menzel, 1977; Hertel, 1980). Since it was extremely difficult to perform intracellular analysis on visual interneurons (and even to this day, there have been no further investigations of neuronal coding of color information in the bee brain either in our lab or elsewhere), we switched our emphasis to psychophysical studies, in which we took advantage of the possibility of easily training bees to color stimuli. Backhaus (Backhaus and Menzel, 1987) used these data as the basis for his model of color vision in the bee, which correlates very well with our neurophysiological findings and additional behavioral results (Menzel and Backhaus, 1991). Brandt and Vorobyev (1997) showed that Backhaus' model was one of a general class of models which psychophysical methods have shown all have identical levels of precision. At this time, Lars Chittka was also working on modeling color vision in our lab; he used data on color discrimination in various hymenoptera species. He developed a pragmatic, even though not completely coherent graphic model of color discrimination, the color hexagon. These three—Backhaus, Vorobyev, and Chittka—made fundamental advances in this discipline, but had mighty clashes of opinion among themselves. Our attempts at further experimentation—striving to reach a unified bee color vision model that could be accepted by all three

of our experts—unfortunately did not succeed. Therefore, this problem was dropped, to be clarified by someone in another lab somewhere. There are serious problems involved: (1) too little data exist to resolve the problems caused by the non-linear relationship between color loci, as determined by a receptor-based model, and color discrimination; (2) the role of adaptation, especially its temporal dynamics, is still largely unknown; (3) spatial aspects of color vision have been briefly touched upon, but still require very thorough study (this is a topic currently active in my lab); and (4) higher order color vision phenomena (color constancy, color sensations, color evaluation, and meaning) are only understood at a basic level. My doctoral dissertation contributed something to the latter topic, namely, that color stimuli are evaluated independent of their receptor-related properties such as threshold and discriminability. For example, colors are discriminated equally well in the violet portion of the spectrum (around 400 nm) as they are in the blue-green portion (490 nm), but violet is learned much more quickly and at a higher level of performance than blue-green. After 30 years of research, we still do not have a clear explanation of this phenomenon. It makes lots of sense biologically, since blossoms that hymenopterans visit and pollinate (foremostly, the large hymenopterans [Menzel and Shmida, 1993]) are predominantly violet and blue in their blossom colors and blossom patterns. The co-evolutionary relationship between blossom color and color vision mentioned here is a subject that has interested me since my student days. It was a surprising discovery to find that this signal-receiver matching has no effect on the spectral characteristics of the photoreceptors in the pollinating insects' compound eyes, but does have an effect on their central nervous evaluation function. Rather, we found that the spectral characteristics of the receptors constitute an optimal peripheral filter system for all colors (in the spectral range from 300 to 650 nm [Vorobyev et al., 2001]).

The strength of the neuroethological approach, as used in our color vision studies, may be demonstrated by the following example: a blossom's shape and/or color pattern plays a decisive role in how a pollinating insect recognizes, lands on, and manipulates that blossom. Current explanations for pattern recognition in insects are at least incomplete or even faulty: do insects measure the pattern's flickering frequency as they fly over the flower (flicker frequency hypothesis), or do they see a pattern only when its image appears at exactly the same spot on the retina where it appeared when the animal first saw that pattern (retinotopic matching hypothesis), or do they simply measure the directions of all border lines and sum them up in three categories arranged 120° to each other (directional feature detector hypothesis) and sum these up in respective directional channels? In order to demonstrate the tasks involved in pattern recognition and the deficits of the explanations offered so far, we studied the bee's pattern generalization and abstraction capabilities (Giurfa, Eichmann, and Menzel, 1996). When bees learn different bilateral symmetrical (or asymmetrical) patterns, they

transfer this ability to the discrimination of completely new symmetrical and asymmetrical patterns. All three hypotheses mentioned above and used so far to explain pattern recognition in insects can be dismissed by these results: the flicker frequencies do not differ between such patterns; the patterns cannot be matched to a retina-stable template, and the directional components of the contrast borders do not provide a specific feature of such patterns. The bees need not only discriminate between such patterns, but must extract a common feature (symmetry) and learn to associate this to reward. It turns out that bees are not only able to perform this generalization, but they can learn the reciprocal task much more quickly, thus demonstrating a certain capacity for abstraction. None of the existing models for pattern recognition can explain this performance. Therefore, we must assume that insects' ability to perceive chromatic and achromatic patterns is much more powerful and flexible than we had hitherto believed.

These experiments led us to question whether a brain as small as the bee brain is able to learn rules. To do so, we chose a matching-to-sample experiment (or matching-to-nonsample, respectively), and we demonstrated that such a task can indeed not only be solved, but that the bee transfers its response to new stimuli (Giurfa et al., 2001). The task that bees in our experiment had to carry out was to choose the blue target after seeing a blue signal (given a choice between blue and yellow) and choose the yellow target after seeing a yellow signal (given the same choice). Other bees had to solve the non-sample task (choose the blue target after seeing a yellow signal and the yellow target after seeing a blue signal). After the bees learned the task in the color domain, they were able to solve it without training in the pattern domain and even in the odor domain.

Ultimately, we need to explain such cognitive faculties and many others yet to be discovered in the bee on a neuronal basis. Demonstrating such faculties in a brain of 1 $mm^3$ with fewer than 1 million neurons, will hopefully help us search for and identify neural mechanisms at a reduced level of complexity. Whether insect scientists are able to contribute to such an enterprise is not at all clear, but we shall try, working together with our colleagues who work on "big brains" (Menzel and Giurfa, 2001).

### *Learning and Memory*

After reading McGaugh's *Science* article (1966), I was eager to find out whether bees have short- and long-term memory (STM, LTM). Indeed, they do (Menzel, 1968a). The next step was to localize the consolidation of STM to LTM in the brain. We succeeded at this using the PER paradigm (see above) and found that robust learning can be observed after one-trial conditioning, even when the head capsule had been opened and the brain was made accessible to recording and manipulation. Using thin cold probes (200 $\mu$m in diameter), we were able to reversibly switch off small areas of the brain at

different times after conditioning (Menzel et al., 1974). These experiments determined the particular importance of the bee brain's mushroom bodies in creating memory, even before studies on *Drosophila* came to similar conclusions (Heisenberg et al., 1985). It also became clear that memory is created not only in the mushroom bodies, but also in the primary sensory neuropil, the antennal lobe, an idea that we verified years later using other methods (Hammer and Menzel, 1998).

Back then, in 1975, experimental psychological procedures had not yet been systematically applied to study the PER paradigm. Since I was immersed in ethological tradition, with its rejection of experimental psychological concepts and techniques, I had no idea of the required testing procedures. I did, however, know from reading the literature that this knowledge was urgently needed. I got some preliminary impressions from a workshop held by Bitterman and Lolordo in Germany in 1976 (Bitterman et al., 1979). A subsequent collaboration with Jeff Bitterman during his stay in our lab in 1982 led to ongoing intensive behavioral-analytical studies of the PER paradigm in our group (Bitterman et al., 1983). Many paradigms were tested and found to lead to phenomena of conditioning similar to what are seen in laboratory mammals.

I'd like to dwell on one paradigm—the blocking phenomenon—because it led to controversial results that are still unresolved, even though the researchers involved (Bertram Gerber and Brian Smith) have been working cooperatively on clarifying it. In blocking, a novel stimulus is not learned if it occurs together with an already-learned stimulus. Brian Smith (Chandra and Smith, 1998), a former postdoc in my lab, demonstrated blocking, but Bertram Gerber, working on his doctorate in our lab, could not (Gerber and Ullrich, 1999). Both used rather similar conditioning procedures, but partially different odors, and one worked with German bees, while the other worked with American bees. If the nationality does not count, it is likely that unknown properties of the conditioned odor have a stronger impact on blocking than hitherto believed. I mention this to show that discrepancies in results need not necessarily lead to a breakdown in personal friendship and professional communication. This was, however, not always the case in connection with the PER paradigm. Jeff Bitterman, for example, was unsuccessful with PER conditioning in his lab (even though he had previously observed the experiments in our lab [Bitterman et al., 1983], and he then felt it necessary to include in his lectures his opinion that PER conditioning is a hoax. This gave me, during lectures in the United States, the opportunity to present a live conditioning trial, carried out on the overhead projector, and the bees erased all doubts with their convincing demonstration.

We still needed to prove the usefulness of the PER paradigm for physiological studies. One of my graduate students, Juliane Mauelshagen, succeeded here by using intracellular recording to show that a single identified neuron, the PE1 (a mushroom body-extrinsic neuron), selectively changes

its response properties to odors when an animal learns (Mauelshagen, 1993). The next step was even more important. My graduate student Martin Hammer recorded from another single identified neuron, the $VUM_{mx1}$, (Hammer, 1993), and proved with elegant experiments that $VUM_{mx1}$ excitation represents the reinforcing component during olfactory conditioning. He did this, after penetrating the neuron with an intracellular electrode, by substituting the sucrose reward in odor conditioning by current injection into this neuron. A forward pairing of odor and VUM excitation led to the same increase of conditioned responding in the animal as in normal conditioning when sucrose was used as a reward. A backward pairing of US and CS did not lead to learning in either experimental condition. This was a major breakthrough. The VUM's morphology was reconstructed, and it showed that the CS and US pathways anatomically converge at three locations (antennal lobe, mushroom body input site, and the lateral region of the brain) in both sides of the brain. This unique structure appears to be the substrate for the distributed memory trace (see above). The putative transmitter of $VUM_{mx1}$ was identified with immunocytological methods (octopamine), and this led to the possibility of running a substitution experiment using local octopamine injection as the US (Hammer and Menzel, 1998). Meanwhile, we know that there are only 2 VUM neurons with the morphology of $VUM_{mx1}$, although the class of VUM neurons has 15 members. Thus, two neurons in the bee brain may be sufficient to represent the reward pathway in olfactory learning. It is most likely that no other VUM neuron is involved in visual learning, because no other VUM neuron converges with the visual neuropils in the bee brain.

Martin Hammer was an exceptional scientist, intellectually very strong and experimentally most skillful, and a gifted lecturer. He was also a true friend and extraordinary co-worker. Martin died in a car accident in 1997.

As mentioned above, intracellular electrophysiology is not an easy task when carried out within the bee brain, and neither are extracellular recordings. Somata of central neurons of insects are electrically disconnected from the integrating and conducting parts of the neurons. Thus, little current is available extracellularly. Against this background, it is rather impressive to see what graduate students and postdocs in the lab have learned about learning-related plasticity in the central nervous system (e.g., Grünewald, 1999; Mauelshagen 1993).

Nowadays, it has gotten quite a bit harder to attract a student to a research topic which requires high frustration tolerance, and the intracellular studies carrying the most risk are reserved for my own experimental work. The reason is not that students are less dedicated, but rather that new techniques are more attractive, particularly imaging techniques. Indeed, these new approaches have turned out to be most useful in studying both olfactory coding and neural plasticity related to olfactory learning (Faber, Joerges, and Menzel, 1999; Galizia and Menzel, 2000). The bee brain is

well-suited for these studies, because selected areas can be exposed to the microscope under conditions when the whole animal learns and remembers an odor stimulus. The normal sensory inputs and motor outputs are intact, and under favorable conditions the animal may even be able to display motor responses. In my view we are on the verge of a new journey into a normally functioning nervous system using multiphoton-microscopy and intelligently designed sensing dyes. What the bee brain may be able to contribute in these new endeavors is an insight into neural mechanisms involved in accomplishing a cognitive task of midlevel complexity, e.g., natural forms of learning that transcend elementary associative processes, memory processing over many hours and days in a fully functional brain, configural and context-dependent learning and memory retrieval, attentional components in learning and memory, decision making under competing memory conditions, and the like. The question will be whether we can manage to handle and interpret the enormous amount of data from imaging a large number of neurons under such conditions, a task that can only be accomplished by intensive collaboration with colleagues from the theoretical disciplines.

A short note on how we started with the imaging experiments. In 1991 I received the prestigious Leibniz Prize from the DFG, the German Research Council, which came with $1.5 million. For the first time I had the chance to start new research projects without being forced to justify and document that I was qualified for the work. I decided to establish three new labs, each of them devoted to an experimental approach that I had never before been involved in and that had not yet been applied to the study of the bee brain: imaging, patch electrophysiology, and biochemistry. For the imaging project I recruited two graduate students (Jasdan Joerges and Armin Küttner) who, like me, had no experience whatsoever with optical measurements of neural or cellular functions. We only had our fantasies and no clear ideas about how to get optical signals from the bee brain. No research institution would have ever given us money for this undertaking. Back then, the digital cameras and the computers had to be programmed by the user—not an easy task for two biology students. The major problem was the preparation, and we worked hard for two years before we found a way to get the FM ester of Ca-green into the neurons and were able to measure signals from the dye and not from the moving brain.

The biochemistry lab was established by Uli Müller, who had been involved in protein chemistry with the *Drosophila* brain. Uli turned out to be a wonderful addition to the lab at a time when several people (Martin Hammer, Brian Smith, Frank Hellstern, and Bertram Gerber) had to test all the wonderful paradigms in the literature on associative learning (see above). He managed to measure kinase activities in single antennal lobes at very short intervals after single and multiple trial conditioning. The notion of STM and LTM in the bee brain, established by behavioral tests at the beginning of my scientific career, was successfully put to mechanistic scrutiny

for the first time. I remember the excitement when we discussed his first set of data on PKA activity and the involvement of NO synthase on LTM, but not on STM induction (Müller, 1996). One might argue that it might not be necessary after all to test such basic concepts of the cellular correlates of STM and LTM, since *Aplysia*, *Drosophila*, and the many studies on LTP and LTD in mammals had already told us the story. I disagree wholeheartedly! General mechanisms in biological functions are discovered only through comparative studies. Furthermore, any species and any selected component of neural function has its own phylogenetic history and cannot be assumed at the outset to represent a general phenomenon. Specific adaptations of species to their ecological niches shape the functional components, and there is no way to distinguish between the specificities and the generalities. Take, for example, protein synthesis and LTM induction. When we found that 24-hr retention does not depend on protein synthesis in bees, we had a hard time getting the data published (Wittstock, Kaatz, and Menzel, 1993). Meanwhile, we know that bees are not as special as thought; they rely on translation-dependent early LTM and transcription-dependent late LTM as other animals do, but on a different time scale (Menzel, 1999).

### *The Bee in Its Environment: Choice Strategy, Navigation, Communication*

Karl von Frisch said that observing a bee colony is an endless source of insight: that the longer one watches, the more one observes, and the more there is to be observed. Working with free-flying bees in their natural environment has been a constant throughout my research work. I repeatedly went back to just observing their behavior inside and outside the colony, and most of the questions that were followed up in laboratory studies stem from these observations. There has been additional motivation for me. Bees come in large numbers and look alike. When you have worked with a group of bees for a while you will identify individuals on the basis of their behavior; however, it is normally not possible to recognize an individual bee, a prerequisite for any careful study. In my view, Karl von Frisch was so successful with his research because, from the very beginning, he identified bees individually using dots of colored paint on their thoraces. He designed his experiments so that he knew exactly what each bee had been exposed to or had experienced before he tested it. I used von Frisch's colored dot method throughout my life, but we also developed all kinds of automatic recognition and testing devices to keep track of individuals, making the behavioral tests more objective; taking advantage of the large number of potential experimental animals; saving time, effort, and the risk of unpleasant experiences (watching bees at the hive entrance can lead to attacks and stings); and automating data collection.

One example might suffice. When we wanted to study bee choice strategy, my long-term co-worker Uwe Greggers, an excellent engineer, built computer-controlled feeders that detected an individual bee; provided a particular volume of sucrose solution according to a particular computer program (e.g., simulating a constant flow rate of sucrose solution), with a precision in the nanoliter range; and recorded the behavior (feeder handling, licking time, etc.). Four such feeders formed a patch in which bees performed hundreds of choices per bout, and each of the choices was recorded with its characteristic parameters (Greggers and Menzel, 1993). The huge amount of data and their computerized format allowed testing rather sophisticated models of choice performance (Greggers and Mauelshagen, 1997; Fülöp and Menzel, 2000).

Another topic studied over two decades is navigation. Whereas von Frisch and his co-workers, as well as current researchers (Thomas Collett, Rüdiger Wehner, and Mandyam Srinivasan), focused on the sensory and perceptual aspects of navigation (e.g., the role of the polarized light pattern, mechanisms of visual landmark recognition, time sense, and sequential views of landmarks), we were more interested in the cognitive structure of spatial orientation. Initially, I believed (as other researchers did) (Wehner and Menzel, 1990) that long-distance navigation is fully described by the assumption that bees establish vector memories from path integration and that such vector memories are associated with large-scale landmarks. When Gould (1986) came up with the proposal that bees might also refer to a geometric representation of experienced space, we performed a large number of experiments that dismissed this proposal. Although this dismissal is still correct, Gould's speculation is substantiated by new data. The problem with all studies on bee navigation is that only the initial flight path could be recorded after the bee was released at an unexpected site (vanishing bearings). During this initial flight phase, the bee follows the vector it would have taken if it had not been transferred to a new site. However, if the bee's full flight path is recorded using a radar tracing technique, we recently found (unpublished data) that the bee is able to return in direct flight from practically any location around the hive within a radius of approximately 500 m, indicating that bees refer to an allometric representation of space which allows them to localize themselves according to landmark constellations and to fly along the shortest route back to the intended goal. Such an intended goal is usually the hive, but can also be the feeding place.

von Frisch's famous discovery of the bee dance is supported by an overwhelming battery of impressive data (von Frisch, 1965), but a direct proof is lacking. A direct proof would be to trace the flight path of a bee recruited by a dancing bee and show that the recruited bee flies exactly according to the information gathered from the dancer. This proof is now available. Using the same radar technique, we documented a large number of flights

by recruited bees and found that indeed bees perform a vector flight whose direction and distance were indicated by the dance.

## Epilogue

"Bees are insects; their nervous centers are, as far as their anatomic evolvement goes, paltry, as compared to the human brain. Nevertheless, these creatures are able to tell their peers about a goal that is important for the entire colony." Karl von Frisch wrote that in 1965 at the end of his book on bee dance communication and orientation. von Frisch, Lindauer, and many other researchers devoted their entire professional lives to understanding the remarkable achievements of these small insects. My contributions are marginal when compared to the heroic deeds of my scholarly predecessors. Along with my co-workers, I was aiming for a paradigm change, from describing phenomena to analyzing neuronal mechanisms. I was inspired by the general "new beginning" in neurosciences in the early 1970s; by the enormous advances made in the methodology of measuring brain functions at this time; and by the example set by my older colleagues, Franz Huber, Ernst Florey, Werner Rathmayer, and Hubert Markl. However, I also had to free myself of some constraints which had been established by the strong German traditions in ethology and sensory physiology. In these zoological disciplines, experience-dependent adaptation by organisms is not held to be a subdiscipline; many influential zoologists even believe that this should not and cannot be considered a legitimate field of study.

When I ask myself what I have learned so far from my studies of how the nervous system works, I can suggest this answer. (1) We expect too little from small brains. One million neurons allow the bee to sense a huge sector of environmental energy distributions; to steer the body in elegant flight, even under rough weather conditions over long distances, and most effectively between a patchwork of potentially attractive food sources; to adapt the sensory and motor circuits such that effective behavioral control, well-timed expectations, and appropriate communication with its community occur; and to implement rules from sequences of learning. Little brains do not appear to produce more stereotyped behavioral patterns than big brains. There is also no indication that a small brain, by necessity, has a more limited memory capacity, at least within the boundaries of its cognitive faculties. Experience-dependent neural plasticity, and the memory trace resulting from it, is such a basic property of nervous systems that it does not require any particular level of network complexity or total number of neurons. The primary parameter for brain size is body size, and the additional function components with relatively increased brain size are very hard to uncover, indeed. (2) The intelligence of simple heuristics is underestimated, and cognitive tasks may require much less "cognition" than usually believed. The brain does not work in isolation, but is embedded in the functional

properties of its sensors and actions. What these peripheral organs solve does not need to be solved by the brain. The complex polarization pattern of the sky, for example, is preanalyzed by the structure of the compound eye, and the brain receives not just generally useful information, but information selected for just one task, namely, to detect the great circle through the (unseen) sun such that the sun's azimuth can be calculated (Wehner, 1992). An astronomer would be unhappy with such a measuring device, but the pilot of a plane or the captain of a ship, facing the same problem as the bee (estimating the position of the sun from a patch of blue sky in an otherwise overcast sky), would find the combined hardware/software system immensely useful. The same argument applies to brain function. For example, the storage capacity and temporal dynamics of appetitive STM in bees appear to be adapted to their food sources (flowers), which are rather unreliable, provide very little food, and grow in patches (Menzel, 1999). Such heuristics are not exclusive to small brains; any brain, including the human one, takes advantage of them (Gigerenzer and Selten, 2000). (3) Rather similar environmental demands are made of small and big brains. Are different neural strategies implemented in small and big brains to solve similar problems? I do not believe so, and in particular, I do not consider small brains to be less flexible and less quick to adapt. Franz Huber asked me nearly 40 years ago why plankton rotiferas learns; he didn't ask "Why do you think such little nervous systems learn?" This is the key issue. If an animal species has an extended lifespan (in the case of the bee, the colony's lifespan is the deciding factor), and the individual animals are exposed to a changing environment, their nervous system will develop strategies to cope with these changes effectively, irrespective of the absolute size of its brain. This does not mean that the neural and cellular mechanisms are the same in small and big brains, but the mechanisms should be related to each other because of common phylogenetic histories.

For the reader who has never worked with bees, my opinion about the irrelevance of absolute brain size will sound strange and unconvincing. I can only recommend studying and watching these wonderful animals and getting caught up in their impressive behavior. It could become a lifelong commitment.

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