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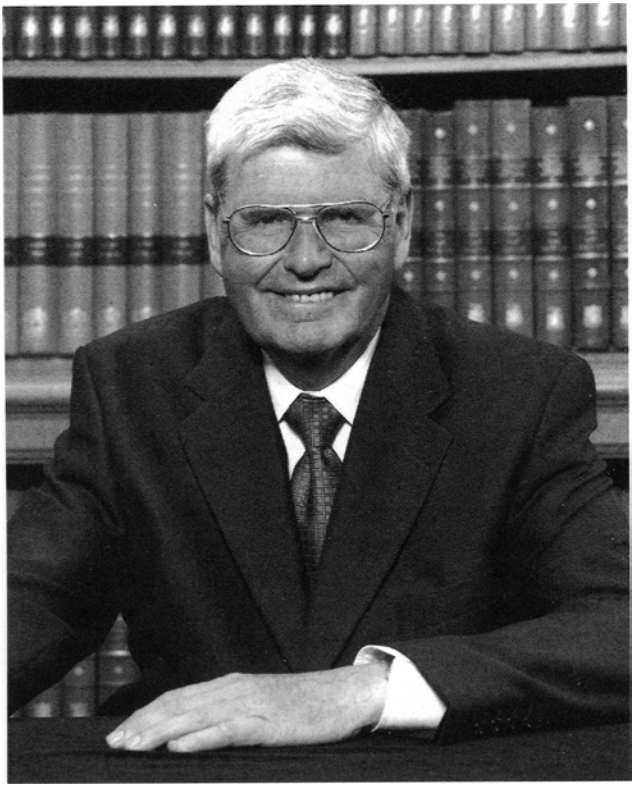

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University of Oslo, M.D. (1954)
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Per Andersen pioneered the analysis of the physiology of the hippocampus. He described the trisynaptic circuit, pioneered the development of the hippocampal slice, discovered inhibitory neurons in the hippocampus, and helped establish long-term potentiation as a tool for the study of neuronal plasticity.

Per Andersen

Playing with the Seahorse

I thank the Society for Neuroscience and the Editor of *The History of Neuroscience in Autobiography* for the invitation to share with neuroscientific colleagues, younger and older, some of my experiences in our literally exciting field of investigation.

Family and School

Of the many factors of importance for a scientific activity, I think the values you develop through your upbringing may be the most relevant. In both verbal and practical ways, my parents insisted that education was the essential thing. With limited resources, they both made their utmost so that their four children could receive the best education possible. Fortunately, our Scandinavian system allows for public education, up to and including university education. In the suburb of the small, quiet city of Oslo, I enjoyed a happy childhood, living in a favorable position for outdoor life, a Norwegian national pastime.

I enjoyed school, all the way from the early days through high school. I was particularly engaged by physics. However, as the years went by, I was more and more taken to the idea of being a physician. School work was relatively easy, in particular, science and mathematics. Other subjects, particularly essays, called for more maturation than I could muster at the time. However, by concentrating, I got through the numerus clausus barrier and could enter the medical curriculum.

Scientific Introduction

In the medical curriculum, I was fortunate to meet some outstanding neuroanatomists who set me on the scientific path. By their own example, they showed me the importance of well-informed guidance, genuine excitement, and quality standards. The first was Jan Birger Jansen, who in 1930 revived the Norwegian neuroscientific tradition which was started by Fridtjof Nansen through his doctoral thesis from 1887, later to be a famous polar explorer and high commissioner for refugees under the Union of Nations in Geneva. Jansen, supported by the Rockefeller Foundation, created the Brain Laboratory at the Anatomical Institute, which soon attracted

a set of young, eager collaborators. Between them, Jansen and Alf Brodal created the so-called Oslo school by concentrating on experimental studies of the cerebellum and its connectivities. Jansen's enthusiastic and instructive lectures on the brain emphasized the magnitude of the controlling and regulating tasks undertaken by the brain and how it influenced virtually all other bodily functions. These thoughts awoke a desire to learn more about this topic and to take part in the search for understanding the brain's control functions. Later, after I obtained a student's assistantship to help in simpler demonstrations, I was fortunate to enjoy Jansens eminent leadership, helping and encouraging his subordinates far more than most scientific leaders. The whole institute felt like a family, with him and his lovely wife Helene as the central figures. Having lost my father when I had just turned 17, Jansen became a sort of father figure for me.

Neuroscientific Apprenticeship

By providence, Birger R. Kaada returned to Oslo from his two-year studies at Yale and McGill. Until this time, about 1950, teaching of neural function at all universities was dominated by clinical syndromes and reflex studies. Kaada, who was trained by John F. Fulton, Wilder Penfield, and Herbert Jasper, was granted laboratory space at the Anatomical Institute by Jansen and told us a series of new and exciting stories, in which electrical recording from brain structures and even individual cells added a new dimension. When he announced that he wanted two student assistants for his research, I eagerly applied and was fortunate to be accepted early in 1951, just as I turned 21 years old. I had started on my neuroscientific career.

Kaada had made an elaborate electrocorticographic study of the so-called rhinencephalon, comprising much of what later has been termed the limbic system. He was interested in examining the physiological roles of specific subdivisions. Thus, he asked Jan Kristian Schøning Jansen, the son of Professor Jansen, and myself to take part in a study with implanted stimulation electrodes in awake cats. We did these experiments in addition to the usual medical curriculum. The way we found time was to drop some of the lectures and theoretical discussions, but not any of the clinical demonstrations. In addition, we got used to long working days.

Stimulation of the amygdala complex in freely moving cats caused licking, chewing, salivation, and retching, but also emotionally colored behaviors, as if the cats were frightened or angry. In contrast, hippocampal stimulation gave much less dramatic responses, but a slowly developing reaction which we called the orienting response. It was as if the animals became aware of something surprising or new in the contralateral environment. The same reaction followed stimulation of the medial frontal cortex and the anterior and middle cingulate gyri. No doubt, the many hours at the microscope during the following histological analysis and the painstaking

reconstructions of electrode sites and lesions provided an anatomical insight which has been highly useful later in life. Eventually, Kaada taught us how to plan and write an article on our findings. I still remember the excitement on seeing our names in print as authors of a real scientific article.

Later, I realized how fortunate we were in being introduced to neuroscience by such experienced and dedicated supervisors. Kaada, as well as Jansen and Brodal, emphasized the importance of a sharply formulated problem and then the selection of an appropriate method. Alf Brodal was particularly keen that the chosen problem should not only be clearly defined, but be of biological significance. "Only attack real problems," he used to say. The basic training I received from Kaada, Jansen, and Brodal, supported by their own adherence to sound scientific principles, has been more valuable than is easily measured.

After some years with stimulation of limbic structures in freely moving cats, I got my own project. This time also the inspiration came from a close colleague, Theodor Blackstad, who had just returned from a year studying brain anatomy in Paris. In 1949, Brodal received from Walle Nauta in Zürich a new method for tracing fiber degeneration, even before it was published. This was the famous Nauta 1950 method. Blackstad tried it out on hippocampal pathways and was tremendously rewarded. Fiber degeneration in this structure stood out as a painting of Joan Miró, with black stripes on a yellow background. For example, after an entorhinal lesion, the degenerated perforant path appeared as a black band in the molecular layer of the dentate fascia. So intense was the degeneration that it could easily be seen by the naked eye! In a moment, this slide of Blackstad's set my entire scientific course. Immediately, I saw that this would make a fabulous preparation for a neurophysiologist interested in cortical physiology. By stimulating a proper selection of input fibers, I could engage a set of synapses located to a restricted part of the dendritic tree of the target neurons.

Within a few weeks, I started the first experiments, and with beginner's luck I got some very large and apparently simple signals in the first few experiments. However, after this initial success, things got more complicated, and I had to struggle for several years before I saw light at the end of the tunnel. Here we come to a condition for scientific progress which was not present in Oslo in the early 1950s! Today, a beginner in neurosciences has the advantage to join a number of excellent neuroscience programs and can enjoy instructive textbooks and a large number of review books and articles. Above all, she or he can enjoy the information plethora available on the Internet. In Oslo in 1952, when I started the first hippocampal electrophysiological experiments, very little help was at hand. Although Kaada had recorded gross electrocorticographic signals, he had little experience with evoked potential analysis. Jan K.S. Jansen and myself, Kaada's two first pupils, therefore, had to find out on our own how to proceed. In all Scandinavia, there were few people to ask for help. Nearly all the many outstanding neuroscientists

in Sweden had worked on problems related to spinal cord or bulbar or retinal mechanisms. Few, if any, had studied field potentials, the gross signals generated in a central structure after synchronous activation of a major afferent source.

In short, Jan and I had to fend for ourselves. His interest was cerebellar connectivity, linking into the work by his father and Brodal. I was captivated by the elegance, the stringency, and the beauty of the hippocampal histology. Thus, we started with histology. In my case, I cherished the two-volume book by Santiago Ramon y Cajal, translated to French (1911). Here, I may, perhaps, interject a point of satisfaction for European scientists. Because I enjoyed French, the Ramon y Cajal volumes were not too difficult. I devoured them. What a genius! And his countryman, Lorente de Nó, had written a masterpiece on Golgi-stained hippocampal neurons in 1934, also a great source of information. These two masters of the Golgi method gave me tremendous stimulation through the histological details provided and also a number of ideas for physiological thinking.

But, classical anatomy aside, how could I translate the electrical signals I saw into a meaningful picture? Here, I was supported by two giants in the history of neuroscience, Fréderic Bremer and Alan Hodgkin. Bremer was the father of the two important preparations, encephale isolée (a brain isolated from the spinal cord by a section above the C1 segment) and cerveau isolee (the brain isolated from the lower brain stem by a section above the mesencephalon). He wrote a survey of his experiences in *Physiological Reviews* (Bremer 1958), and his logical and clear exposé was a great help. In 1952, Alan Hodgkin and Andrew F. Huxley published their famous set of four papers, which later earned them the Nobel Prize. Hodgkin also wrote a review of this work in *Biological Reviews* in 1951. This became my neuroscientific bible. At first, I found the article extremely difficult because of all the terms and processes I had not met before. I do not know how many times I had to read it before I got the main ideas right. Over and over again, but slowly the major ideas took hold, and I could start to use this information in the interpretation of the hippocampal signals I recorded.

In parallel, I read the 1953 book of John C. Eccles, *The Neurophysiological Basis of Mind*. This book explained in cellular terms many of the results of Sherrington, but for me this book was less important than the Hodgkin review. A different story was, however, the small, red-covered book of his, *The Physiology of Nerve Cells*, in which he summarized the first few years' experience with intracellular studies of motoneurones. At this time, the small red book of Mao was much talked about. For me, and thousands of other neuroscientists, Eccles' small volume would be our Famous Red Book. Given as the Herter Lectures at the Johns Hopkins University in 1955, Eccles managed to give a wonderfully authoritative survey of cellular motoneuronal physiology in a way that could be used as a guideline for studies of most other nerve cells. If Hodgkin's *Biological Review* article

was my neurobiological "Old Testament," Eccles little red book became my "New Testament." Feeling I was on my own, however, I developed a certain degree of inferiority. Other neuroscientists had their education from large universities with a proper training in basic topics, not the least biophysics, chemistry, and mathematics. I acutely felt that my medical training, adequate as it probably was for work as a clinical doctor, was inadequate for the basic scientific enterprise.

The reader should not get the impression that I was the only fledgling neuroscientist with difficulty in understanding brain signals. At the time, probably all of us who tried to understand evoked brain signals were uncertain. Probably surprising to many today, we were not that many who worked on the hippocampus. Some pioneering work was done by Richard Jung and Jan F. Tönnies in Alois Kornmüller's laboratory in Berlin. In 1938, they discovered the low threshold for seizure development in the hippocampus. In the same year, Kornmüller, who for years was searching for a physiological correlate to the Brodmann areas, reported with Jung that the hippocampus displayed a large amplitude sinusoidal activity which they coined the theta activity. To my knowledge, in the middle 1950s there were only five scientific groups working with hippocampal field potentials, spontaneous or evoked. These groups counted Brian Cragg and Lionel Hamlyn at University College London, Pierre Gloor and his associates at Montreal Neurological Institute at McGill, John D. Green and Ross Adey with colleagues at the Brain Research Institute at UCLA, Arnaldo Arduini and colleagues in Pisa and, finally me, working by myself in Oslo. Somewhat later, Jim Olds in Ann Arbor made significant additions, and Eric Kandel and Alden Spencer in Karl Frank's laboratory in Bethesda started their remarkable collaboration. To various degrees, we all struggled with interpretation of the extracellular signals recorded from the hippocampus, either after a triggering stimulus, after spontaneous activity, or during an epileptiform seizure activity.

The first unit recording from individual brain cells was, in fact, also made in the hippocampus by Renshaw, Forbes, and Morison in 1940. Green and Arduini rediscovered the theta waves in 1954 and noted that discharges of single hippocampal units were in moderate synchrony with the theta waves. Brian Cragg and Lionel Hamlyn in London were in 1955 the first to record sharp, spike-like signals which were conducted slowly along the apical dendrites after local synaptic excitation. These signals my colleagues and I later named population spikes and proved through recording of a large number of single unit discharges that they were composed of a large number of near synchronously discharging pyramidal or granule cells (Andersen et al., 1971a).

Guided by Bremer, I interpreted the local negative slow waves as signs of excitatory synaptically induced depolarizations of the target neurons. By using the histological evidence from Blackstad's experimental work, I found that commissural activation gave extracellular negative waves exactly in

those areas where Blackstad found terminal degeneration. I must admit that I found the thesis work rather tedious. The tradition was that you had to do it all yourself to show your independence and that you were in command of all aspects of the relevant scientific work. An additional element was the fact that I lost the help of Sarah Mørch, the charming artist of the Anatomical Institute. She got cancer, and Jansen would not signal to her that the outlook was bad. Consequently, for more than a year he refused to hire somebody in her place so as not to add to her worries. The result was that I spent nearly every evening in the artist's room, trying to make my own figures from oscilloscope prints and histological micrographs. The artist's room was next to Jansens office. Because he came in every evening for an extra session, undisturbed by the hustle of the day, we came to see each other quite a bit, working as we were in neigboring rooms. Although he concentrated on his work in his own office, he sometimes needed some material from the outer rooms. Quite often, he found me struggling over my figures. He usually came with some encouraging words. I got the impression that he liked to see that I kept at it, but he never commented on the artist's absence. Just as the figure-making took a considerable time, I accept that this training later gave me an upper hand toward people who had not made their own films, prints, line drawings, reversals, enlargements, composites, and lettering.

In those days, we recorded all signals on the oscilloscope face with a camera, initially fully manually operated and later with a semiautomated system that still needed a manual push for every sweep to be saved. A successful experiment could generate about 200 ft or more of 35-mm exposed film. Returning the next day, the first task was to salvage the film containers and develop the films. After fixing and rinsing, the impossibly long films were dried by hanging in one of the tall staircase towers between the basement and the third floor for a few hours. Therefore, everyone in the whole institute could know whether it had been a successful experiment or not. Later, we had to mark each of the several hundreds, or thousands, of traces with India ink by reference to the experimental protocol. In those days, there were no computers and few semiautomatic measuring devices. Nearly all measurements were made by placing the marked films on a light box covered with translucent millimeter paper, and the latencies and amplitudes were measured with an accuracy of a tenth of a millimeter. With experience, it was amazing how good the trained eye can be. For critical measurements, we always used two or more investigators who did not know the results of the others, and in special cases, we used projectors giving enlargements of the original records.

Toward the end of the thesis work, I received a call from Professor Ragnar Granit in Stockholm, whom I met when he was external examiner for Kaada's thesis. He asked me whether I would like to come to his institute to give a seminar of my work. It was like lightning had struck! First, I was

excited beyond belief! Second, how could I afford it? Being the first invited seminar in my life, I did not know that people who invite you to give a seminar usually provide both travel and accommodation. I think that Granit understood because he quickly added that I would get a train ticket by post and that I could stay at Hotel Eden "because I have some shares in that hotel." What a wonderful person! Obviously, I was ever so grateful. Coming to, however, I started to worry because the famous Curt von Euler, who had worked on the hippocampus with John Green at UCLA, was Granit's next-in-command. What would he say about my records and interpretations. Maybe I was in for a scientific slaughter?

The Stockholm trip was a revelation. It was the first time I experienced the international brotherhood of science. People were not only friendly, but they treated me as one of their own, as if I really had something to contribute. Obviously, there was opposition, but in a constructive way. In the end, I felt utterly rewarded. Throughout my career, Ragnar Granit and Curt von Euler remained my close friends, two eminent scientists whose memory I honor.

The thesis eventually saw the light of day. At the time, I was happy that the work was done, but I had no idea about its reception and certainly no feeling for its possible future use. In particular, I did not expect to return to it more than very occasionally. Posterity has shown, however, that I have been using all the papers in the thesis quite extensively, a source of quiet satisfaction for a mature neuroscientist. Before the dissertation I was scared stiff, mostly by the reputation of my external examiner, Professor Curt von Euler. I knew he was a gentleman, but how was he as a Ph.D. examiner? Curt used the rule I later heard from my friend Tomas Hökfelt about a similar skirmish: the opponent "showed his claws, but did not use them." A highly civilized behavior!

Throughout the thesis work, I felt a strange, Janus-like effect. Much as I enjoyed finding apparent explanations for synaptic activation of hippocampal neurons, the weakness of my scientific education became all too obvious. My consequent lack of confidence caused an urge to join a first-class laboratory where I could receive top-level training. Once again, my guardian angels Jansen and Brodal came to the rescue. Both belonged to a small group of international neuroscientists, led by the neuroendocrinologist Wolfgang Bargmann, which had yearly meetings in Europe. Eccles was also a member. One sunny day Brodal asked me whether I had thought of going to Australia. I understood immediately what he meant and felt that my heart took a few somersaults. In my very private dreams I had entertained the thought of being trained by Sir John. But in real life? Never! However, this incidence illustrates how important it is to have good supervisors. In Eccles eyes, the Oslo school stood for quality. Brodal wrote and got an immediate positive reply. Later, Eccles told me that this expectation was one of the reasons he said yes to Brodal's inquiry. Here, I can reveal one of Eccles' relatively few mistakes. He believed that I was a trained neuroanatomist, coming from

the Oslo group of anatomists. I was, however, not quite without anatomical knowledge. I had been an Instructor at the Brain Dissection Course for the medical students for a few years. Although different from the brains of lower animals, there is still a considerable similarity. A thorough understanding of the three-dimensional relations and some of the gross connectivity turned out to come in very handy later on.

Professor Jansen's excellent relation with the Rockefeller Foundation was probably a major factor behind my stipend, granted in 1961. I was later told that it was one of the last Rockefeller stipends to European scientists because the Foundation had made a strategic change to switch its support to Africa and Asia, in view of the higher prosperity of most European nations. One difficulty was the fact that the Rockefeller Foundation granted travel assistance to my wife and me, but not to our three children. When Professor Jansen heard about that, he immediately said that I should leave that to him. About a week later, he had a solution. Not only had he got hold of money for the children's tickets, but he had arranged so we could go by air. He felt that looking after three children, one only eight months old, for six weeks on a boat would be too strenuous, particularly for my wife. More than anything, this shows what kind of man he was. Obviously, I was more than grateful, but I was anxious to know where the extra money had come from. There were rumors that previous, unexplained financial miracles had been paid by Jansen himself. Thus, I politely said that I hoped that my children's ticket could be reimbursed by a scientific fund. He made as if he was irritated and asked me, "Who is the Boss at this Institute, you or me?" I had to confess that he was the boss. So, he said, with a flicker of a smile, "So leave that one to me, will you?"

Australia and Sir John

My stay in Australia was a fantastic period. From the first to the last day, it was a stay colored by excitement, intense learning, new discoveries, friendship, and a deep satisfaction with the field as such. The main factor was John Eccles himself. The many young international pupils who flocked around his pulpit called him Prof, a term I think he liked a great deal. In addition, there was the excellent working conditions, because the Australian authorities had created one of the few research schools in the world. The superb working and research facilities were thoroughly enjoyed. For us youngsters in the crew, it was like basking in the sun. With the best of equipment, the best of collaborators and technicians, and the best neuroscientist leader in the world, it was a dream. Our setting in the Australian community added to the excitement. Canberra is a garden city with about 20 million fruit trees planted along the boulevard-like streets. The spring flowering has to be seen to be believed! The Aussies, as the indigenous population is called, are a delightful flock, open, honest, and enclosing. All our family came to love them.

Fig. 1. A group of the many colleagues and friends of Sir John C. Eccles who celebrated his 90th birthday in Frankfurt in May 1993. From left to right, 1st line; Masao Ito, Per Andersen, Helena Eccles, Sir John C. Eccles, Piergiorgio Strata; 2nd row: Mario Wiesendanger, Henri Korn, Janos Szentágothai; 3rd row: Manfred Klee, Jeff Watkins, Joszef Hamori, Roger Nicoll; 4th row: Ian McDonald, Hans Kornhuber, Yngve Løyning.

Among the many findings I was fortunate to be a part of, I would like to mention the description of corticofugal presynaptic inhibition in the spinal cord; analysis of presynaptic and postsynaptic inhibition in the dorsal column nuclei; analysis of rhythmic thalamic responses with recurrent inhibition and postinhibitory rebound as the instrumental mechanism; the finding that hippocampal basket cells are inhibitory; the principle that synapses on soma of pyramidal cells are inhibitory; the finding that cerebellar basket cells are inhibitory; and the discovery of the trisynaptic circuit of the hippocampus.

Spinal and Dorsal Column Nuclei Studies

As a start, Sir John—or Prof—asked me whether I would like to take part in an investigation of a possible corticofugal presynaptic effect on spinal reflexes. Sir John, who knew about the pioneering results of Hagbarth and Kerr (1954) which showed that descending signals from the cerebral cortex could reduce, or even block, spinal signals induced by peripheral

activity, wanted to see whether corticofugal impulse volleys could produce presynaptic inhibition in the spinal cord. Having some experience with cerebral cortical stimulation from our work in Oslo, and prodded by Sir John, I suggested that we stimulate the pre- and postcentral gyri. Our immediate success both pleased and impressed Sir John, presumably creating an advantageous position for further collaboration with the young lad from the north. We found that a corticofugal burst of stimuli created the same dorsal root potential and increased the excitability of afferent fibers in the dorsal roots that followed spinal nerve stimulation.

I suggested to Prof that we should try to look for presynaptic inhibition in the dorsal column nuclei because these had a fiber and cell arrangement that allowed recording very close to the fiber terminals. Prof had predicted that the mechanism involved axo-axonic synapses that acted on the terminals themselves. The regular anatomy of this system allowed us to get intra-axonal records from dorsal column fibers as close as 0.5 mm from their terminals. Consequently, the intracellularly recorded depolarization had a large amplitude and was associated with enhanced fiber excitability, just as in the case of spinal afferent fibers.

Thalamic Mechanisms

Following a detailed analysis of the transmission through the cuneate and gracilis nuclei and the associated pre- and postsynaptic inhibition (Andersen et al., 1964b–e), Prof was eager to proceed up to the next station of the somatosensory system, the ventrobasal nucleus of the thalamus. For this approach, we needed some precision of the placement of the recording electrodes. Prof had not used sterotactic procedures before and was genuinely surprised that Tom Sears and I were able to find the ventrolateral nucleus. During a visit to the John Curtin School for Medical Research (JCSMR) by King Bhumipol of Thailand, Eccles showed him around and explained what we were doing. Pointing to Tom and me, he said, "They have to find this little speck of nerve cells in the middle of the brain, and quite amazingly, they hit it every time!" Naturally, we greatly enjoyed these admiring words of his.

While Prof was an accomplished dissector of peripheral nerves and spinal roots, he always left the surgery of the brain to me. We needed to remove the dorsal part of the cortical mantle without getting too much bleeding from the many vessels there, whereafter I sucked away the hippocampus to expose the web of arteries on the dorsal aspect of the thalamus and tried to find an area for penetration of the recording electrodes. Fortunately, it usually worked and reinforced Prof's belief that I was a real neuroanatomist!

When we recorded from thalamic neurons in response to stimulation of an appropriate skin nerve, we were struck by the large size of the excitatory postsynaptic potentials (EPSPs) and that they were composed of a

small number of elementary steps. An additional surprise was the large and long-lasting hyperpolarization that followed. It answered to the various tests we had for inhibition, so we concluded it was an IPSP. However, because Prof never had seen such amplitudes and durations in spinal cord neurons, it took some time before he was convinced. Once that occurred, though, he was the most excited of us all and told everyone around how huge the inhibitory processes were in the brain. Still, the most surprising finding in the thalamic cells was the large depolarizing responses, measuring tens of millivolts and lasting for some 20 msec or more, that appeared as unitary events just after the IPSPs. This was an entirely new response type. When we tested whether the IPSP could be elicted by antidromic activation of thalamo-cortical neurons, and thus be part of a recurrent loop, we saw to our further surprise that the recurrent IPSPs also were followed by the depolarizing wave response. Further, a hyperpolarizing current pulse gave a similar reaction as well. Influenced by the enhanced excitability of peripheral nerve fibers after an anodal current, Eccles named the reaction post-inhibitory rebound (Andersen and Eccles, 1962). Later work, notably by Llinas and Jahnsen (1982) and by David McCormick's group (von Krosigk et al., 1993), has shown that the original name was not without foundation. The response is due to calcium influx following resetting of calcium conductance mechanisms by the prominent hyperpolarizing IPSP. Another important factor is the I_h current, of which we were ignorant in 1962. This current is activated by hyperpolarization and provides the depolarizing drive to elicit the rebound response. An additional surprising finding was that there was not one, but a set of repeated IPSPs in ventrobasal thalamic neurons in response to a single stimulus to a peripheral nerve or to the somatosensory cortex. In extracellular recordings, we noted that there was a cluster of cell discharges on top of the rebound response. Many neurons fired nearly synchronously, and each of them emitted a burst of spikes. Such repeated burst discharges were reflected by a set of cortical waves in the appropriate projection area from the thalamic location. I remember how it made me recall the oscillatory responses described by Adrian in 1941, which he interpreted as repeated thalamic activations. In the thalamic work (Andersen et al., 1964 a,f), one of the collaborators was an old friend and colleague of Prof's, Chandler McCuskey Brooks from Downstate University, New York. This real gentleman had been working with Eccles in Dunedin, New Zealand, in 1946. The result was the first description of the focal potential, a field potential resulting from the near simultaneously discharging motoneurones in response to a fiber volley in the relevant peripheral nerve or dorsal root (Brooks and Eccles, 1948). This was the extracellular counterpart of the EPSP which Brock, Coombs, and Eccles discovered in 1951. Chandler was a highly experienced scientist, quiet and reflective and without any high-brow manners. It was a privilege to work with him on these experiments and in the later analysis.

Several of the discoveries led to letters to *Nature*. The two years I spent with Sir John created eight such letters. We were so proud, because it meant that out efforts were appreciated by the rest of the world. Unquestionably, the application of intracellular recording on problems from the central nervous system was an important factor. But equally important was Prof's drive and ambition—he really wanted to discover new land. It was so exciting. Every day was like a birthday party, all the new information and insight were like precious gifts. I woke up every morning eager to get started at work and wondering about what we would find out today. Fortunately, my family also enjoyed the Australian way of life so I could enjoy my work and spend truly long hours in the lab. Weekends were free, though, at least in general.

Hippocampal Synapses

After nearly a year with work on presynaptic inhibition and on the somatosensory system, Sir John came one day and proposed to start investigations on the hippocampal pathways. I was thrilled because some months earlier he had fleetingly suggested that we should concentrate on spinal and brain stem mechanisms during my Canberra time, leaving me as he said "to tackle the hippocampus when you return to Oslo." At the time, I was slightly disappointed, but obviously accepted his proposal. With his changed mind, however, I was thrilled since I knew that our progress would be much faster, and I enjoyed my good luck.

I had used rabbits in my previous work, but Prof preferred cats. Following the routine for spinal cord work, they were anaesthetized by barbiturates. I do not know how wise this choice was because the signals had much lower amplitude than those I was used to. Once we got intracellular records, my apprehension was somewhat allayed. Nevertheless, the use of barbiturate may have had some advantages because barbiturates enhanced inhibition as Eccles later showed in his last experimental paper in a collaboration with Roger Nicoll (Allen et al., 1977). We exploited the experience I had with the field potentials and used a set of afferent sources to the CA1 neurons. With Prof's and Chandler's experience (Brooks and Eccles, 1948), it was now much easier to interpret the field potentials. From the start, Prof was struck by the long duration and smoothness of the field potentials. He suspected something was wrong. I tried to convince him that this was to be expected in the hippocampus. Only slowly did he accept my standpoint, however. The whole situation changed in a wink as soon as we got our intracellular recordings. This turned out to be more difficult than Prof had anticipated. There were several reasons for this situation. Motoneurones are hardy cells. They can be penetrated repeatedly and can withstand impalement by quite coarse electrodes. Therefore, most of the Dunedin and Canberra motoneuronal work was made with microelectrodes with input resistance of a few megohms and a tip of about 1–1.5 μm. A great advantage

of spinal cord work was the ease with which one could apply mechanical clamps securing good stability. Finally, most reflex and single cell work was made in the lumbar and sacral spinal cord after it had been separated from the upper segments by a transverse cut in the lower thoracic region. This procedure removed much of the longitudinal movement otherwise conveyed by the respiratory pump. Eccles was fortunate to have excellent mechanical and electronic engineers around him. George Winsbury designed both the fine mechanical clamps and the micromanipulators which probably were the finest in the world at this time. The stimulation and recording unit constructed by Eccles' long-time collaborator, the physicist Jack Coombs, was superb and a major reason for the Canberra success. In the hippocampus, the situation was very different. The cells did not tolerate impalement with coarse electrodes. In addition, mechanical movements from circulation and respiration were quite marked. It took quite some time to learn how to draw and fill higher impedance electrodes and to adjust the amplifier system accordingly. Unfortunately, we had nothing similar to the spinal cord equipment to help us stabilize the hippocampus. We tried to apply a Plexiglas pressure foot with a central hole for the recording electrode, but the pressure could easily be too heavy and damage the hippocampus. We tried several other approaches, pouring liquid agar so as to make a rigid lid to reduce the movements and having a closed system by having only narrow holes drilled in the skull to allow the recording and stimulating electrodes. In addition, we tried fast and small volume respiration volumes and higher respiratory rates, and a pneumothorax system with metal tubes through the thorax wall connected to rubber balloons to reduce the transmission of lung to chest wall movement.

None of these trials was fully successful. However, although the quality and length of the recordings were far from ideal, we got sufficiently many observations to draw some qualitatively valid conclusions. In this regard, it is interesting to recall something Eric Kandel told me some years back. He described how he and Alden Spencer (Kandel, et al., 1961) succeeded in getting excellent records already in their second experiment. If that had not happened, they might well have given in, he told me, because after the glorious start there were only failures for a full year.

A frequent observation was that virtually all inputs produced an IPSP. Excitatory responses were less frequent, but when EPSPs did occur, they always had a few millisecond shorter latency than the IPSPs. As Kandel and Spencer first observed a year before us, antidromic activation of pyramidal cell axons gives rise to IPSPs. We hypothesized that there was an intercalated interneuron in the circuit. Our main reason was the latency difference of about 1–2 msec between the EPSP and IPSP, the widespread distribution of the IPSPs suggesting a distributing mechanism, and finally, the frequent observation of ripples on the initial phase of the inhibitory potentials suggesting its mediation by a high-frequency discharging cell. We searched for

such postulated interneurons in areas of the hippocampus where histologists had pointed out the presence of what could be non-pyramidal cells. We found a number of cells that filled the adopted criteria for interneurons: they fired in bursts, but at a lower frequency than pyramidal cell bursts; were often located outside the pyramidal layer; and showed converging effects from different afferent fiber systems.

Identification of Inhibitory Synapses

The identification of these interneurons and their synapses was, arguably, the most dramatic experience I had in Canberra. Impressed by the ubiquity of the IPSPs and their large amplitude, we exploited the special histological arrangement to find their source of origin. We turned to the field potentials and their distribution along the main dendritic axis of the CA1 pyramidal cells. We noted that the onset of IPSPs was associated with a positive extracellular wave when recording from the pyramidal layer. By charting the amplitude distribution of the field potential, the peak was consistently located to the pyramidal layer, irrespective of the afferent fibers used. I remember very well the evening when I showed him the complete set of graphs, all pointing in the same direction. We were disussing our data in his office at the end of an experiment, the famous 11 PM tea break. Since both Kandel and Spencer and we ourselves observed that the IPSPs reversed by chloride injection or diffusion, the hyperpolarization was likely to be mediated by inward movement of chloride ions, in other words an outward current, following classical rules. Consequently, Eccles explained to me that the chloride current generates the outward current and thereby the hyperpolarization of the membrane. Because the field plot had its maximal amplitude in the pyramidal layer, the hyperpolarizing current flows across the soma membrane or a region very closed to it.

> I nearly yelled, because I both saw the light and beamed with delight:
> "Sir, given the conclusion that the inhibitory current flows across the soma membrane, I can tell you which cell type and synapses that do it!"
> He stared at me, but I went on:
> "Cajal has drawn both the cell, its synapses and how it connects to the pyramidal cells."
> "Where?" he said, surprised about my boyish excitement, but clearly starting to think I had a point. He had never heard about such interneurons before.
> "In his volume 2," I nearly shouted. "Let me show you!"
> We ran down the corridor. A super thing about the JCSMR was that the well-equipped library was open round the clock.

> We rushed in, and since I had so often searched Ramon y Cajal's two-volume (1911) masterpiece, I found Figs. 473 and 474 straight away, showing the beautiful basket cells and their elaborate relation to the many pyramidal cells they innervate. Prof was elated, starting to laugh, and exclaimed:
> "Here it is, here it is!"

I did not quite understand what he alluded to, but later he said that he saw what he had been chasing so long: the first example of an identified interneuron in the brain and, above all, the first identification of inhibitory synapses in central nervous structures. He had himself identified Renshaw cells as inhibitory interneurones in the spinal cord, but not found their synapses. Further, E.G. Gray in 1959 described the symmetric and asymmetric synapses in electron micrographs, although he made clear that the available evidence did not allow a distinction of their physiological roles. However, although both types were found in abundance, both in the hippocampus and in the neocortex, we did not know the identity of the parent neurons nor of the target cells. The closest step to identification came in an influential paper by Lionel Hamlyn (1963) in which he described the various bouton types which contacted hippocampal pyramidal cells. However, in the days before marking substances for a cell or cell type, he could not know the origin of the fibers attached to the boutons.

But, in November 1962, we succeeded in Canberra. It was difficult to sleep that night. The next day, Prof came into my little 60-square feet cubicle and kept on rejoicing. I had a big homemade chart of the hippocampus on the wall with the key cellular elements depicted. He pointed and pointed, and soon, as was his habit, he had taken over and explained to me how all the cells were arranged and how they interacted and told me how we would proceed. Fantastic!

> After some time, I ventured:
> "Prof, maybe we should check whether the basket cell arrangement is a general organization or only something peculiar to the hippocampus."
> He did not understand at first. I went on:
> "There is an additional structure with basket cells with a very similar termination on their target neurons—the cerebellum."
> His answer was very disappointing:
> "Oh no, when Raggen and Charles could not make head and tails of it, we will not manage either."

He referred to a paper in the *Journal Physiology (London)* by the Nobel laureate Ragnar Granit and Charles Phillips, well known for his corticomotoneuronal studies (Granit and Phillips, 1956). They intended to exploit

Phillips' long experience with intracellular recording from motor cortex in baboons and record intracellularly from cerebellar Purkinje cells during various reflex situations. For some reason, it proved very difficult. Admittedly, they discovered the burst discharge, which we know today is due to the intense climbing fiber activation, and called it the "inactivation response," but did not acquire good enough records to unravel the underlying mechanism. This had to await the work by Eccles, Llinas, and Sasaki (1966a).

Cerebellar Studies After All

I was very disappointed, but as usual my respect for him prevented any open protest. However, as had happened in our work on hippocampus, a long fortnight later, he came one day into my cubicle and mused: "I wonder whether we should test the basket cell idea in the cerebellum. It is a good idea, you see!" I have to assume that he remembered my proposal on the same issue only some weeks earlier, but he made no remark in that direction. It did happen that he "adopted" ideas from others. Be that as it may, I was excited and told him which option I could see for a suitable experimental approach, an idea he adopted straight away. I had followed Anders Lundberg's work in Lund, Sweden, on the many spinal afferent systems to the cerebellum. In addition, just before I left Oslo, Jan K.S. Jansen and I had made a study of the effects of local stimulation of the surface of the folium, through which I got acquainted with the field potential and its reversal with depth. The fact that it was rejected by the *Journal of Neurophysiology* did not prevent me from acquiring useful experience for our initial cerebellar work in Canberra. We also tested both cerebellar and hippocampal inhibition for possible glycine sensitivity, but found that neither were influenced by strychnine at doses which completely blocked spinal glycine-mediated inhibition. This provided a backdrop for the discovery by Ito and his collaborators (Obata et al., 1967), who found that the Purkinje cell-mediated inhibition on vestibular neurons was mediated by gamma-amino-butyric acid. A few years later, a further Canberra group led by David Curtis discovered that hippocampal inhibition also was GABAergic (Curtis, 1970). Eccles also had a previous engagement in cerebellar neuroscience. His second publication was, in fact, a collaboration with D. Denny-Brown and E.G.T. Liddell (1929) on the effect of cerebellar stimulation on spinal reflexes.

With our previous experience, we quickly found that the field potential profile was very similar to that of the hippocampus and that the Purkinje cells also showed large and long-lasting IPSPs. In addition, we found cells discharging with high-frequency bursts during the rise time of the IPSP. These neurons were found at a depth corresponding to the expected position of basket cells. Consequently, we put forward the hypothesis that recurrent collaterals of Purkinje cells activated basket cells, which in turn disynaptically induced IPSPs in a number of neighboring Purkinje cells. Looking back,

it gives some satisfaction to know that I could help in the start of Eccles' glorious last scientific endeavor, which he carried through in a remarkable collaboration with Janos Szentágothai and Masao Ito, namely, the analysis of the properties of cerebellar neurons and the principles behind their interactions (Eccles et al., 1967).

Finally, I received additional training in Canberra by working with David Curtis, the father of the iontophoretic analysis of neuronal activity. In a most efficient collaboration with Jeff Watkins and later with Graham Johnston, he developed this method to give us a new view of the effect of transmitters and their receptors in central nervous synapses. We discovered that thalamic neurons were highly sensitive to iontophoresed acetylcholine (ACh) with a latency approaching that of the Renshaw cells in the spinal cord. This meant that ACh was likely to play an important role in the control of the excitability level of thalamic neurons and thereby of the cortical cells which they bombarded with impulses (Andersen and Curtis, 1964). Today, we know that this system is essential for the general cortical arousal system and an important factor in the manifestation of Alzheimer disease symptoms. Naturally, we also observed the sensitivity of thalamic neurons to application of glutamate and N-methyl-D-aspartic acid (NMDA). In 1962, we did not have the classification of the glutamate-sensitive receptors generally accepted today through the work of Jeff Watkins and his collaborators (Watkins and Evans, 1981), so we had to be content with a description of the effects that we elicited.

I was extremely fortunate to be able to work consistently with Sir John throughout my two years in Canberra, usually two and sometimes three times a week. Altogether, we must have made close to 200 all-day experiments together. This gave me invaluable experience, my main scientific capital, in fact. The usual experiment started at about 8:00 AM and lasted until about 2:00 AM the following night. Our wonderful technicians, Sheila and Carol, had already fetched the cats in the animal house and anaesthetized and shaved them. We, the younger members of the team, put in the tracheal tube for free airways or artificial respiration and venous cannulas for intravenous infusions of fluid or drugs. Then followed the preparation of the peripheral nerves, which we dissected free and provided the end with a cotton tie and loop for good electrode contact. We dissected from 8 to 13 nerves in hindlimb experiments and 3 to 5 nerves when forelimb afferents were asked for, sometimes bilaterally. These dissections usually took us several hours and then came the time for the laminectomy to expose the spinal cord and its attached roots. Eccles was proud to demonstrate his surgical abilities, so he often took part in the dissection. Each time he announced: "It won't take me more than 10 minutes!" His pupils did not protest, but did not quite believe him either. He was particularly proud of being able to split the peroneal nerve in its muscular and skin subdivisions, each only about a third of a millimeter in diameter. These ran together for about 20 mm

enclosed in a common sheath. For experimental purposes, it was useful to separate them, however. It was impressive to watch how the famous 60-year-old scientist concentrated on this task of dexterity, a task he solved perfectly every time I saw him do it.

During the recording session, Eccles was the captain, sitting in front of the camera and shooting pictures at a frightening speed since we could not know how long the penetration would last. I was number 2, as they say in the navy, having the responsibility to take notes of stimulated nerves, amplifier settings, and all the other parameters in the complicated operation. With Prof's formidable speed, it was a challenging task. If things went too fast, he used to say: "Don't worry, I remember it all!" Fortunately, we worked so close and often together that I felt I could read his mind to some extent, and I could get the correct settings down in the protocol when he shouted some wrong figure. His memory was truly remarkable, but I am afraid that some information was lost. We were usually three in a team, and the third member was operating the micromanipulator and control instruments, in fact, the all-important fishing part of the enterprise. The day after the experiments was used to mark the films and start the tedious measurement phase. Then followed the analysis and eventually the setting up of graphs. That was the rewarding bit, because we could get some insight in the process under examination. On Friday night Prof came along to collect material from us youngsters. He put graphs and notes and film in a big cardboard box. Quite often, when he returned on Monday morning, he had been able to write all or the best part of another manuscript. The handwritten draft was then typed by the secretary before the control phase came when we all tried to improve on the draft.

Things changed somewhat when we started on experiments on the dorsal column nuclei, where we needed preparation of forelimb nerves, and on thalamic and hippocampal tissues, where no nerve preparation was needed. Here, Prof had no previous experience and he left the forelimb surgery to his younger colleagues. The dorsal column and brain surgery fell to me. For this task, my training as an anatomical lecturer in Oslo came in handy. The exposure of the dorsal column nuclei was relatively simple by ventroflexing the head, allowable because of the tracheal tube, and by gentle removal of parts of the occipital bone. For the hippocampal experiments, we needed to remove the neocortex, a procedure I had carried out time and again in Oslo. I had found a set of small tricks to reduce the bleeding from the skull bones and from the neocortical edges left by the suction. For the thalamic experiments, I needed to remove the overlying hippocampus in order to see the relevant anatomical landmarks. I think some of my colleagues will feel with me when I say that it hurt somewhat to set the suction pipette into this gleaming white structure, so pristine in shape, having given me my vocation and income for years, and just remove it into the bucket. Shameful! The thalamus appears much less glorious. Covered in a dense network of arteries and veins, its

dorsal surface looks directly untidy. As one gets to know its inhabitant neurons, however, one recognizes that the rough and red surface is just a camouflage for some of the most interesting and challenging neurons in the brain.

The Trisynaptic Circuit

The last story I will tell from the Canberra period is the discovery of the trisynaptic circuit. Sir John had been the undisputed leader in all the other experimental series in which I took part in Canberra. When it came to the trisynaptic circuit, I was on my own. That is to say, I had two great collaborators with me, Birgitta Holmqvist from Sweden and Paul Voorhoeve from the Netherlands. But this time I was the leader and had the starting idea and the control of the experiments. Once again, the background had been drawn up by neuroanatomists. The big master, my hero Santiago Ramon y Cajal, had made a splendid diagram, summarizing the major points of hippocampal structure in Fig. 479 in Vol. 2 of his *Histologie de Système Nerveux* from 1911. More than anybody else, his rich research findings had inspired and guided me through my initial years. But the diagram contained one error. An arrow indicated that the CA1 neurons were sending their impulses along axons traveling forward to the CA3 neurons and into the fimbria and, thus, out of the hippocampus toward the septum and hypothalamus. My last effort in Canberra was to turn that arrow around. The main target of CA1 neurons is in the exactly opposite direction, namely, the posteriorly lying subiculum.

In the spring of 1963 (Southern Hemisphere version), Prof was away for a grand tour of the world of lectures and symposia. He had asked me whether I knew an interesting problem which could keep Birgitta, Paul, and myself busy in that period, and my answer was a big yes. For a long time, I had wondered where the CA1 neurons sent their impulses, either as the Ramon y Cajal idea went down to hypothalamic nuclei to influence autonomic homeostasis or to other sections of the hippocampal formation for whatever function. Because this was my show, I decided to use rabbits, my own favorite. In urethane-cloralose anesthetized animals, we stimulated the main input to the hippocampal formation, the perforant path, and we recorded simultaneously from three stations: the dentate granule cells, the CA3, and the CA1 pyramidal cells. The initial effect of the perforant volley was the excitation of granule cells as seen by both field potential and intracellular records. The next station was the excitation of CA3 neurons, although their excitability was much lower and only a minor fraction gave discharges. Raising the stimulation rate improved the engagement prominently, however. With a clearly longer latency, the CA1 pyramidal cells were the third group of cells to be recruited, again much better if we used a short train of stimuli. Perhaps the most convincing piece of evidence was the effect of a surgical cut of fibers between the CA3 and CA1 areas. The CA3 activity was not changed, but all CA1 signals vanished altogether. So, the

signals traveled from CA3 to CA1 and not in the direction that Ramon y Cajal had drawn. Some years later, my group showed that the main CA1 output is to the subicular neurons, thus finalizing what we called the trisynaptic circuit. We should add, however, that much remains to be learned about the physiological significance of this circuit, and it may well be that much hippocampus-dependent activity is mediated by other pathways.

All fairy tales have a happy end, so also here. My Canberra period ended in November 1963, but not before an incredible occasion occurred. By a night call, Prof was notified by a Melbourne newspaper that he had received the Nobel Prize for Physiology or Medicine, as it is called. He refused to believe it, thinking it was a hoax. The reason was that he twice before had gotten false announcements about the Nobel Prize and had decided to be utterly skeptical. However, when later in the day, his old time friend from the Oxford days "Raggen" Granit called from a meeting in Italy to congratulate him, Prof accepted the fact. What a day! I immediately helped to organize an impromptu lab feast and ran out in town to buy the necessary champagne. John Hubbard, a long-term Kiwi visitor (New Zealander), and Robert Schmidt (an inventive German) made the in-house arrangement and announcement. Then, we invaded Prof's office with an accolade so intense that I felt he had some difficulty in swallowing our overexcitement. Clearly, he was pleased beyond description. Still, I feel that his collaborators and admirers of all ages that day were perhaps even more excited and happy than he was himself. It was as if we had a part in the achievement, even if the prize was given for discoveries made in the early and middle 1950s, partly in Dunedin and partly in Canberra, nearly 10 years before our term in the John Curtin school. Obviously, most of us had expected it to occur. However, the real thing is something else. It was a high point in my life and in those of Eccles' many Canberra colleagues.

On the way home, we traveled across the United States. I had written to many of my American colleagues in the field, most of whom I had not met, and received a most overwhelming response. Every one of them wanted to hear about results from Canberra, and many of the meets gave rise to lifelong friendships. This was a new experience to me. I shall never forget, and stop thanking for, the generosity I met then and later from my U.S. colleagues. I understood that the various aspects of international fraternity that I had experienced in Australia were only a small fraction of the vast brotherhood of similarly thinking people, everyone possessed by the idea to understand more of the nervous system.

Setting Up My Own Laboratory

Coming home from Canberra was quite a transition. On the one hand, the reunion with family and friends was fantastic. While we were in Australia, the Cuban crisis occurred, and for some days there I remember how scared

my wife and I were that we might never be able to return to a normal Norway and Europe. During those days, we realized how far from the rest of the world Australia was. Over the last 25 years or so this has changed, but in 1962 the feeling of distance was real. An Adelaide professor has used the term "the evil of distance" for the feeling many Australians have had about their cultural and social isolation from United States and Europe. During the Cuban crisis, we felt that evilness forcefully in our close family.

Our reunion with family and friends in Oslo in 1963 was emotional and reminded me how much our background means. Although the two Canberra years no doubt were the best two years of my scientific life, the homecoming brought back to me other aspects of life, above all the importance of your close family and friends. These feelings, coupled to the intense pleasure of my family in our national peculiarities such as skiing, sailing, and hiking, made up my mind: we would like to stay in Norway.

Nobel Festivities in Stockholm and a Papal Symposium in Rome

Through the kind assistance of Ragnar Granit I was able to secure a ticket for the Nobel festivities in Stockholm when Sir John would receive his Nobel Prize together with Sir Alan Hodgkin and Sir Andrew Fielding Huxley. The Swedes know how to make a festival! With 50,000 red roses from the city of San Remo decorating the Stockholm Concert House, the best scientists in the world received their diplomas, medals, and prizes from the hand of King Gustav Adolf II, himself an accomplished archeological scientist. Prof got his prize for the work on the ionic basis for spinal inhibition. The prize winners were asked to give a set of lectures at other Swedish universities. I was very pleased to hear that examples of central inhibition made up a major theme in his talks that week.

In the winter of 1964, Eccles invited me to a symposium on Brain and Conscious Experience to be held in the Vatican under the auspices of the Pontificial Academy of Science of which Sir John was a prominent member. Created in 1936, the Pontificial Academy arranges a Study Week every year in which a central theme is discussed. Although some of the participants were religious, most were not. Only one demand was made: The group must decide on which points the group could not agree and which experiments had to be conducted to resolve the disagreement. The meeting place was grandiose: the house of Pope Pius IV, Casa Pio Quattro, with an undescribable roof, painted by Michelangelo. Even if we were housed in such clerical surroundings, the discussions were very direct, not least the response to our hosts' proposals for cortical mechanisms where the mind could meet the brain. I was impressed how people could retain their deep respect and friendship in spite of quite strong feelings for or against non-physical explanations for aspects of conscious behavior. It was particularly interesting to hear how

Roger Sperry rejected a simple religious description of willed action, but at the same time had great difficulties with a total rejection of determinism. In his talk he said: "There may be worse 'fates' than causal determinism." The meeting was a glorious lesson in the breadth of scientific knowledge, but also about the willingness to hear each other out, in spite of obvious and at times strong disagreements. Sir John dedicated the book that came out of the meeting to two Pontificial Academicians who had deeply pondered about human nature, Charles S. Sherrington and Ernst Schrödinger.

My Own Laboratory

After the glamour in Stockholm, I returned to Oslo and started to set up my own laboratory. I was well received by my home university with much help, not least from my superiors. A new, albeit small, lab was waiting, and some money for equipment was available. Fortunately, I was successful with an application to the NIH for an initiation grant. Maybe the success of my Rockefeller stipend period helped as well? Tom Sears, who is a master experimenter, came across from the United Kingdom with his family and helped me to set up the new instruments and procedures and get the first experiment going. In 1964, it was supremely rewarding to record nerve and cell activity in my own little laboratory!

Having seen the excellence of the best university groups in the world, I realized that any hope for success of my own neurobiological research had to rest on a strategy which exploited whatever special advantage was available at the University of Oslo or in the not too distant vicinity. One considerable asset was the neuroanatomical group in Oslo and another was the relatively large number of well-educated young people eager to work on problems related to the nervous system.

I count myself fortunate to have been able to assemble around myself a number of Norwegian and foreign scientists, in all more than 80, who have contributed greatly to various hippocampal or thalamic problems. Among the topics we managed to attack with some success, I would like to mention the identification of spine synapses as excitatory (1966); the realization that direct thalamo-cortical connections are the main substrate for the alpha type rhythmic activity in the EEG (1968); the discovery of the lamellar organization (1971); the introduction of the transverse hippocampal slice (1971); the identification of hippocampal output systems (1972); the discovery of long-term potentiation (LTP, 1973); the first intracellular recording from hippocampal slices (1975); the input specificity of LTP (1977); the equipotentiality of excitatory dendritic synapses (1980); two types of GABAergic responses in hippocampal pyramids (1980); linear summation of EPSPs (1983); f/I relations for hippocampal pyramidal cells (1984); dendritic depolarization is essential for LTP induction (1986); behavioral learning promotes new spine synapses (1994); behavioral learning

promotes short-lasting synaptic enhancement (STP, 1995); LTP depends on phosphorylation through PKC and CaCaMKII (1988); LTP depends upon the cytosolic tail of NMDA receptors (1996); LTP is absent in mice lacking the A-subtype of AMPA receptors (1999); in such GluR-$A^{-/-}$ mice, LTP is rescued by re-expression of A-subunits (2000); and lamellar orientation of directly recorded CA3 axons (2002).

One of the first tasks we tackled was to identify the functional nature of four afferent hippocampal systems. Here, serendipity occurred. Blackstad, whose Nauta-stained sections set me on the hippocampal path, was working on a method whereby a nerve fiber from a given source could be identified in the electron microscope. With colleagues from the Anatomical Institute, he gave the first description of the electron dense boutons belonging to previously lesioned fibers (Alksne et al., 1966). Using this method, we first stimulated four different fiber systems in isolation and observed monosynaptic excitation of their target cells by intracellular recording or by recording field potentials with cell discharges. We also charted the region of maximal synaptic effects to know where to look for histological evidence. After having lesioned these fiber systems, they were examined by Blackstad a few days later in the electron microscope. All four excitatory fiber systems had degenerating boutons associated with dendritic spines (Andersen et al., 1966). These results gave a functional role to the electron microscope (EM) observation of E.G. Gray (1959) of two synapse types in normal cortical tissue. Gray cautiously stated, "At present there is no evidence to suggest that type 1 and type 2 synapses are functionally different." Only a few years later, Eccles (1964) and Andersen and Eccles (1965) came close, but did not quite make this suggestion, largely because of a lack of evidence for the location of excitatory synapses. With our combination of functional and EM degeneration data from 1966, we could now propose a simple rule: excitatory synapses on two cortical cell types, hippocampal pyramidal cells and dentate granule cells, were located to dendritic spines while inhibitory synapses were located to the somata of these cells. However, the last point had to be modified quickly after Eccles et al. (1966b) found that cerebellar stellate cells, which terminate on dendritic shafts at various distances from the cell body of Purkinje cells, also were inhibitory. Further, while most excitatory boutons are located to spines, there are several exceptions. Hence, the synaptic categorization is not quite so rigid as we proposed in our simple rule in 1966.

Between 1967 and 1970, I deserted my dear hippocampus to take up a challenge derived from our thalamic studies in Canberra. Listening to the loudspeaker, Tom Sears and I, working together in Eccles' laboratory, heard that there often were series of burst discharges without any stimulation. When we recoded these events, they looked remarkably like those we both recognized from our electroencephalographic experience, where the cortical counterparts were called barbiturate spindles. Much charting remained, however, not least at the cortical level to determine the nature of these

thalamocortical responses and the location of the rhythmic pacemaker, if any. In this endeavor, I was lucky to be joined by Sven A. Andersson from Gothenburg University who had worked in Vernon Mountcastle's laboratory in Baltimore. We alternated between experiments in Gothenburg and Oslo and became close friends. So much so that Sven, who is an accomplished carpenter, is responsible for a good deal of my mountain cabin in the ranges of central Norway. Our main scientific result was that the spindle waves of various cortical areas were closely controlled by the rhythmic activity of the thalamic projection nuclei and not by the intralaminar or midline nuclei, going against a common opinion at the time. Sven and I wrote a book describing our results, *The Physiological Basis for the Alpha Rhythm* (1968). Until it appeared, the emphasis had been on the so-called unspecific nuclei of the thalamus. We feel that the book introduced another aspect and helped to reorient peoples' ideas about the alpha rhythm.

Long-Term Potentiation

No question, this phenomenon is the single topic which has created the most intense interest among my colleagues. The phenomenon consists of a period of enhanced synaptic transmission after a short session with high-frequency stimulation of a set of afferents to the hippocampal formation. The great interest derives from the many LTP attributes which could support learning and memory. In my thesis work in the late 1950s, I often observed a slow decline of the hippocampal potentials, a sort of fatigue I thought. However, in such cases much could be restored by a few seconds worth of high-frequency stimulation. In my thesis, I noted that a few seconds of 10-Hz stimulation gave a synaptic enhancement which could last from 4 to 6 min (Andersen, 1960). Interesting as they were, I felt it was still not long enough to distinguish it from posttetanic potentiation (PTP). When Terje Lømo joined me in 1964, I showed him this stimulation trick. We compared the effect of raised stimulation frequency on excitation and inhibition. In our intracellular records, we found that the recurrent inhibition remained unchanged for several seconds before a small decline, probably because of a changed internal chloride concentration. Excitatory responses, on the other hand, showed a dramatic increase during the tetanic stimulation and remained enhanced for minutes afterwards. We saw this as a candidate for a learning process. In fact, in 1965 we concluded in a symposium article, not published until 1967, that the posttetanus increased responses were short lasting, they could be seen as "an example of primitive synaptic learning" (Andersen and Lømo, 1967). A major change occurred when Terje gave a series of tetanic stimulations. Now, the enhancement could last for more than 1 hour after the stimulation. This long duration convinced us that we had observed a new phenomenon, different from PTP. The first description of this LTP effect was given by Terje at the Scandinavian Physiological Congress in Åbo in

Finland in 1966 (Lømo, 1966). I talked about the phenomenon at a meeting in London in 1967. In the audience sat Tim Bliss who had just completed his thesis on neocortical plasticity. He was highly impressed by our preliminary results and wanted to come to Oslo for a postdoctoral study. Here, he and Terje made a set of critical experiments and, with a clever use of an experimental and a control line, found nearly all the important properties: the long duration, the physiological induction rates, and the synapse specificity. Hence, the Bliss and Lømo (1973) paper is rightly regarded as the birth of LTP, although they used the term long-lasting potentiation. Later, my colleagues and I showed input specificity of LTP because it only occurred at the tetanized synapses of a given cell while a set of control synapses remained unchanged (Andersen, 1977). Other highlights were the finding of McNaughton et al.'s (1978) of the cooperativity phenomenon (many fibers need to be co-active), the discovery by Collingridge, et al. (1983) that the NMDA-channel blocker 5-amino-valerate blocks LTP but not synaptic transmission, and Wigström and Gustafsson's (1986) demonstration that pairing of postsynaptic depolarization and synaptic activation could induce LTP.

The Lamellar Organization

While in Oslo, Bliss took part in an additional investigation with an interesting result. By antidromic and orthodromic activation of four different excitatory pathways, we found that they all were oriented nearly transversely to the longitudinal axis of the rabbit hippocampus, an arrangement we coined the lamellar organization (Andersen et al., 1971a). The term suggests that the majority of connections in the trisynaptic pathway are along one plane, but not exclusively so, since excitation was also found to either side, only less well developed. Some people misunderstood the term and felt we had hypothesised an exclusive activation of a thin sliver of tissue, while some of the fiber systems involved show a much broader distribution. The lamella should be taken in a statistical sense only, since our original curves showed a ridge-like structure of activated tissue and not a thin sheet.

The lamella gave rise more or less directly to a useful preparation, the transverse hippocampal slice (Fig. 2). For many years, I had tried to develop an isolated preparation of the whole or part of the hippocampal formation. I had tried various methods, from small chunks kept in hyperoxygenized saline at low temperature to slabs taken from hibernating hedgehogs, which in those days crawled in plenitude under the hedges in our family garden. Nothing was successful. I knew about the pioneering work of Henry McIlwain with various isolated slice types. The work on the pyriform cortex was particularly promising (Yamamoto and McIlwain, 1966). However, the tangential sectioning employed by McIlwain would be likely to lesion the hippocampal neurons. With the lamella idea in hand, a transverse slice appeared possible. My colleague Knut Skrede went over to London,

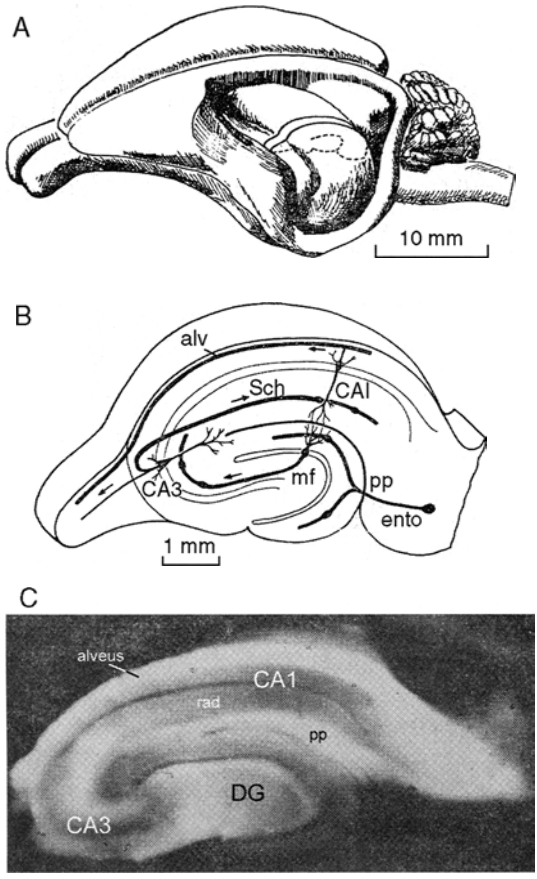

Fig. 2. The transverse hippocampal slice. (A) The lateral part of the neocortex of the rabbit has been removed to expose the large hippocampal formation. (B) The orientation of a lamella is indicated and the main intrahippocampal pathways are seen to lie in the same, lamellar plane. (C) An unstained transverse slice as it appears in the recording chamber, with the three major subdivisions marked (CA1, CA3, DG [dentate gyrus]) and two myelinated fiber bundles labeled (alveus, carrying the axons of the CA1 neurons; pp, perforant path with fibers from the entorhinal area to the dentate gyrus; and CA1 rad, stratum radiatum, a favorite region for study of dendritic synapses. In CA1 the cell body layer is seen here as a black stripe.

where Chris Richards, an associate of Tim Bliss' at Mill Hill and a former pupil of McIlwain, was kind enough to show him how to cut and handle slices from the pyrifom cortex. With a minimal budget, Knut was able to get the first transverse hippocampal slice going in Oslo. Within weeks we knew it was a winner, showing us all the usual field potential properties we knew

from intact preparations. Knut and Rolf Westgaard demonstrated the versatility of the preparation in the first report on transverse hippocampal slices (Skrede and Westgaard, 1971).

An Oxford Sojourn

I abstained from the authorship because these two colleagues had worked so hard, in part in my absence, while I spent half a year on sabbatical leave to work with Charles Phillips in Oxford. Charles had arranged for me to be a Visiting Fellow at Trinity College, a most interesting and agreeable stay. The college life was fantastic, a glimpse of a wealth of tradition mixed with people of charm and peculiarities as well. This was my first and only opportunity to work with monkeys. By microstimulation, we studied the origin of cortical neurones that could drive motoneurones monosynaptically as signaled by single units in the electromyogram of small hand muscles. Our results showed that area 4 cortico-motoneuronal cells were not assembled in tight columns as one of the popular hypotheses maintains, but rather were dispersed over a considerable area, although mainly in layer 5, in an arrangement we called a colony of cortico-motoneuronal neurons (Andersen et al., 1975).

Intracellular Experiments in the Hippocampus

Back in Oslo, I was joined by a number of young neuroscientists, in all more than 80, too many to name all. Philip Schwartzkroin was special by being willing to put in a large effort to make sufficiently fine micropipettes to give acceptable intracellular penetrations of hippocampal neurons, whereby he amply demonstrated the advantages of the slice preparation (Schwartzkroin, 1975). The excellent performance of a newly designed amplifier by our electronic engineer Trond Reppen made the job easier. By iontophoretic application of glutamate, Phil Schwartzkroin and I found that minute currents were still effective provided the electrode tip was at certain localized "hot spots" inside a double cone-shaped volume corresponding to the apical and basal dendritic trees. In response to a long application pulse, the initial discharges were assembled in a burst, whereas the remainder consisted of relatively regular low-frequency discharges. Each of these steady state discharges was, however, preceded by a slowly rising depolarization. Thus, glutamate application causes spike discharges through several mechanisms, one depending upon fast depolarization and a different one probably depending upon a slow conductance (Schwartzkroin and Andersen, 1975).

In 1980, we published two papers in the *Journal of Physiology* which created some interest. In the first paper, we described that iontophoretic application of GABA could elicit two completely different responses

depending on the application site. Delivery to the soma region gave hyperpolarization, while delivery to certain dendritic regions gave depolarization (Andersen et al., 1980a). In the second paper, we compared the efficiency of various afferent fibers lying at different distances from the cell body of CA1 pyramidal cells in hippocampal slices. Surprisingly, with the exception of the soma and the peripheral fifth of the apical dendritic tree, all other parts of the afferent fibers were equipotent, assuming that the constant stimulation current excited roughly the same number of fibers (Andersen et al., 1980b). Later, Iver Langmoen and I found that stimulation of two such fiber bundles created EPSPs that summed linearly such that the summed input gave an EPSP which was exactly like the algebraic sum of the two subdivisions elicited alone (Langmoen and Andersen, 1983). More recent work has shown that this picture must be modified, in that both cable attenuation and peripheral boosting mechanisms exist.

Over the years, I have been lucky to take part in some interesting discoveries. However, you cannot win all the time. As years go by, the latter seems to become more and more common. In 1985, my colleagues Øivind Hvalby, Massimo Avoli, and I were beaten close to the finishing line. We wanted to study the conditions underlying the induction of LTP. Looking at the field potential distribution during 100-msec-long tetani, we concluded that the dendrites receiving the synaptic input had to be depolarized above a certain amount to observe subsequent LTP. Therefore, we hypothesized that the coactivation threshold discussed by McNaughton et al. (1978) was represented by local dendritic depolarization. If so, we should be able to induce LTP by artificial depolarization and couple that to low-frequency synaptic activation, in itself unable to give LTP. I wanted to avoid spike discharges during the priming such that any effect should not be ascribable to cell discharges as such. This was a mistake. We paired just subthreshold, intracellularly delivered depolarizing current with synaptic activation at the end of the current pulse, but could not detect any clear effect. My former pupil Holger Wigström and his colleague Bengt Gustafsson, both in Gothenburg, did the same type of experiment. Neither of us knew about the other group's activities. Holger and Bengt had arrived at the same idea along a different route. They observed that blocking of GABA-mediated inhibition greatly reduced the threshold for LTP induction. Supported by field potential recordings, they also predicted the importance of dendritic depolarization for LTP. With much stronger depolarization, they observed a positive effect of pairing in the form of long-lasting enhancement of a test synaptic input, exactly as for tetanus-induced LTP.

In our laboratory we tried an alternative procedure. We produced dendritic depolarization by local delivery of glutamate and paired the response with low-frequency synaptic activation. Here, we saw a long-lasting enhanced response to a test stimulus, similar to the Gothenburg results (Hvalby et al., 1987). Again, without knowing of the other group, we both

sent a letter to *Nature* and both had our manuscripts rejected. In Oslo, we tried to follow the advice of the referees which meant new experiments and, consequently, more time. In the end, our revised manuscript was rejected as well. Holger and Bengt went about it differently and published their result as a short article in *Acta Physiologica Scandinavica* (Wigström, Gustafsson 1986). Two longer and well-documented reports of theirs appeared later that year and in the next year in *Journal of Neuroscience*. So they deserved to win, but slightly bitter it was.

Molecular Studies of LTP

In 1984, I got a phone call from Torsten Wiesel at the Rockefeller University asking me if I was interested in being a candidate for election to The Neuroscience Institute, run by Gerald M. Edelmann at the same university. What a lovely surprise! Thirty-six associates met twice a year to discuss principles of brain organization and mechanisms, in particular, cortical functions. I had met many oustanding scientists before, but never so many in one and the same room. It was enormously stimulating and enjoyable. Gerald M. Edelman, Gerry among friends, who received the Nobel Prize with Roger Porter for their analysis of the immunoglobulin molecule, was a tremendous host with his broad knowledge, from brain mechanisms to music. I am very grateful to have been a member of this Institute for nine eventful years.

Among the many benefits was to meet new colleagues. I made a lasting and warm friendship with many of them, including Paul Greengard. Paul pioneered the discovery of protein phosphorylation as a major mechanism for control of central nervous processes. Because LTP was associated with calcium influx, we wondered whether protein kinases could be engaged and, if so, which one. Paul's laboratory provided blockers of various protein kinases which we loaded into microelectrodes and injected into individual CA1 neurons. The strategy was to see whether LTP was prevented in the impaled cell, while it appeared as normal in the field potential generated by surrounding cells. Other laboratories had shown that the calcium-calmodulin protein kinase II (CaMPKII) was involved. We compared the effect of blockers of this kinase with antagonists of cAMP-dependent protein kinase (PKA) and of diacylglycerol-dependent protein kinase (PKC). Blocking the effect of PKA did not change standard LTP, but blockade of the other two did. The effective concentration to produce blockade was considerably lower for the PKC blocker, suggesting an important role for PKC in LTP generation (Hu et al., 1987).

Another branch of our work also involved molecular neuroscience. During the late 1980s, it became increasingly clear that the enhanced synaptic current which is the hallmark of LTP could be explained by a change of the AMPA receptors involved. This could happen either by a changed configuration of the receptor channel itself or by a recruitment,

aggregation, or insertion of new receptor molecules. Peter Seeburg at the Max-Planck-Institute for Medical Research in Heidelberg had cloned the genes for AMPA and NMDA receptors, simultaneously and independently of Stephen Heinemann's group at the Salk Institute. Peter was collaborating with Bert Sakmann, of patch clamp fame, to analyze the functional properties of these molecules, with many of the experiments made by recombinant molecules being expressed in frog oocytes or cultured human embryonic kidney cells (HEK). Bert and Peter asked me whether my group would join them in an effort to study the molecular processes underlying induction and expression of LTP. Obviously, my colleagues and I were delighted. This collaboration has now lasted for about 15 years and has been both productive and agreeable. A piece of good luck helped considerably. In 1987, I won a prize from the Norwegian Research Council which gave my group firm support for five years. This prize, supplemented by allotments from Bert's and Peter's own grants, made it possible to acquire adequate instrumentation and to keep together a research group dedicated to this molecular LTP analysis. This collaboration has been a pleasure, and we feel we have made considerable progress. Perhaps the most significant observation was that mice which lack the gene for the A-subunit of the tetrameric AMPA receptor fail to develop LTP, while ordinary low-frequency synaptic transmission remains intact. The pivotal role of AMPA receptors with A-subunits for LTP expression appears as an important observation (Zamanillo et al., 1999). Another exciting result was the dramatic reduction of LTP in mice lacking the cytosolic tail of the 2A-subunit of the NMDA receptor (Sprengel et al., 1998). As is often the case in science, for each new advance more questions are raised. Apparently, there is a complex molecular arrangement in the postsynaptic density of spines, involving both AMPA and NMDA receptors and binding proteins linking these to the cytoskeleton, which influence a variety of mechanisms for receptor changes involved in various stages of the LTP expression. There are enough problems for another life!

Rewards

Many would agree with me that for a scientist, the highest reward is when your own research results have given a glimpse of a new insight into a major problem. The intense pleasure derived from the fact that you have made a useful contribution to human knowledge is hard to explain to other people. That being said, another reason for satisfaction is the acceptance and appreciation received from your colleagues outside those in your own research group. I am particularly grateful for the consistent and strong support I have received from Vernon Mountcastle and Eric Kandel in the United States; from David Curtis and Steve Redman in Australia; from Ragnar Granit, Anders Lundberg, and Sten Grillner in Sweden; and from Tom Sears and Tim Bliss in the United Kingdom.

A highlight of my career was my election to be a Foreign Member of the National Academy of Sciences (NAS) in Washington, D.C. in 1994. Being an European without any extended period of research in the United States, my main knowledge about the NAS was the journal *PNAS*. I did not know enough about the importance of the Academy and its many other activities. Only when I attended the welcome ceremony for inauguration of new members did I understand the high regard in which the fellowship of American scientists holds the distinction of being a member of this honorable institution. After learning how many hurdles there are for a candidate before the final success and how hard and long my proponents must have worked, I was more than grateful and indeed somewhat embarrassed. How could I deserve such a distinction? Equally moving was the large number of kind letters that I received from so many American neuroscientists, even from people I had not heard from for decades.

In March 2002, I learned that I was nominated as a candidate to the Foreign Membership of the Royal Society of London, and in May, I received a letter from Professor Julia Higgins, Foreign Secretary of the Royal Society (RS), that I was elected Foreign Member of the Royal Society of London for Improving Natural Knowledge. It was as wonderful as unexpected. This time I knew a bit more about the institution. Because I had worked both in Canberra and Oxford, I had appreciated the extremely high regard in which my Commonwealth colleagues hold a fellowship in RS and the other activities of this society, notably the professorships and fellowships that the RS offers. Once again, I felt a mixture of pride and embarrassment, knowing the large number of colleagues who clearly deserve such a distinction. Also, I know that my supporters must have been eager and persistent. Because both the National Academy of Sciences and the Royal Society conduct their elections in great secrecy, I am unaware of my proponents and can only thank them indirectly, as in this article.

The election to the Royal Swedish Academy of Science in 1991 was not only a great honor, but has a practical advantage in that I am allowed to nominate candidates to the Nobel Prize in Physics and Chemistry. Because chemistry includes biochemical topics, I have used this opportunity for nomination of outstanding neurochemists. As a Nordic professor in physiology, I have had the priviledge to nominate candidates for the Nobel Prize for Physiology or Medicine, an opportunity I have used every year since I became a professor in 1972.

Looking back, one of the most rewarding aspects of my scientific life has been to make so many international friends. There is something very special about science. The combination of hard and long-lasting work and competition, often fierce, must be set against the collaboration with intelligent, highly motivated individuals. For a really good result, I feel that friendship between the participants is an essential element. An important factor is trust. Because the quality of the results depends so much upon the care

invested by the team members, they have to trust each other. The growth of the mutual trust and friendship in the many research groups in which I have taken part is one of the best experiences of my scientific activity. Although the scientific exercise can be quite strenuous, and sometimes directly disappointing, one of the tangible rewards is to be surrounded by persons with deep knowledge and good intellects. To have the opportunity to enjoy considerate arguments or debates, and to be allowed to share information at all levels, is a nearly invaluable aspect of science, a gift I have cherished deeply.

As a small contribution from our side, my wife and I have asked many scientists to come with us to our mountain cabin, well placed for hiking and skiing. Here, we have had the pleasure of greeting a number of visitors from abroad and have also tried to teach them the glorious sport of skiing in between good meals and evenings in front of the open fire.

Although science is competitive, I have often met unselfish friendliness, even magnanimosity. Maybe I am easily fooled, but my impression is that generosity is most often shown by people who are of the highest quality, while persons showing more mundane behavior may be less agreeable.

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