Journal of Biomolecular NMR, **27:** 1–12, 2003.
KLUWER/ESCOM

Perspective

Kurt Wüthrich: Biographical note*

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I was born in Aarberg, Switzerland, on October 4, 1938, and during my childhood I lived in the small town of Lyss in the Berner Seeland. At the time this was a rural area of farmland, forests and rivers. The roots of the Wüthrich family are in an even more rural, mountainous area, the farming village of Trub in the Emmental near Bern. My mother's family owned the Restaurant 'Bären' and a bakery in Lyss. My grandfather, Otto Kuchen, enjoyed fishing and hunting, and his jugged hare dish was a widely known fall season delicacy at the 'Bären'. My interests during childhood were largely influenced by our living in an old farmhouse, where my second grandfather, Jakob Wüthrich, had been a farmer. Although my father, Herrmann Wüthrich, took up an occupation as an accountant, he remained very much attached to his upbringings and our family produced a wide range of farming goods. My mother, Gertrud Wüthrich-Kuchen was the true center of our family life. In addition to raising me and my two younger sisters, Elisabeth and Ruth, she did marvelous things in the kitchen, tended our big garden, raised fowl, and was involved in various activities in the community.

My intense contacts with the rural environment of plants and animals awakened my interest in natural science at an early age. In particular, I acquired a thorough knowledge of the behavior of all sorts of water animals, mostly through observations made while enjoying all aspects of work and fun with a private trout river. On rare occasions I still enjoy fishing trips, and I am a member of the Mercury Bay Game Fishing Club in Whitianga, New Zealand, which lists Ernest Hemingway and Zane Grey among its all-time membership. With regard to my professional life, I had set my mind on becoming a forest engineer. Although I subsequently changed my mind in this regard, I still enjoy tending the family forest, which now contains trees that were planted by three generations of our family, starting with my grandfather.

At the Mercury Bay Game Fishing Club in Whitianga, New Zealand, 1987.

My formal training toward an academic profession started in 1952, when I transferred from the village schools in Lyss to the Gymnasium in the nearby 'bilingue' city of Biel/Bienne. During the Gymnasium years my interests widened beyond forestry and fishing. We had the good fortune that our science and language teachers were either former University

With my parents, Hermann and Gertrud Wüthrich-Kuchen, and my two sisters Elisabeth and Ruth in the garden of our home in Lyss, Switzerland, 1944.

professors, who had left their academic positions elsewhere in Europe during the Second World War and found a haven in Biel, or followed the then common practice of using a teaching assignment at Gymnasium level as a stepping-stone for an academic career. At age 14 to 18 we were a group of seven students specializing in 'natural sciences' who were thus trained in mathematics and physics at university level, and I happily accepted the challenge. According to my mother, it was during those years that I got used to working through the nights. Another focus was the French language, French literature, and French theatre and movies, which was largely motivated by the fact that the composition of our class as well as our teachers represented the bilingual character of Biel/Bienne. The Gymnasium Biel was informally attached to the Swiss Federal School of Sports and Gymnastics in nearby Magglingen, and thus my interest in competitive sports was awakened. These three areas all play an important role in my life up to the present days. Physics and mathematics are key activities in my professional life, professional visits in Paris and 'les provinces' are combined with the sampling of French food, wine and culture, and I not only obtained the 'Eidgenössisches Turn- und Sportlehrerdiplom' as one of my University degrees, but also played in a competitive soccer league well beyond the age of 50.

By now I can look back on 40 years of intense involvement with techniques referred to as 'magnetic resonance spectroscopy'. At the outset in 1962 and throughout my graduate studies there was electron paramagnetic resonance (EPR spectroscopy). EPR was complemented during my postdoctoral training from 1965–1967 by nuclear magnetic resonance (NMR) spectroscopy applied to chemical physics projects, and since the fall of 1967 I have used NMR for studies of biological macromolecules. From there it was a sinuous avenue that led by 1984 to the NMR method for protein structure determination in solution. Our results were occasionally met with doubts and disbelief, so that considerable moral strength and perseverance was at times called for.

During my student years from 1957–1962, NMR spectroscopy was just being introduced as an analytical tool in chemistry, molecular biology was not yet established as an independent discipline, and the initial three-dimensional protein crystal structures at atomic resolution were just emerging. My education at the University of Bern could thus not possibly cover the areas of our current research. The faculty and the student classes in Bern were small in numbers, with three physics students and seven chemistry students starting in 1957. From my curriculum in chemistry, physics and mathematics, I best remember intense work in linear algebra, classical mechanics, chemi-

cal thermodynamics, physical chemistry of synthetic polymers, and preparative biochemistry of proteins and nucleic acids. This combination turned out to be an excellent foundation for my later scientific activities. The last two years of formal education, from 1962 to 1964, were spent at the University of Basel, majoring in sports and getting a Ph.D. in chemistry. Studying sports included about 25 weekly hours of intense physical exercise as well as premedical courses in human anatomy and physiology. Combined with experience gained from observations made on myself in the pursuit of competitive sports, this provided an additional dimension to my education. The subject of my Ph.D. thesis in inorganic chemistry with Professor Silvio Fallab was the catalytic activity of copper compounds in autoxidation reactions, and for this project the availability of a state-of-the-art EPR spectrometer in the Physics Institute was a great opportunity.

Studying natural sciences has always been a lot of fun for me, but nonetheless my mind was quite solidly set on a career as a high school teacher with a heavy involvement in sports. In parallel to my studies in natural sciences, I extensively yielded to what I thought to be my vocation. Thus, during the years 1957–1962, I spent part of each winter as a ski instructor in Swiss mountain resorts. From 1959 to 1965, I had part-time jobs in high schools, first teaching physics at the Kantonsschule Solothurn, then chemistry at the Gymnasium Biel, and finally gymnastics at the Mädchengymnasium in Basel. These teaching assignments also had an important impact on my personal life. In 1961, while on my job as a ski instructor in the resort town of Saanenmöser in the Berner Oberland, I met my wife, Marianne Briner, who at the time was an elementary school teacher. We were married in 1963, and Marianne then joined me in studying sports at the University of Basel, graduating with the 'Eidgenössisches Turn- und Sportlehrerdiplom' and specializing in modern dance. After the graduate student and postdoctoral years we started a family, with our son Bernhard Andrew being born in 1968 in Berkeley Heights, NJ, U.S.A., and our daughter Karin Lynn joining us in 1970 in Greifensee near Zürich, Switzerland.

After finishing my graduate studies I spent another year in Basel concentrating on EPR studies of metal complexes in solution. In the spring of 1965 we moved to the USA, where I joined Professor Robert E. Connick at the University of California, Berkeley, for postdoctoral training. We used NMR spin relaxation measurements of ^{17}O, ^{2}H and ^{1}H in addition to EPR for studies of the hydration of metal

With my wife Marianne, son Bernhard and daughter Karin in front of our apartment building in Greifensee, Switzerland, 1972.

Bob Connick in my office at the ETH Zürich, 1981.

As a postdoctoral fellow in Berkeley, 1966.

With, from left to right, Karin, Marianne and Bernhard in the desert near Tucson, AZ, U.S.A., 1984.

ions and metal complexes. The Berkeley period was devoted to intensive work on the theory of nuclear spin relaxation, group theory and quantum mechanics, which was motivated by Bob Connick's weekly group seminar, a graduate course on 'Group Theory and Quantum Mechanics' by Michael Tinkham, and an intense collaboration with another Swiss postdoc, Alex von Zelewsky, who soon thereafter accepted the chair of inorganic chemistry at the University of Fribourg in Switzerland. Over the years, Marianne and I returned at regular intervals to Berkeley, to renew the friendships of the 1960s and revive fond memories.

In October 1967 I joined the Biophysics Department of Dr Robert G. Shulman at Bell Telephone Laboratories in Murray Hill, New Jersey. I was given responsibility for the maintenance of one of the first

superconducting high resolution NMR spectrometers, which operated at a proton resonance frequency of 220 MHz, and I was otherwise free to use this instrument for 'research on protein structure and function'. Due to my background, my interest was focused on metal centers rather than on polypeptide chains, and all my initial projects in high resolution NMR had to do with hemoproteins. Using blood sampled from my arm in the first aid station, a Japanese colleague at Bell Laboratories, Dr Tetsuo Yamane, prepared 'hemoglobin (KW)', and within a few months we found entirely new avenues of deriving information on structure–function correlations from the NMR spectra of hemoglobin and other hemoproteins. These projects were a lucky choice: With the limited sensitivity and spectral resolution of the instrumentation available in 1968, the special spectral properties of hemoproteins were a great asset for successful NMR applications. Many years later, the unique NMR spectral features that enabled the early work with these metalloproteins had an important role in various aspects of the development of the NMR method for three-dimensional protein structure determination.

In October 1969 I returned to Switzerland to join the ETH Zürich. From the start I was equally well equipped with NMR and EPR instrumentation as previously at Bell Telephone Laboratories, and during the following 32 years the ETH provided us in regular intervals with the most advanced NMR equipment. Until 1975 I was working with a small group of students, a chemical engineer, Rudolf Baumann, who has stayed with me throughout all these years, and a postdoctoral associate with a physics Ph.D. in solid state EPR, Dr Regula Keller, who pursued highly successful research with hemoproteins from 1970 to 1982. In 1973, Gerhard Wagner decided to do his graduate work with me. Gerhard then stayed with the group until 1987, pursuing a classical European academic career with Habilitation before settling as a Professor at Harvard Medical School. Being able to keep outstanding junior scientists as research associates over extended periods of time was a special privilege enjoyed by senior faculty in the traditional 'European system', and the continued presence of Rudolf, Regula and Gerhard during most of my initial 15 years in Zürich was a key factor for success with our research program.

In Zürich, we continued research on hemoproteins with the use of NMR and EPR spectroscopy, where the biochemical work was mostly done by groups outside of the ETH who joined us for collaborative projects, and the spectroscopic work was done by Regula Keller, myself and a succession of graduate students. In addition, we started a program of systematic studies on the application of NMR techniques with polypeptides and small proteins. Spirits were kept high by successful studies of cyclic peptides in collaboration with the Head of the Institute of Molecular Biology and Biophysics, Prof. Robert Schwyzer, the observation of unexpectedly well-resolved and long-lived NMR lines of amide protons in the small protein basic pancreatic trypsin inhibitor (BPTI), and the discovery of 'ring flips' in BPTI. On the main line of research, which should lead to a method for protein structure determination in solution, there was only little progress. In 1975, in an attempt to survey the state of the field of NMR spectroscopy with biological macromolecules, I wrote the monograph *NMR in Biological Research: Peptides and Proteins.* There were two principal conclusions from this venture that should greatly affect the continuation of our work plan. First, I fully realized that we had been extremely fortunate in choosing hemoproteins as a focus for our early NMR efforts. Second, it became clear that attempts of the early 1970s to derive *de novo* three-dimensional protein structures from conformation-dependent proton chemical shifts was not a promising approach, independent of whether these shifts were caused by intrinsic or extrinsic diamagnetic or paramagnetic probes. We thus had to look for novel avenues for NMR structure determination, where hemoproteins with their unique NMR-spectral properties could be an ideal testing ground for new ideas.

Shortly after I had learned my lessons from writing the 1976 monograph, the conditions under which I could pursue my work evolved in quite important ways. After working for more than 5 years with a small group of students and research associates from the environs of Zürich, and being able to spend long hours of my own time at the bench and on the NMR spectrometers, I found myself suddenly surrounded by more than 20 postdoctoral fellows and students from all over the world. At around the same time, I also started to travel quite extensively in all parts of the world, with a first visit to India at the end of 1974, and a first 'round-the-world' trip including stops in the U.S.A. and in Japan in the fall of 1975. The visits to India and Japan resulted in new, lasting friendships with local colleagues, and also in attracting a number of most talented postdoctoral fellows to Zürich. Ever since, professional travel has become an important part of my activities. Over the years this also included

The President and the Secretary General of IUPAB with their wives during a diplomatic mission in China, 1983. President Professor Richard Keynes and Ann Keynes are on the left and right, respectively.

visiting faculty appointments at the University of California, Berkeley, Cornell University in Ithaca, NY, Johns Hopkins University in Baltimore, MD, the California Institute of Technology in Pasadena, CA, the Scripps Research Institute in La Jolla, CA, RIKEN in Tokyo, Japan, and the University of Edinburgh, U.K. Spending part of my time in these places of highest standards added greatly to my quality of life as well as to the progress of our research in Zürich.

The international aspect of my activities got a special boost in 1975, when – out of the blue – I was elected to membership in the Council of the International Union of Pure and Applied Biophysics (IUPAB). There was little work involved in this assignment, but in 1978 my IUPAB affiliation changed to being its Secretary General, and with this I also became a member of the 'General Committee' of the International Council of Scientific Unions (ICSU) and of the ICSU Standing Committee on the Free Circulation of Scientists. During the six-year term as Secretary General the demands on my time were thus quite heavy. Fortunately, Marianne agreed to run the IUPAB office. This made things easier, since she would travel with me and we dealt with the IUPAB business in makeshift offices temporarily installed in hotels all around the world. The sunny side was that I got to know many prominent scientists, whose names I had previously mostly known from the textbooks. For example, structural biology was represented in the IUPAB Council from 1978–1981 by Britton Chance, Henryk Eisenberg, David Phillips, Frederic Richards and Akiyoshi Wada, a true center of excellence! In the business meetings as well as in the social gatherings, we spent much of our time discussing the latest research advances long before they appeared in print. There was a particularly close collaboration with the IUPAB Presidents during my tenure as Secretary General, Professor Setsuro Ebashi and Professor Richard Keynes. Richard Keynes is a great-grandson of Charles Darwin. During IUPAB-related joint travel in Europe and the Far East in 1982/83, I listened to a more and more enjoyable but seemingly endless series of presentations of his 'Darwin Lecture' commemorating the 100th anniversary of Darwin's death; in return, Richard lived through a heavy dose of biomolecular NMR spectroscopy.

Through my association with ICSU and IUPAB, I also got involved in entirely novel business. Most notable in hindsight were negotiations during the period 1980–1983 about joint adherence of China and Taiwan in international science organizations. We eventually defined terms and conditions for adherence to IUPAB of both 'The Biophysical Society of China located in Beijing, China' and 'The Chinese Biophysical Society located in Taipei, China'. This involved extensive, highly formal correspondence, as well as visits and

At dinner during an ICSU General Committee meeting in Munich, Germany, 1985. To my left is Professor Jorge Allende from Chile, to my right is Professor Raymondo Villegas from Venezuela.

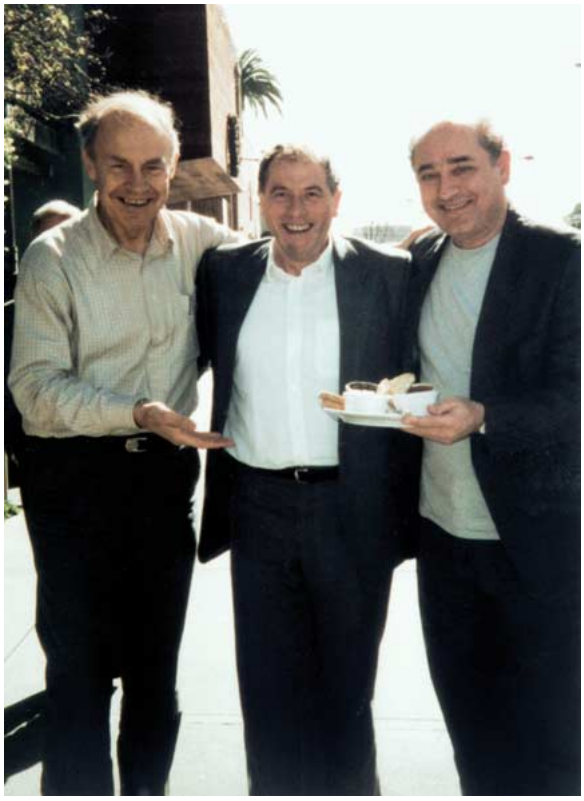
Addressing the audience during the opening session of an IUPAB/ICSU/UNESCO-sponsored 'Winter School on Magnetic Resonance in Biology and Medicine' in Cairo, Egypt, 1986. To my left is Professor I. El Gohari, who has over the years been the Egyptian delegate to numerous IUPAB functions.

With Professor Chen-Lu Tsou, enjoying the beautiful scenery of Wuxi, China, during an IUPAB/ICSU-sponsored Summer School on Biophysics, 1992.

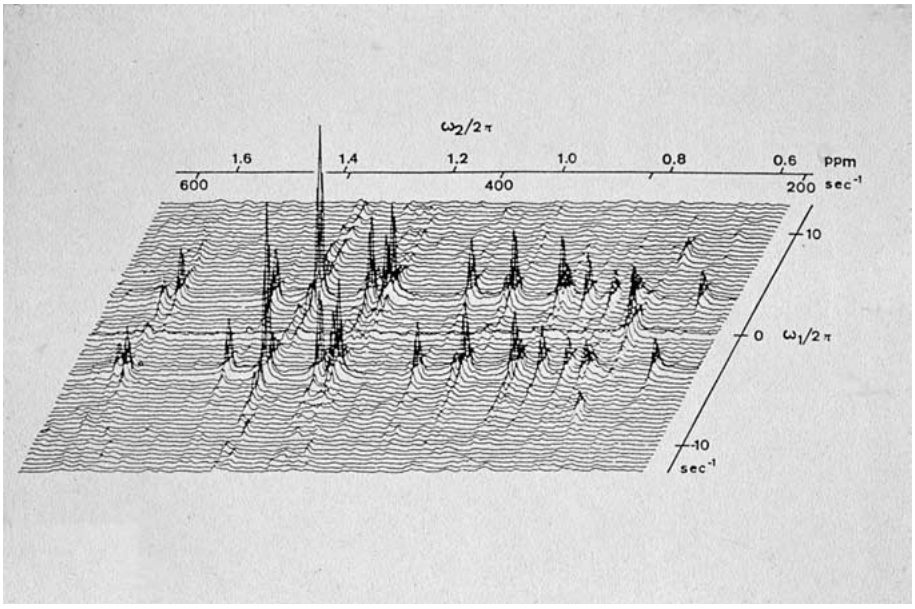
A dinner party during a visit with Professor Setsuro Ebashi (second from the right) in Okasaki, Japan, 1996. Mrs Ebashi is next to Marianne, and Kuniaki Nagayama, who started 2D NMR with proteins as a postdoctoral fellow with Richard Ernst and myself in the late 1970s, is on the left wing.

personal negotiations with Government and Academy officials in both countries. I also participated in IUPAB and ICSU programs of support for scientists in developing countries, and I organized summer schools and symposia in Africa, the Far East and Latin America. This all greatly influenced my outlook to the world. Although each year the IUPAB-related activities and my research-related travel kept me out of my laboratory for several months, the effect on our research was overall highly beneficial. As a bonus, I gained experience in directing a research group at a distance, and my junior associates could test their own initiatives during my absences.

With all the new talent assembled in my group by 1976, we started to develop new NMR experiments and novel algorithms for the structural interpretation of NMR data, which eventually resulted in the NMR method for protein structure determination. This included the identification of the nuclear Overhauser effect (NOE) as a NMR parameter that can be related in an unambiguous way to three-dimensional macromolecular structures. We made use of the outstanding resolution of parts of the hemoprotein NMR spectra for calibrating NOE distance measurements with the then-available one-dimensional (1D) NMR techniques. In addition to Regula Keller, Sidney Gordon, a sabbatical visitor, made a key contribution with the introduction of the 1D 'transient NOE' experiment. Subsequently, the NOE had a key role in the approach used



Visiting the University of California, Berkeley, 1997. Dudley Herschbach happened to visit on the same day. Lunch at 'Chez Panisse' was running late, so our host, Alex Pines, carried the desserts along to the seminar room.



The first two-dimensional proton NMR-spectrum of a protein, recorded by Kuniaki Nagayama, 1997.

Tim Havel and Mike Williamson in front of a computer displaying the three-dimensional structure of the protein BUSI that we had just solved, 1984.

for obtaining sequence-specific assignments of the many hundred to several thousand NMR lines in a protein. The 'sequential assignment strategy' was initially implemented by Gerhard Wagner and a diploma student, Andreas Dubs, using 1D NOE and spin decoupling experiments. In parallel with the 1D NMR investigations on NOEs and NMR assignment, 'a 2D J-resolved spectrum' development of two-dimensional (2D) NMR techniques for macromolecular studies had been started in 1976 as a joint project with Professor Richard R. Ernst (Nobel prize in chemistry 1991). In 1977 the first 2D NMR spectrum of a protein was recorded, and by 1980 we had assembled four 2D NMR experiments that provided for the initial protein structure determinations: COSY (2D correlated spectroscopy), SECSY (2D spin-echo correlated spectroscopy), FOCSY (2D foldover-corrected correlated spectroscopy) and NOESY (2D nuclear Overhauser enhancement spectroscopy). It was a lot of fun at the time to decide on these acronyms! Soon my group started to use 2D NMR experiments in daily practice, and the experience from more than a decade of one-dimensional NMR spectroscopy with proteins was happily and profitably married with the new potentialities of 2D NMR.

By 1982, complete sequence-specific assignments had been obtained for a small protein, BPTI, and for the polypeptide hormone glucagon bound to lipid micelles. This was published in a series of four 1982 papers. Although the first one of these papers already outlines the presently used protocol for protein structure determination by NMR, it took two more years of intense work on metric matrix distance geometry algorithms and their implementation in efficient software packages before the first NMR structure determination of a globular protein, bull seminal protease inhibitor (BUSI), could be completed. A large number of brilliant junior scientists working in my group from 1976 to 1985 contributed directly or indirectly to this result: Gerhard Wagner was involved in each step of the project; Kuniaki Nagayama and Peter Bachmann devised the first generation of 2D NMR experiments for studies of biological macromolecules and wrote the software needed to handle such data with the then-available limited computational facilities; Anil Kumar recorded the first 2D NOESY experiment with a protein; Gerhard Wider made key contributions to 2D NMR spectroscopy and to the sequential assignment method; Werner Braun, Martin Billeter and Timothy Havel started a tradition in my laboratory of theoretical work on the structural interpretation of NMR data; Peter Strop prepared BUSI and worked on its resonance assignments; finally, Michael Williamson and Timothy Havel actually solved the structure of BUSI. They all, and many additional students and postdoctoral associates from the 'heroic period' 1976–1985 have in the meantime started highly successful independent academic careers.

View from my office in our home in Wengen, Switzerland, during my first-ever sabbatical, 1984–1986.

The completion of the first NMR structure of a protein brought new, unexpected challenges. When I presented the structure of BUSI in some lectures in the spring of 1984, the reaction was one of disbelief and suggestions that our structure must have been modeled after the crystal structure of a homologous protein. Apparently the structural biology community had thoroughly adjusted to the role of NMR as a method that could provide some exotic supplementary data, but which would not be suitable for *de novo* structure determination at atomic resolution. The criticism raised had two major consequences. The first one resulted from a discussion with Robert Huber (Nobel prize in Chemistry, 1988), after a seminar in Munich, on May 14, 1984. Robert proposed to settle the matter by independently solving a new protein structure in his laboratory by X-ray crystallography and in my laboratory by NMR. For this purpose, each one of us received an ample supply of the α-amylase inhibitor Tendamistat from Hoechst AG. Virtually identical three-dimensional structures of Tendamistat were obtained by NMR in solution and by X-ray diffraction in single crystals, which settled matters once and for all. This was particularly comforting in the context of the fact that the subsequently solved NMR structure of metallothionein was completely different from an independently solved metallothionein crystal structure (it took six years before the crystal structure was redetermined and found to coincide with the NMR structure!). The second consequence was that I asked for a sabbatical leave and ended up in Wengen, a beautiful mountain resort in the Berner Oberland. This was possible because I was also finishing my 6-year term as the Secretary General of IUPAB in the summer of 1984. Considering the critical reaction to the initial NMR structure determinations, I felt that it was important to document our work in a complete and detailed fashion. I thus had good reasons to honor my commitment of writing a monograph on the Baker Lectures, which I had delivered in 1983 at Cornell University. As I spent much of the time alone in Wengen, with my family joining me for weekends and vacation periods, work progressed well. 'NMR of Proteins and Nucleic Acids' covers primarily work in my research group during the period 1977–1984. It also turned out that directing my research group at a distance was surprisingly successful, and since the manuscripts were typed in Zürich from my handwritten notes, it helped that even ordinary mail was still reliably delivered within one day within Switzerland. It was therefore an easy decision for me to extend the stay in Wengen from the originally planned 6 months to 18 months. Besides the deskwork, important occupations in Wengen were skiing in the winter, and jogging and mountain climbing in the summer. According to my diaries I did not miss a single day of skiing from December 1, 1984 to April 10, 1985. This made up for having stayed away from the ski slopes during the 14 years from 1971 to

1984 because of my other professional activities. I also returned to the skiing outstation of the Federal Sports School in Mürren for a much-needed overhaul of my skiing technique, and participated in the organization of the famous Lauberhorn ski race in Wengen.

In the spring of 1986, after a second winter of skiing in Wengen, I had thoroughly cleaned up the backlog of unpublished material, in addition to having finished work on the Baker Lectures monograph. Protein structure determination by NMR had by then found its believers, as documented by the fact that the first printing of my new book was sold out within a few weeks. For us a new chapter had to be opened, and we established contacts with biochemists and molecular biologists for the real test of the NMR technique in applications to biologically interesting systems. By 1990, a collaboration with Professor Walter Gehring of the Biocenter at the University of Basel yielded structure determinations of the *Antennapedia* homeodomain and its complex with the operator DNA. Using this structure as a platform, additional NMR experiments provided entirely novel insights into the role of hydration water for specific DNA recognition. A NMR structure determination of the cyclophilin A–cyclosporin A complex was pursued as a joint project with two former graduate students, Hans Senn and Hans Widmer, and their research team at Sandoz AG. It had immediate practical impact, since the structure of the bound immunosuppressant turned out to be very different from the only other structural information available at the time, i.e., crystal and NMR structures of free cyclosporin A. It was, for all involved, a completely unexpected and for many reasons surprising result! In yet another exciting collaboration, with Professor Rudi Glockshuber at the ETH Zürich, we completed a structure determination for the C-terminal half of the mouse prion protein in April 1996, barely 10 days after the BSE-crisis in Great Britain broke into the open. With this timing, the prion protein structure had high visibility also in the popular media. In 1997 we succeeded to characterize the structure of the intact prion protein, and found that the N-terminal half of the molecule forms a highly flexible, extended 'tail'. The prion protein thus presented a striking illustration of the unique power of NMR to characterize partially structured polypeptide chains. Others among the more than 70 protein structure determinations completed in my laboratory functionally relate to enzymology, toxicology, chaperone-mediated protein folding, and intercellular signaling.

The biological and biomedical projects pursued during the past 16 years with the use of the NMR technique have added and still add greatly to the quality of my professional life. In these endeavors, the quite extreme specialization needed to maintain a high standard of structure determination breaks open in that I learn about an ever-increasing range of biological systems and biomedical problems. I feel very fortunate that my field of specialization thus leads me to an education in biology from people who have high standards, and who sometimes even tend to consider me as one of their own.