Gottfried Otting outside the Australian Research Council-funded 800 MHz NMR facility at the Australian National University.

Science is international: the best research institutes recruit members without regard to nationality, and scientists may have to move to do the best research. Moving also widens the horizon, as Gottfried Otting discovers.

Travels with Nuclear Magnetic Resonance

Adventures in Chemistry – Heidelberg

As a chemistry undergraduate in Heidelberg, Germany, I was given the task to synthesise KS_2. The recipe was simple: heat potassium metal with sulfur in a 1:2 ratio in an inert solvent. So I set off to the chemical store with a beaker and asked the storekeepers for a few grams of potassium, together with "some protecting liquid." With just one year of inorganic chemistry under my belt, organic chemistry was still mysterious to me. I knew that storing potassium under oil prevents oxidation, but the storekeepers were equally uncertain about the identity of the oil. "Just give him some petrol ether," one of them suggested, and off I went with my beaker containing a solid piece of potassium and a bottle of petrol ether. Back at the lab bench, I covered the potassium in the beaker with the petrol ether and started to cut the oxidised surfaces off the metal. Strangely, gas bubbles started rising from the potassium, faster and faster, until – whoosh, the beaker was alight! A flame 30 cm tall. What should I do? I took a deep breath and blew hard. This put out the flame. Lucky! But what next? I suspected that the fire could start again any time.

It ended with a broken beaker, a sizeable fire on the floor and a lab assistant extinguishing the fire. I spare the reader the details – they are embarrassing. Only later I learnt that petrol ether, unless specially dried, contains sufficient humidity to react with potassium, generating hydrogen. All would have been quite safe, had I only waited for the gas evolution to settle down. When I told the storekeepers the story, they thought it was really funny!

The tale illustrates how the chemistry curriculum in Heidelberg aimed at training independent, practically experienced chemists. It was a long and hard study. Over three-quarters of the full-time students starting in chemistry would drop out before the midterm ("Vordiplom"). I soon realised that my strengths were more in physics and physical chemistry than in chemical synthesis. I was also itching to leave home.

Choices and Chances - Freiburg

I went to the University of Freiburg in Breisgau after the Vordiplom. The mass spectrometrist there didn't offer a student project, so I joined Dr H.-H. Limbach's lab. He was an NMR spectroscopist in the Department of Physical Chemistry. I would go on to do my Honours ("Diplom") year in his lab too. Since he was on sabbatical that year, I also asked Professor Zimmermann (the head of department) about a project in electron paramagnetic resonance (EPR), but he advised me to stick with NMR and Dr Limbach. I was left alone to synthesise an ^{15}N-labelled compound that seemed easy to make, but was sensitive to water and obstinately difficult to purify. I ended up spending most of my Honours struggling with this compound. If synthesis was so hard, wouldn't it be wiser to try and improve technology? Computers were becoming accessible, NMR and mass spec were advancing. Don't Nobel Prizes favour new techniques?

A friend of mine had subscribed to the *Scientific American*, which he greatly enjoyed reading. One day, he was accidentally sent two identical copies. He gave one of them to me. It was difficult reading, but a short notice caught my eye. It said that Professor Kurt Wüthrich at the Swiss Federal Institute of Technology (ETH) in Zürich was using two-dimensional NMR spectroscopy to determine the three-dimensional structure of proteins. It said that the hydrogens of several proteins had already been mapped.

In 1984, less than two hundred protein structures had been determined by X-ray crystallography. An alternative method for protein structure determination seemed very interesting indeed! I read Wüthrich's book, *NMR in Biological Research*. A colleague of mine referred to the ETH in Zürich as "the best technical university in Europe." I paid Wüthrich a visit in Zürich. I also spoke to a former PhD student of his, who was very positive. In addition, there was an NMR spectrometer with the highest magnetic field available at the time (500 MHz), five-fold higher than what I had access to in Freiburg! Wüthrich agreed to take me as a PhD student based on my performance as an undergraduate student.

When I told my supervisor that I was going to leave, he was very disappointed, not only because I was leaving, but also because of my choice. "If you want to go to Zürich, you could at least have gone to Richard Ernst!" I was only a student. I had no idea who Ernst was. He would win the Nobel Prize in Chemistry in 1991 for methodology developments in NMR.

The Privilege of Being a PhD Student in Zürich

My time as a PhD student was the best time of my career. The laboratory in Zürich was brimming with outstanding postdocs from all over the world, including the US, Canada and England. There were often professors visiting on sabbatical. Many of the postdocs would later advance to professorships in their home countries. The language in the lab was English and the Swiss were in the minority.

The projects were exciting. The postdoc who had determined the first protein structure ever by NMR had only just left when I arrived. New NMR techniques were developed in collaboration with Professor Ernst's group, but also in Professor Wüthrich's group. The lab had stand-alone computers for processing. A PhD student had developed graphics software to display protein structures. Funding never was an issue. Technical staff was there to help with the spectrometers, the computing, and the drawing of figures. My colleagues were fun and it was wonderful.

As a PhD project, I was offered either to express and purify a protein for NMR or to continue with a protein structure determination project left behind by a previous postdoc. With my mixed experience in synthetic chemistry, I chose the structure determination project. Soon after my arrival, Professor Wüthrich started to work on his second book, which appeared in 1986. Much of the writing he did in a chalet in the Swiss Alps. I was lucky that he was absent, because my project wasn't going so well. The NMR spectra of my protein weren't good enough to determine the structure. I couldn't even reproduce the previously published assignments. I needed to get better spectra and started by trying to understand the fundamentals of NMR.

Once a month, all of us had to produce progress reports. In my spare time, I had continued the development of a Danish program for analytical product operator calculations. If nothing else, it gave me a thorough understanding of two-dimensional NMR experiments in terms of the product operator formalism recently published by the Ernst group. I found that my protein yielded a few new peaks in a double-quantum spectrum. When I put this in my report, Professor Wüthrich didn't look too pleased, but nonetheless told me to write it up in a manuscript. I continued not making much progress with my protein. Instead, I developed further technical improvements to NMR spectroscopy that were useful to the lab. Later, a different laboratory sent a purer protein sample, I could correct the original assignments, and the structure was determined by Professor Steinmetz during one of his sabbaticals in Zürich.

Two-and-a-half years into my PhD, Professor Wüthrich suggested that I write my thesis and stay on afterwards. I hadn't thought about the future and took the opportunity. There was little advantage in doing a postdoc overseas, as the world came to this lab. My wife-to-be was one of the visitors. She came from Australia to visit her postdoc sister.

Professor in Stockholm

Four years after my PhD, I was headhunted by Professor Rigler from the Karolinska Institute in Stockholm, Sweden, for a chair in Molecular Biophysics. I wasn't so keen, but Professor Wüthrich encouraged me to put my hat in the ring. When I was offered the position, I started to negotiate: I would bring two of my colleagues from Zürich, I wanted two technical staff, two PhD students and computer equipment. The Karolinska granted it all. Funding for a high-field instrument (600 MHz) was already in place. I couldn't say no.

For the first one-and-a-half years, I lived at the Wenner-Gren Centre. This is a futuristic ring of apartments built for visiting scientists located in the centre of the triangle formed by Stockholm University, the Technical University and the Karolinska. The Wenner-Gren Centre is a fantastic invention. Scientists come with their families from all over the world, but are allowed to stay for no longer than two years. Kids and parents mingle in the courtyard. It's a vibrant community, where newcomers get an easy introduction into the peculiarities of daily life in a new country. Countless lasting friendships and scientific contacts have been forged there.

The King of Sweden and I: Wallmarkska Prize of the Swedish Academy of Sciences, 1996.

The Karolinska Institute elects the Nobel Prize winners for medicine. The Nobel Prize plays a very big role for the institute. Nobel hopefuls are always willing to give seminars at the Karolinska, resulting in a mind-blowing seminar program. Members of the Nobel committee collaborate with the best laboratories of the world. Local advisory boards are easily manned with the world's top experts. The benefits are priceless.

I had been naïve, assuming that all the promised positions would be tied to my chair, as it used to be in Switzerland and Germany. Soon after my arrival, however, I was told that most of the funding was only start-up funding. "Don't worry. The reputation of the Karolinska is second to none. It will be easy to attract external funding later on," I was told. It turned out to be different. Sweden may be leading the world in R&D funding as percentage of GDP, but this is not reflected in the grants available to university researchers. The department adopted a funding formula where research activity was measured by number of publications multiplied by impact factor. The formula required the equivalent of one *Nature* paper every year to win the salary for one PhD student. Einstein wouldn't have done well in this system... I spent many sleepless nights worrying about finances and submitted grant applications wherever I could. I started to look for a job elsewhere.

Collaborations are fun and broaden the horizon. In Stockholm, I profited greatly from collaborations with outstanding Eastern European scientists, in particular my long-standing friend Edvards Liepinsh, now professor in Riga, Latvia. Nicholas E. Dixon from the Australian National University (ANU), now professor at the University of Wollongong, became an especially important collaborator. He visited Stockholm and it was he who urged me to apply for a Federation Fellowship at the ANU. I was tired of writing grant proposals and wrote this one only because he insisted.

Housewarming: the Canberra bushfires in 2003 went through our backyard three weeks after moving in.

Professor at the ANU

The phone call from the Australian Research Council (ARC) CEO, Professor Vicki Sara, in 2002 was as exciting for me as the famous phone call from Stockholm must be for others. We moved, with two children born in Sweden, to Canberra after exactly ten years in Stockholm.

Only after having been at the ANU for some time, I began to realise what a fantastic and unique place it is in the context of the Australian university system and, indeed, internationally. Not many places live and breathe academic scholarship like the ANU. No other university I have been at has a similar spirit of collegiality. I regret that I wasn't at the ANU in the earlier days, when it was still free of the constraints of the triennial funding cycle, leaving room for big projects that take more time.

With the help of ARC funding and excellent collaborations in Australia, my research has gained in focus. I have a wonderful group and the projects are as exciting as never before. I believe that we are now in a position to turn NMR spectroscopy into one of the best techniques in early phase drug discovery, with significant benefits for pharmaceutical research.

What's in a Name?

Which discipline does NMR belong to? In Freiburg, I was a physical chemist. In Zürich, I was in the Department of Molecular Biology and Biophysics. In Sweden, I was professor of molecular biophysics in the Department of Medical Biochemistry and Biophysics. At the ANU, I am sailing under the flag of biological chemistry. I view myself as a structural biologist. As an interdisciplinary subject, structural biology has roots in chemistry, physics and biology, but is not at the core of any of these classical disciplines. It is important to recognise that the name of a department does not necessarily define the research going on within its walls.

Take-Home Message

What take-home message is there for graduate students? Picking a supervisor who went on to win a Nobel Prize proved to be a very lucky moment for me! (Kurt Wüthrich won a Nobel Prize in chemistry in 2002 for the development of NMR for 3D structure determinations of biological macromolecules in solution.) Mobility helps. I am sure that far fewer opportunities would have come my way if I had stayed in my home town. Not to speak of the exhilarating feeling to find oneself at the epicentre of groundbreaking research! Over 20 years after the first protein structure determination by NMR spectroscopy, we still have our hands full with new NMR developments.

The 800 MHz magnet is one of Australia's highest field NMR systems.