

Six Sorcerers & One Apprentice

This is the story of six top scientists who were kind enough to guide me, as a complete newcomer, in learning the tricky business of unstructured research. I had been unable to find any accepted do-it-yourself manual that could be of any practical use to someone setting out on a research career. I read a book by Bright Wilson, but it did not offer any deep insight into the *philosophy* I was looking for. The arcane art of the pure researcher must be passed down from established experts - the giants in their field. Luck was on my side, for I found some remarkable men at the top of their game; what follows is an account of how, in their different ways, each one gave me a much-needed helping hand. How I came to work with them is largely covered in the story "*As Luck Would Have It*". There it will be clear that I had little choice in the matter, apart from recognising true leaders when I found them. So here is my personal list of six great sorcerers: Rex Richards, Anatole Abragam, Robert Pound, Ionel Solomon, Martin Packard, and Wes Anderson.

Sir Rex Richards FRS - Fellow and Tutor in chemistry at Lincoln College, Oxford in the 1950s.

Rex Richards was one of the very first to appreciate that the newly discovered phenomenon called nuclear magnetic resonance could have unexpected applications in chemistry. Against all the odds, he set out to build his own NMR spectrometer from scratch, despite the perceived wisdom that heavy magnets and masses of electronics had no place in a chemistry laboratory. Rex was an ideal tutor for undergraduates, a charismatic lecturer in physical chemistry, and an excellent research supervisor, so my fate as an NMR spectroscopist was sealed at an early age.

War surplus radar equipment featured heavily in this enterprising radiofrequency project, and I was lucky enough to have followed a radar course in the RAF. Indeed 90% of my doctoral research was devoted to building electronics for the excitation, detection and measurement of the resonant frequencies of the arcane nuclei lithium, cobalt, gallium, indium and thallium. Much of this work was purely exploratory, but it was Rex who suggested that the NMR spectra of aqueous solutions of cobalt-III complexes would have important implications for Ramsey's theory of the chemical shift, because the cobalt atom has a low-lying electronic state that dominates the calculation of the nuclear shielding, and which also gives rise to the colour of these complexes. This interpretation was confirmed by measuring the NMR frequencies and comparing them with the visible/ultraviolet *wavelengths* for symmetrical cobalt complexes. The result was a straight-line graph that confirmed that the reciprocal of the appropriate electronic energy gap was the dominant parameter determining the cobalt chemical shifts. It seemed that NMR did have some useful applications in chemistry after all.

I learned a great deal by simply observing Rex in action - teaching by osmosis. Rex clearly understood the importance of a "hands off" style of supervising research. A neophyte student was allowed the chance to shrug off the doctrine (inherited from the undergraduate courses) that there is always a correct, prescribed way to attack a scientific problem. For the very first time, one could use one's own initiative and perhaps discover new things for oneself. Trial and error, with a large dose of the latter. I

suppose it was inevitable that, many years later, I adopted a similar *laissez-faire* approach to supervising my own students. As an analogy, I am reminded of an almost surreal episode recounted by our youngest daughter Louise. One day, on a visit to Magdalen College, she was passing the old squash courts when "it started to rain ducklings". Together with another girl, Louise tried to catch these fluffy little balls before they hit the hard ground. The ivy-covered walls of the squash courts must have been over 15 feet high, but Mama duck had decided that the time had come to ease the ducklings out of the nest so that they could find their own way to the river Cherwell and learn to fend for themselves. Darwin would have been very pleased. I found that my own research students seemed to fall neatly into two distinct groups (a) highly motivated ones who would have been seriously hindered by any micro-management, and (b) others who were not really interested and who would soon graduate to careers outside of chemistry. In this aspect the Oxford Part II (research) year has proved to be a valuable exercise to help young students make a choice about their future career.

In retrospect I realize that in the background Rex had been quietly guiding my career. In a sense he was a father figure to me, for I had lost my own father in 1940. Rex was instrumental in arranging my next position at a renowned magnetic resonance laboratory in France, in the belief that immersion in an environment of physicists would be a good idea. Better than I, he understood what my future *métier* should be. In a sense we are both *physiciens manqués*, rather than chemists. So in the summer of 1957 I went to work as a *stagiaire* at Saclay. As a wise precaution I took some evening classes in Oxford in colloquial French.

Professor Anatole Abragam, *Chef, Service de la Physique des Solides et de Résonance Magnétique, Centre d'Etudes Nucléaires de Saclay, France.*

The incredible intellect of Anatole Abragam was evident to everyone who met him. His comprehensive notes on magnetic resonance were already the stuff of legend. At that time, they took the form of two paperback volumes, written in French, and no longer obtainable in bookshops owing to the enormous demand. He was busy converting this material into his new book "Principles of Magnetic Resonance" published in English in 1961 by the Oxford University Press. Naturally the focus was largely on the physical aspects of magnetic resonance, for the great surge in chemical applications had yet to take place. This immense work soon became the "Bible" for magnetic resonance aficionados. Many ideas for new experiments can now be traced back to almost passing remarks in that book, but one has to admit, it was never an easy read. Anatole had spent a year in the Clarendon Laboratory, and he held Oxford in high esteem. Perhaps that is one reason that he took the trouble to find me a slot in his group. To visitors he liked to joke that he kept me there simply to calibrate his English, but I am pretty sure that he was making a play on the word *étalon* (a calibration standard) because this also translates as stallion.

For someone like myself, trained as a chemist, the sudden immersion in a cold bath of pure physics at Saclay felt like another relentless application of Darwin's prescription for survival of the fittest. The physicists at Saclay were trained in the rigorous mathematical formalism characteristic of the French higher education system (particularly *l'Ecole Polytechnique* and *l'Ecole Normale Supérieure*). This stood in sharp

contrast to the Oxford emphasis on a practical "nuts and bolts" approach to research. One is reminded of the unashamedly *practical* steam engine invented in Britain, whereas the key theories of thermodynamics that flowed from analysis of heat engines were developed in France. Here is one example of this cultural divide. Anatole Abragam was amazed to see a young Oxford chemist using a lathe to fashion an NMR probe - cutting a screw thread on the inside of a hollow Perspex cylinder with the intention of maximizing the filling factor of the radiofrequency coil. By contrast, the French physicists tended to delegate any such mechanical work to the support technicians, tacitly accepting any limitations of this second-hand solution. A chemist seeks pictorial descriptions of physical phenomena whenever possible; the physicist looks for mathematical rigour. Sometimes I found my colleagues dangerously overconfident in their blackboard calculations; once they were quite surprised when I challenged a computation that concluded that the concentration of a particular component in solution was 210 Molar!

At that time the Overhauser effect was a fairly new concept; indeed at first the acknowledged experts in magnetic resonance found it very hard to accept Overhauser's predictions. As I was trying to understand this rather surprising phenomenon, a Saclay colleague told me "Oh, you just have to write down the equations". This is of course true, but I believe that simple every-day ideas can offer valuable insight into the Overhauser effect (see for example the ski analogy set out in "*A Handbook of NMR*" page 143). A mathematical equation is just a shorthand representation of reality; we should always bear in mind that every variable carries a physical meaning. My own experience has been that physical intuition is often more productive than mathematical formalism for finding new experiments in spin choreography. On the other hand, our Oxford group did come across one marked exception to this belief. During a routine density matrix calculation, Tom Mareci observed that the conversion of double-quantum coherence into an observable NMR signal is best carried out by setting the pulse flip angle to 135° (instead of the traditional 90°) since this allows the determination of the signs of the double-quantum frequencies. My two years at Saclay certainly taught me the importance of the rigorous theoretical approach, but I still harbour the suspicion that scientific breakthroughs are more often triggered by insights gleaned from pictorial "hand waving" visualizations. Of course intuition can sometimes mislead, but then this quickly focuses one's attention on the unexpected counter-intuitive finding, and the resolution of this conflict can be rewarding.

At that time the key project in Abragam's group was to use all kinds of clever tricks to align the nuclei in a solid sample at very low temperature in order to prepare a polarized target for the particle physicists to bombard. After many years of really hard work they gradually achieved a degree of polarization approaching 100%, a *tour de force* that perhaps never received the full recognition that it deserved. Here lies the dichotomy - should one seek for the quick *eureka* moment, or work towards an important long-term goal? Watson and Crick managed the enviable trick of successfully combining both. Abragam himself commented that although there were many brilliant Frenchmen in scientific research, it appeared to be the Anglo-Saxons (Americans and British) who took the lion's share of Nobel prizes. An unfortunate obsession with the purely theoretical approach perhaps?

Some years after I left Saclay, Abragam asked me to translate his book "*Réflexions d'un*

Physicien" into English. His own command of English was excellent, so I could only assume that he was too busy with more important matters to undertake the translation himself. The book in question consisted of a compilation of short articles and some letters that he had written at various times. He told me that he would leave the details entirely to me, but he omitted to say that one or two sections had originally been written in English and later translated into French, leaving open the possibility that Anatole could have a laugh by comparing the English originals with my translations. This was my first foray into preparing an actual book, and it served as a useful dry-run when I set out to write a book of my own.

Robert Pound, Professor of Physics, Harvard University, USA

By a fortunate turn of fate, Robert Pound was taking a sabbatical at Saclay during the academic year 1957-58, and he took me under his wing. Bob had been part of the prestigious Radiation Laboratory during the war and he retained an active interest in all things electronic, particularly those related to radar. Among magnetic resonance spectroscopists he was perhaps best known at that time for his "Pound spectrometer", a regenerative oscillator/detector that allowed one to scan large radiofrequency ranges in search of weak "unknown" NMR frequencies, without the need for high-gain amplification. Yet physically the device was very simple - a mere double-triode vacuum tube. I had built a copy of this "Pound box" for my doctoral research at Oxford. Naturally I was delighted at the idea of working with one of the real pioneers of NMR, a key figure in the Harvard research group (Purcell, Torrey and Pound) that shared a Nobel Prize in physics in 1952 with the Stanford group (Bloch, Hansen and Packard).

Realizing that I was interested in high-resolution NMR applied to chemistry, Bob suggested I should work on a project involving two of his untried ideas. The first was a novel concept to employ weak modulation sidebands (rather than the main radiofrequency transmitter) to detect the NMR signals. He suggested that in this manner we should be able to use the very simple Pound spectrometer as the detector. Although this marginal oscillator device operates at such a high radiofrequency level that normally it would completely saturate high-resolution NMR signals, the use of modulation sidebands of low modulation index would circumvent this drawback. The Pound-Watkins spectrometer was versatile because it had a wide operating frequency range and required no high-gain intermediate-frequency amplifiers. Incidentally we worked from some primitive photocopies of Watkins' doctoral thesis, kept in a vice because otherwise the pages curled up and became unreadable.

I built the radiofrequency parts of this new high-resolution spectrometer from scratch, including that notoriously tricky item - the probe. A radiofrequency probe is very sensitive to field distortion from trace inclusions of paramagnetic material, such as tiny particles of iron (one prescription was to boil in hydrochloric acid all the plastics that had been machined). Furthermore the magnet that I borrowed was not intended for high-resolution work, so the available field uniformity was unknown. Consequently I was disappointed (but not terribly surprised) to discover that all the resonance lines that I recorded were broad (about 200 Hz) whereas we were aiming at a resolution of a fraction of 1 Hz. Once I had eliminated all the practical problems of materials that made up the probe, I began to wonder whether the regenerative feature of the Pound

spectrometer might be the culprit, enhancing the broadening by radiation damping. Now the key paper on radiation damping was that of Bloembergen and Pound, so it was with some trepidation that I suggested to Bob that this might prove to be the Achilles heel of his device. By this time, Bob had returned to Harvard and was incredibly busy on a brilliant new experiment to measure Einstein's gravitational red shift (Pound and Rebka). However, after a flurry of transatlantic letters I eventually convinced him that radiation damping was indeed the problem, so I replaced the Pound spectrometer with a conventional transmitter and all was well again. With the misplaced excitement of youth I was thinking of writing a brief communication to warn about radiation damping in regenerative oscillators, when a casual visitor to Saclay pointed out that Lösche's group in Leipzig had already analyzed this problem in an East German scientific journal that we had all overlooked. Take home message for beginners: if all else fails, read the literature.

Bob's second idea involved a super-regenerative oscillator, essentially a pulse-modulated Pound box with the feedback turned up very high. He had already used this machine to detect aircraft by radar. Consider first of all the condition where the oscillator is quenched by the gating pulse. Then, once the gate is slowly opened, the high degree of regeneration induces a rapidly growing oscillation where the phase is triggered by random circuit noise. After the exponential build-up of these noisy oscillations, the gating pulse quickly quenches them, and the cycle is repeated. The radiofrequency spectrum of this sequence of incoherent pulses spans a broad frequency band. However if there is a returning radar echo stronger than the circuit noise, this triggers the subsequent oscillations in phase, and the oscillator becomes coherent. Essentially the device has "locked on" to the radar echo.

An analogous regime is established if the super-regenerative oscillator is used to excite an NMR signal, for this would trigger the conversion from incoherent to coherent mode. So I set out to build this device. Here the cultural divide showed up once again. Conventional wisdom suggests that the Q-factor of an NMR coil should be as high as possible, for this improves the signal-to-noise ratio. On the other hand, a high Q-factor in a super-regenerative oscillator tends to "pull" the desired NMR frequency. When I asked Bob what kind of compromise should be adopted, he embarked on pages and pages of differential equations - a very long calculation that never did converge to a useful conclusion. So I simply went ahead with the Q-factor I already had. In the NMR application, the wideband incoherent oscillator excites a free precession signal from any point within that broad frequency range. If this signal exceeds the circuit noise, the subsequent oscillations become coherent, synchronized with the NMR Larmor frequency. When the main magnetic field drifts, the oscillator frequency follows, maintaining the appropriate NMR resonance condition, thus compensating the magnet instability to a very high degree (with errors less than 0.5%). Fed to a second (high-resolution) NMR probe, this radiofrequency signal keeps the second field/frequency ratio essentially constant so that excellent stability is achieved. We probably had the most stable high-resolution spectrometer at that time, permitting very slow scanning rates of the order of 0.2 Hz per second, such that the usual transient sweep "wiggles" were not observed. However the Saclay physicists were not at all interested in high-resolution experiments ("When the chemists arrive, it is time to move into another field") and my equipment was soon banished to a basement *oubliette* when I left.

Ionel Solomon, Polytechnician and Saclay physicist.

Ionel does not fit into my rather glib generalisation about the French physicists. Although he graduated from the same rigorous Gallic educational system, he also had a natural gift for visualizing the behaviour of nuclear spins in a simple pictorial manner. For this reason he was an ideal teacher and supervisor, and helped me enormously, particularly after Bob Pound had returned to Harvard. In one instance he very gently led me to discover for myself why my radiofrequency amplifiers were misbehaving. The problem was solved by teaching me about the concept of a "grid stopper", a trick that prevented positive feedback.

Ionel had written the first analysis of the effect of chemical exchange on NMR spectra - formalized in the famous "Solomon equations" (*I. Solomon, Phys. Rev. 99, 559, 1955*). As one practical example, they describe the complex chemical exchange behaviour of hydrogen fluoride, with and without small traces of water. This was the first use of "I" and "S" to designate two coupled spins (in adopting this nomenclature we unwittingly render homage to Ionel Solomon). Incidentally Ionel was a visiting scientist at Harvard at the time of this work, and benefitted from advice about the chemistry of hydrogen fluoride from Rex Richards, who was also visiting Harvard at that time. It was a small NMR world in the 1950s.

I was fortunate to work in the same room as Ionel and was able to observe him in action every day. On one occasion, in an Oxfordesque manner, Ionel was playing with the NMR spectrometer, and quite by chance discovered a completely new physical phenomenon (his "penicillin moment"). While applying pulses to the radiofrequency crystal in the Varian spectrometer, he observed a strange new response that had the appearance of a new kind of echo. Other mortals might have dismissed this unexpected effect as an instrumental glitch (of which there were many), but Ionel persisted, deduced exactly what was happening, and was able to maximize the new response by adjusting the pulse length by trial-and-error. This was the first rotary echo, analogous to the Hahn spin echo, but attributable to refocusing in the spatial inhomogeneity of the *radiofrequency* field (*I. Solomon, Phys. Rev. Letters 2, 301, 1959*). The optimum condition corresponds to a 180° radiofrequency phase shift that exactly reverses the sense of rotation of the spin isochromats, bringing them back into focus. Ionel was then able to generate a sequence of multiple echoes (more than a thousand) demonstrating that, in contrast to conventional spin echo experiments, errors in the 180° pulses were not cumulative. This proved to be a new way to study spin relaxation in a liquid sample.

From my own narrow parochial perspective, it seems a pity that Ionel moved out of magnetic resonance soon afterwards. I realize now that this is often the destiny of research scientists. They may change to an entirely new field - Wes Anderson left magnetic resonance and went on to develop an important ultrasound imaging device. Others move into administration and are forgotten by the NMR community. The revolutionary invention of magnetic resonance imaging might have tempted me to change fields in 1973, but at the time I was starting a new appointment at Oxford, so I stayed in NMR spectroscopy. I consider myself very lucky to have worked in the same field for almost sixty years. However, today many more people recognize the term MRI than have ever heard of NMR.

Dr Martin Packard, head of Varian Instrument Division.

When I arrived at Varian in November 1961 I was enormously impressed by the extremely warm welcome from everyone in the group. The whole NMR field was so new that any enthusiast from abroad was accepted, apparently without question. I had been there only a few days when Martin Packard handed me the keys to a car on indefinite loan, a kindness that would have been unheard of in Europe. The car was in fact a rather elderly Ford; the accepted American jargon would have dismissed it as mere "transportation" but it served our family very well indeed. A physics graduate of Stanford, Martin was one of the original pioneers of NMR. He may well have been the very first person to *actually see* an NMR signal (but see below). Following Felix Bloch's suggestion, Martin spent all day vainly searching for the first proton signal from water by slowly varying the magnetic field. It must have seemed like looking for a needle in a haystack because their calculations of the actual magnetic field strength were rather unreliable (in fact the field was too high). It was only after he finally decided to abandon the search for the day and shut down the magnet, that he saw a fleeting water signal flash across the oscilloscope (*F. Bloch, W. W. Hansen and M. E. Packard, Phys. Rev. 69, 127 1946*).

An independent group at Harvard had also observed an NMR signal (*E. M. Purcell, H. C. Torrey and R. V. Pound, Phys. Rev. 69, 37, 1946*). Their report was submitted earlier (December 24, 1945) than that of the Stanford group (January 29, 1946), and it was more comprehensive, but the Nobel committee clearly believed that the East coast and West coast developments were independent and virtually contemporary, and the prize was divided between Bloch and Purcell. Had the Harvard group been judged to have absolute priority, thus scooping the Stanford group, Bob Pound might well have secured a share in the prize. His later brilliant determination of the gravitation red shift might also have attracted the attention of the Nobel committee, but instead they gave the prize to Mössbauer who had discovered the recoilless emission of gamma rays on which Bob's experiment relied. Two near misses in a single lifetime?

Not content with his first discovery, Martin can also lay claim to be the first person in the world to observe a high-resolution NMR spectrum, the famous three lines of ethanol. It was an Indian chemist, Srinivas Dharmatti at Stanford, who had pointed out to the physicists that almost any organic compound should show a proton spectrum of several distinct lines, provided that the magnetic field was sufficiently uniform. For this purpose Jim Arnold built a permanent magnet with resolution approaching one part in 10^8 (see "The Dawn of NMR" in another section of this website). Martin then ran the spectrum of ethanol, and chemistry was changed forever (*J. T. Arnold, S. S. Dharmatti and M. E. Packard, J. Chem. Phys. 19, 507, 1951*). In fact that group later resolved additional splittings on the three chemically shifted responses, but whenever they had a chemist visiting the laboratory, they intentionally degraded the effective resolution to disguise this effect because it represented a rather messy complication to what was otherwise a beautifully simple concept - one resonance for every distinct proton site. One step at a time.

Although Martin Packard was not directly involved in my research at Varian, his

influence was enormous. I suppose one could say that I learned mainly by observing someone who had already "been there, done that". As head of Instrument Division, Martin had the foresight to allow his young scientists to pursue their own interests without interference. Fortunately these enthusiasts were naturally disposed towards investigations that advanced the methodology of magnetic resonance, either to improve Varian instruments directly, or to generate valuable publicity for the company by writing innovative scientific papers in the field. There was little need to assign practical goals; largely unstructured research was producing useful results anyway. As one specific example, our attempts to understand the theory of double resonance led to the development of high-stability NMR spectrometers based on the internal field/frequency lock. This extraordinary freedom of action was possible because Varian was a small emerging company that had only just accumulated a critical mass of young talent. Scientists from abroad sometimes assumed that Varian was one of the many California universities. It was only later, when the company grew much larger, that complacency and stagnation set in. Then top scientists began to leave, and a flurry of young masters of business administration (with no knowledge of magnetic resonance) began to impose the conventional American management philosophy.

Weston Anderson, Physicist at Varian

When Felix Bloch was appointed director of CERN in Geneva, he took his two research students, Jim Arnold and Wes Anderson, with him to Switzerland and told them to write up their thesis work for publication. These became the classic papers on high-resolution NMR. Wes Anderson's thesis was written up in the *Physical Review*, 102, 151, 1956. Compared with our own modest experiments at Oxford in 1956 on cobalt chemical shifts, this classic served as a real wake-up call, demonstrating for the first time the full beauty and versatility of high-resolution NMR of protons. Martin Packard's famous three-lines spectrum of ethanol turned out to be merely the tip of an enormous iceberg, because Wes was able to record well-resolved proton spectra of quite simple organic compounds that showed many chemically-shifted lines, together with their associated fine structure. Physicists had ventured into chemistry, with the result that this new spectroscopy eventually revolutionized the study of molecular structure.

At that time a spectrometer could be thought of as an essentially neutral device. There was a direct one-to-one relationship between the *sample* and its *spectrum*; the operator could not interfere (except for trivial changes in pressure or temperature). NMR spectra recorded in Paris or Palo Alto were essentially identical. Wes took the first steps along a new path where spectra could be *manipulated* by the hand of man. This innovation can be regarded as the forerunner of all the present adventures in spin gymnastics that have made the field so productive. This deliberate intervention involved decoupling protons from protons, demonstrating which pairs of groups were related through the scalar coupling. From this modest beginning flowed more sophisticated manipulations like spin tickling, determination of signs of coupling constants, the measurement of the rates of chemical exchange, and the nuclear Overhauser effect. Few doctoral theses have been so influential in opening up new fields.

For someone who had struggled with solid-state NMR, and with NMR of the "other" nuclei, it seemed clear to me that high-resolution spectroscopy of protons was the way

ahead. Whereas it had taken me many months to determine a single inter-proton distance by recording a Pake doublet from a polycrystalline sample of potassium amide, a high-resolution proton spectrum could be obtained in a matter of minutes and promised a wealth of important molecular data. The idea that even more structural information could be gleaned from double irradiation experiments was an intriguing possibility. One could argue that double-irradiation experiments were just the first step in the "manipulation" revolution. A decade later the invention of two-dimensional spectroscopy by Jean Jeener suggested a brilliant new scheme for recording the kind of information that had formerly been painstakingly recorded by double irradiation.

For these reasons I decided to join Varian in late 1961 and work under Wes' guidance. Immediately the pace of research accelerated. Only three days after my arrival I was asked to give an impromptu evening seminar at Wes' home attended by a handful of Varian enthusiasts. There I showed some slides of spin decoupling experiments carried out previously in England. Harry Weaver, a physicist in the audience, commented that certain features in these spectra seemed to show an effect sometimes given the jocular name "spin tickling". In fact there was no general agreement about what the term actually meant, and nothing had been published about the concept. Incidentally this was an unusual case of an experiment acquiring a name even before it had been properly implemented in practice. Later I realized that any new spin manipulation should always be given catchy name or acronym in order to replace an unwieldy description along the lines "*You remember that pulse sequence where proton polarization is transferred to carbon spins in order to enhance sensitivity?*" Like the early explorers of our planet, we claimed the privilege of naming each new discovery, and thereby establishing priority.

Out of pure curiosity Wes and I decided to look into spin tickling in detail. The basic observations turned out to be relatively straightforward - any NMR transition that shares an energy level with the tickled transition splits into a doublet, the splitting being proportional to the intensity of the irradiation field. In the published article (*J. Chem. Phys.* 37, 2053, 1962) we bowed to political correctness and never mentioned the actual word *tickling*; this necessitated some awkward circumlocution. What did take us quite by surprise was the observation that the new doublets were sometimes well resolved and sometimes poorly resolved. This did not seem to be a mere instrumental glitch. It was Wes who found the explanation. Tickling involves quantum-mechanical mixing of an allowed transition with a connected forbidden transition (akin to Fermi resonance in infrared spectroscopy). There are two kinds of connected transitions, which David Whiffen named *regressive* and *progressive*. When the tickled resonance line is regressively-connected to the observed resonance line, mixing involves a (forbidden) zero-quantum transition. Because the latter is insensitive to the spatial inhomogeneity of the magnet, this situation gives a particularly well-resolved doublet. In contrast, in the progressively connected case, mixing involves a (forbidden) double-quantum transition, which is doubly sensitive to magnet inhomogeneity, so that tickling doublet is poorly resolved. How fortunate to be working with a physicist!

The tickling condition is very sensitive to the position of the irradiation frequency with respect to the centre of the chosen resonance line. If there is a slight offset, the connected doublet becomes asymmetric, one component getting stronger and the other weaker (at very large offsets the weaker line becomes a purely forbidden transition).

Careful adjustment of the tickling frequency to give a symmetrical doublet offers a precise method for measuring line frequencies in a high-resolution proton spectrum, with accuracies approaching ± 0.01 Hz. However highly accurate frequencies were not a major concern to most organic chemists at that time, for they were mainly interested in chemical shifts, where an accuracy of ± 1 Hz was more than adequate for the purpose. Chemists were busy exploring the exciting (and seemingly endless) applications in organic chemistry, and were not really interested in spin tickling.

At that time (1962) spectrometers necessarily operated at quite low magnetic fields (typically equivalent to a proton frequency of only 60 MHz) and there was therefore considerable interest in the computer analysis of strongly-coupled proton spectra. The first step in such programs was the assignment of the observed transitions to an energy-level diagram, something that tickling achieved very effectively. Once this assignment was complete, the iterative fitting program for determining shifts and coupling constants converged reliably and rapidly. Later, as magnets began to be constructed with higher fields, strongly-coupled proton spectra became less common, and computer analysis consequently less important. With hindsight I would now have to admit that tickling experiments aroused only minor interest at that time. Tickling appeared to be an interesting exercise in spin physics, but not terribly productive.

Tickling offers a good example of the dichotomy between curiosity-inspired and applied research. The former is often given the adjective "blue-sky" after the work of the nineteenth century scientist John Tyndall, who set out to show (erroneously as it turned out) that the colour of the sky arises from scattering by dust particles or water droplets in the atmosphere. The alternative category of "focused" research works towards solving a specific problem, such as a search for a synthesis of a natural product like quinine. Both kinds of endeavour are important, and both are useful in their different ways. But we should never assume that "pure" research does not have direct practical uses. In order to study spin tickling we had first to stabilize the field/frequency ratio to permit experiments where the irradiation "tickling" frequency could be held fixed, while the field was held constant and the rest of the spectrum was scanned by sweeping the observation frequency. For this purpose we borrowed an idea suggested by Hans Primas at the *Eidgenössische Technische Hochschule* in Zürich for using an error signal derived from the internal reference compound tetramethylsilane (TMS). There was already a Varian stabilization system that used a mirror galvanometer and two sensitive photocells to provide a correction current to counteract magnetic field drift. However this could not handle very slow drifts of the resonance condition because it lacked an absolute reference point. The insertion of a TMS error signal provided this crucial locking information. Our new stabilization scheme proved to be so successful that it became the basis of the next generation of Varian spectrometers (HA60 and HA100). A project born out of pure curiosity turned out to have widespread practical usefulness after all.

In parallel with this work Wes and I spent some time investigating the details of spin decoupling, calculating the so-called "magic curves" that map the way the structure of a proton spin multiplet changes when its coupling partner is irradiated at various decoupler offsets. Eventually these diagrams evolved into three-dimensional "stacked plots" of intensity as a function of the observed frequencies in one dimension, versus the decoupler frequency in the second dimension. This form of representation

anticipated the later explosion of three-dimensional spectra engendered by Jeener's concept of two-dimensional spectroscopy. The first decoupling magic curve was actually published much later in the *Journal of Magnetic Resonance* 26, 133 1977. Not long after this work we decided that my apprenticeship was essentially complete, and Wes and I moved into separate projects, the most important of which was carried out by Wes, and is described below.

Wes loved practical gadgets and built various devices at home in his spare time. Telescopes and seismographs were two of his favourites. One evening while we were having dinner with several other guests at Wes' house, he asked if we would like to see his latest home-made seismograph in the garage. I don't know how he contrived to do this, but at the very moment that we entered the garage, the pen recorder started to go absolutely crazy. It turned out later that it was recording a major earthquake in Alaska. Since boats in San Francisco Bay were also being visibly shaken by the quake, the extreme sensitivity of Wes' device was not strictly necessary on that occasion. But it was an impressive party trick nonetheless.

Wes' gadget that had the greatest impact of all was one that was never actually tested in practice. The details of this story are set out in section 9.1 Multichannel Excitation in "When Chemists first 'Discovered' NMR" on this website. Wes was the first to appreciate that the accepted frequency-sweep slow-passage regime, used by all high-resolution NMR practitioners at the time, sadly lacked sensitivity. He predicted that simultaneous multichannel irradiation of the entire spectrum would improve sensitivity by a large factor, roughly equal to the square root of the number of independent channels. So he set out to build his "Prayer Wheel", a gadget designed to create a comb of equally-spaced modulation sidebands. It was never used in anger because Wes soon realized that pulse excitation followed by Fourier transformation of the transient NMR signal would achieve the same predicted order of magnitude improvement in sensitivity, and would do so far more effectively. The resulting paper by Ernst and Anderson (*Rev. Sci. Instr.* 37, 93, 1966) changed NMR forever. The actual Prayer Wheel went to the Smithsonian Museum in Washington, DC.

I remain greatly indebted to these six gifted sorcerers who eased my transition from formal book-learning to the exciting arena of scientific research.