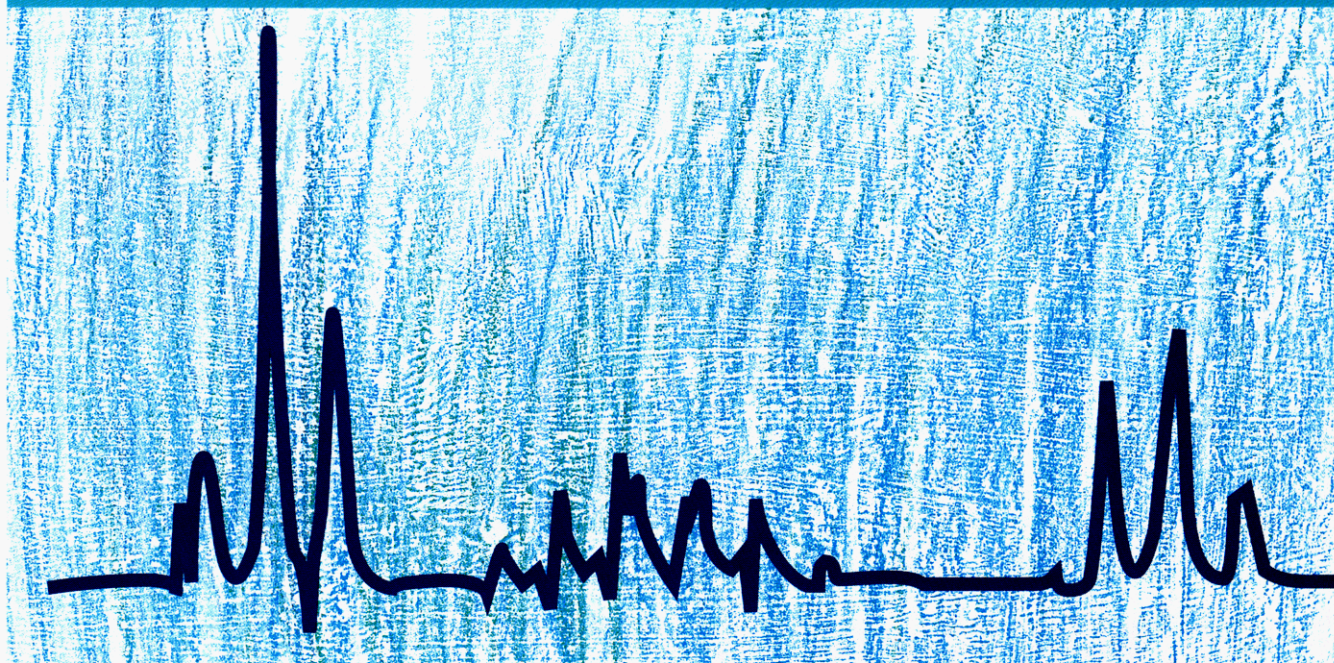


# NMR SPECTROSCOPY IN THE BEGINNING



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The history of NMR spectroscopy differs markedly from that of other spectroscopic techniques. A mere 15 years elapsed between the demonstration of the magnetic resonance of nuclei and widespread commercial sales of functional NMR spectrometers that altered the manner in which the field of organic chemistry was conducted. That period of remarkable development was possible because of a rather unusual confluence of visions, people, and events at Varian Associates that brought about a mutually beneficial merger of science and commerce.

### The stage is set

The demand for synthetic materials during World War II provided an immense impetus for the development of instruments for chemical analysis. In 1946 such instruments became commercially available. There was a steadily growing market for optical and mass spectrographic instru-

ments in the steel and petroleum industries. Organic chemists, who typically were limited to using pH meters, polarimeters, and the Beckman DU spectrophotometer, were considering the first commercial IR spectrometers.

World War II also caused the widespread deployment of the klystron, an invention that made airborne radar possible. The inventors of this device, Russell and Sigurd Varian,

## **REPORT**

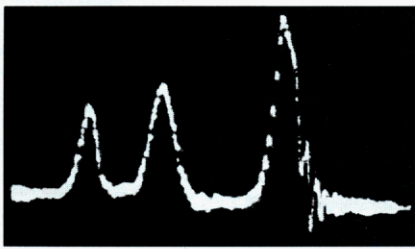
also played an important role in the commercial development of scientific instruments. Russell was a gifted physicist; his brother, an airline pilot, was an informally trained but talented engineer. The Varian brothers firmly believed that scientific innovation should be used to serve society. The klystron came into existence in large part because of their vision of its applications in navigation and air defense. During the course of its development both at Stanford University and at Sperry

Gyroscope, the Varian brothers became close friends with William W. Hansen and the three men began to save enough money to have a laboratory of their own.

When the war ended, Hansen returned to Stanford, where he contributed to Felix Bloch's original paper on NMR. (E. M. Purcell studied the same phenomenon independently at Harvard University and shared the 1953 Nobel Prize in Physics with Bloch for that work. The Harvard group developed a considerable body of the theoretical and experimental work but was not involved in the commercial development.) A few months later, Russell accepted a position as a research associate at Stanford and, with his unique insight, saw the potential application of the new phenomenon to the field of chemistry.

On Dec. 23, 1946, at Russell's urging, Bloch and Hansen signed both a patent application and an exclusive license to "Varian Associates" to develop the commercial applications of the nuclear induction device. (The company was not officially formed until January 1948. Dorothy Varian,





The three peaks of ethyl alcohol as first observed in 1951 at Stanford University.

Russell's widow and a co-founder of Varian Associates, wrote an interesting memoir of the Varian brothers, *The Inventor and the Pilot* [published by Pacific Books in 1983], which includes the history of the company's early years.)

Varian Associates secured research contracts with the U.S. government to develop the klystron for military use and planned to develop a line of commercial tubes. From the beginning, Varian was diversified into two product lines: the klystron, which had rapidly growing markets and mature manufacturing techniques, and NMR devices, which had no market and no manufacturing techniques. These differing situations proved to be extremely fortuitous. The klystron allowed Varian Associates access to the capital needed to grow and prosper while nurturing an emerging technology from infancy to maturity. The partnership of tubes and instruments has continued to provide stability throughout the company's 45-year history.

Ongoing work at Stanford showed that in practice the linewidths of the signals in liquids were limited only by the homogeneity of the magnetic field. Seeking more precise measurements of the nuclear magnetic moments, Bloch and his group developed an electromagnet that dwarfed the motley collection of permanent and electromagnets then being used. While testing it, they found that different liquids containing hydrogen atoms yielded different values for the proton magnetic moment. The variation, recognized as a shift in the field at the nucleus attributable to the diamagnetic screening by the orbiting electrons, interfered with accurate measurement of the nuclear moments. Accordingly, or so the story goes, the physicists christened this irritating obstacle the chemical shift.

The Stanford group indicated that Varian Associates needed a homogeneous 12-in. electromagnet for its research on chemical applications. To help pay for construction of such a

large magnet, the company decided to offer it as a product and issued a data sheet, typical for electronic equipment of that period. That decision changed my life.

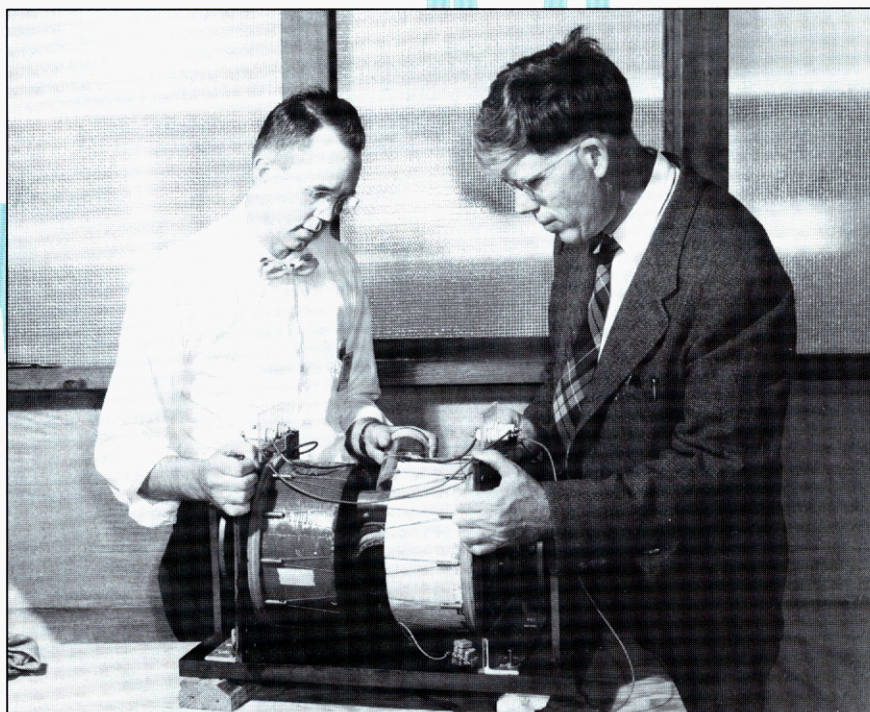
In 1941 I had begun my studies in chemistry at the University of California, Berkeley. In early 1944 the U.S. Navy decided that because I had turned 18, I would make an acceptable radar operator. When Bloch, Hansen, and Martin Packard published their paper, I was on a tanker in the South China Sea, with a considerable fund of new knowledge about electronics and microwave radar. Because of this experience I decided to explore microwave spectroscopy when I began graduate work at the California Institute of Technology in 1948.

My adviser, Don Yost, was an inorganic chemist with a great interest in electronics who also accepted John Waugh as a student that year. Waugh, whose laboratory was adjacent to mine, was using an inhomogeneous electromagnet powered by a bank of submarine batteries to build an NMR device. The electromagnet was capable of generating a magnetic field of several thousand gauss, but the inhomogeneity—coupled with the drift caused by battery fatigue—limited his research to solids in which the natural linewidths were several gauss. Waugh's apparatus demonstrated that interesting infor-

mation could be extracted from the nuclei of atoms, but it was difficult to see many practical applications for chemistry. Nonetheless, I appreciated the simplicity of his detector relative to the microwave spectrometer in my own laboratory.

In late 1951 I completed my thesis work and began a postdoctoral fellowship under Yost. At his request I attended an electronics trade show in Los Angeles to look at the suitability of Varian klystrons for the microwave spectrometer. Although our small research budget clearly could not cover the cost of a klystron designed to meet military specifications, I poked around the exhibit and came across the specification sheet for the 12-in. electromagnet and an accompanying stack of reprints of a "Letter to the Editor" that had appeared in the *Journal of Chemical Physics* (1). It was love at first sight. When I saw the three peaks of ethyl alcohol (see photo at left), I knew what I wanted to work on, and I knew that Varian Associates—demonstrating the foresight to offer a technologically advanced product so early—was where I wanted to work. That decision was bolstered by the fact that Varian Associates, unlike other job opportunities, was near Stanford, not far from my home.

I wrote a letter to the company, suggesting that commercial acceptance of their NMR products by



Russell Varian (right) conferring with Martin Packard, research director of Varian Associates Instrument Division in 1954.



chemists would be greatly accelerated by employing a chemist to develop applications and communicate them to the world of chemists. I also modestly pointed out that I would be available for such a position. By return mail, I received an invitation to visit Varian and discuss my idea with the R&D group. Out of that meeting came an offer of employment. Reporting for work in April 1952, I became the 512th person to join the company.

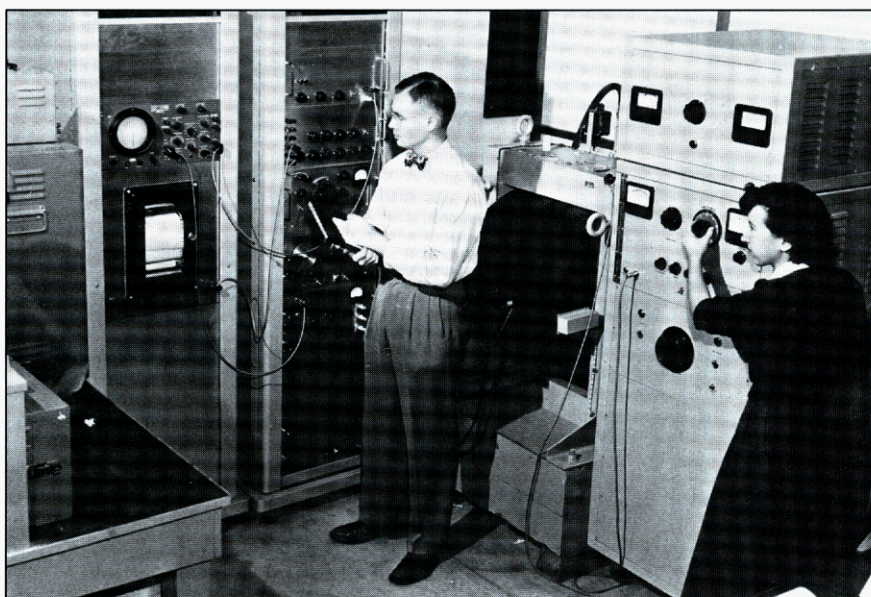
### The first instrument: the HR-30

Discussing the developments that follow without describing the environment in which they occurred would result in an incomplete and misleading picture. The Varian brothers believed in innovation as the best way to generate profits. R&D, followed by an aggressive patent policy and fast-paced product improvement, would minimize the chance of competitors gaining a significant foothold. The small size of the company in the early and mid-1950s made it possible for Russ and Sig to make rounds of the technical projects on almost a daily basis to discuss, suggest, and encourage (see photo below at left).

Not only was there the excitement of working on the leading edge of a technology, but Russ and Sig had created a unique atmosphere in their company. They acted on their belief that every employee had the right to know the significance of his or her work and to be treated with equal consideration and respect. From its earliest beginnings, long before there was a public offering of stock, every employee of six months' duration could buy into the company. Because of those attitudes, employees "were able to care more about what they could contribute to the company than what they could take from it," stated Emery Rogers (a member of the Stanford group [2]).

Not surprisingly, Varian attracted an awesome pool of talent. Packard and Rogers were already part of the Varian team, and Wes Anderson and Jim Arnold joined shortly after my arrival. Warren Proctor and Harry Weaver joined the group somewhat later; Ray Freeman, Richard Ernst, and Howard Hill joined the enterprise at a much later date.

By the time I arrived, Humble Oil Company of Baytown, TX, had ordered an NMR instrument for about \$30,000! A high-resolution instrument—operating at 30 MHz, with a magnetic field strength of 7050 G, and able to resolve the three peaks of



*Virginia Royden and James Shoolery operating the HR-30 prototype.*

ethyl alcohol—was supposed to be delivered by late summer. Rogers was preparing the power supply for the magnet (a replica of Stanford's magnet) for production, and the rest of the electronics was being built by the R&D group, headed by Packard. Packard was the only one who really understood the whole project. As a graduate student in 1945, he had built and operated Bloch's original NMR apparatus and had seen the first nuclear induction signal flit across the screen.

My task was to design and build the radio frequency (rf) unit. The unit consisted of a 30-MHz crystal-controlled oscillator (to irradiate the nuclei) and a low-noise, high-gain receiver at the same frequency (to amplify the incredibly weak signals from the sample). Designing circuits had been part of my graduate work, but I was not a professional engineer. However, I got the job done. When I tested the complete system, which came to be known as the HR-30, I found that it exceeded the guaranteed performance specifications.

With that out of the way, I was ready to get on with applications research, but the second instrument, which I would be using, was still being built. I was given a final assignment: Install the instrument at Humble Oil. I managed to do that by September 1952, and in January 1953 I happily opened the Varian Applications Laboratory, fondly known as the Applab.

By that time, H. S. Gutowsky and his students at the University of Illinois, as well as our team at Varian

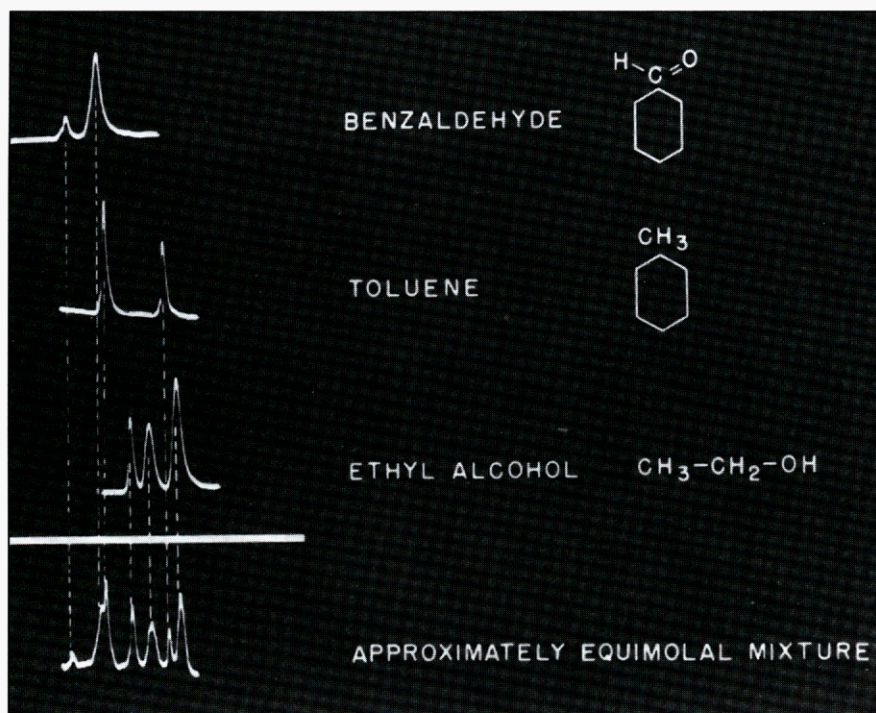
Associates, had resolved the fine structure from chemically nonequivalent protons in molecules and even hyperfine structure from spin-spin interactions between nonequivalent nuclei. Research laboratories with a tradition of exploring new analytical techniques, such as the DuPont Experimental Station and Shell Development, followed Humble Oil as early customers.

Other customers were hard to find. There was a very limited theoretical basis for interpreting the fascinating new spectra. The empirical relationship between observed spectral features and the molecular structure of the sample had to be established. That first step was too important to rely on anything but our own efforts. Thus the main thrust of the Applab during the first few years was to acquire and publish as much data as possible, a strategy that would give the theoreticians the means to test their developing theories, and everyone—including us—the means to interpret spectra.

I began the job I had dreamed of: Almost every new compound I studied would lead to a paper that could be published. It was like prospecting for gold in a field strewn with nuggets. I needed only to pick them up—little or no digging was required.

In 1953 the HR-30 was the state-of-the-art NMR spectrometer. What that meant can be illustrated by comparing it to its popular contemporary, a double-beam IR spectrometer. The IR spectrometer was very stable and gave a highly reproducible spectrum, a sort of fingerprint of





**Figure 1.** Oscilloscope photographs of spectra obtained with the HR-30 for three compounds and for a mixture of the three.

the sample. Most IR instruments would fit on a table, required no special facilities or services, were reasonably easy to operate, and worked with dilute samples.

The HR-30 had none of those virtues. Its 5400-lb. electromagnet required cooling water and heavy-duty electrical service as well as a substantial floor. Although it could reproduce the general features of a spectrum, the finer details were apt to vary with the instability of the magnetic field. Sensitivity was so poor that only neat liquids or concentrated solutions would produce signals visible above noise, and at the 7050-G field strength, the 10-ppm range of the proton spectral dispersion severely limited the interpretability and usefulness of the spectra.

Furthermore, the HR-30 was an operator's nightmare. The photo on p. 733 A shows the Applab HR-30 in 1953. Virginia Royden, a Varian colleague, adjusted the field strength to locate the signals while I acted as the recorder, hurriedly writing down observations of the data as the oscilloscope beam swept across the scope. After locating the signal from a sample of water, we had to place the probe (which contained the rf coils and sample) in the homogeneous spot in the magnet. That spot changed its shape, size, and location with changes in temperature and with the effects of hysteresis caused

by turning the magnet on and off. The search was a hit-and-miss affair; there were many misses before scoring a hit.

When the oscilloscope finally displayed a satisfactory pattern of decaying wiggles, denoting a narrow linewidth, we calibrated the sweep width by generating audiofrequency sidebands of the water signal. If we needed a permanent record, we took a Polaroid photograph of the oscilloscope screen to establish the reference point of the chemical shift of water, and then quickly—before the field could drift very far—we replaced the water sample with the sample being studied and took a second photograph.

Figure 1 shows spectra we obtained with the HR-30. In spite of the shortcomings, particularly when compared with current results, we were very proud of our data. We were ready to begin sharing the great news with the scientific community.

Not long after I opened the Applab, Rogers was appointed marketing manager for Varian's Instrument Division. We decided to build on the widespread acceptance of IR spectroscopy in creating an image for NMR spectroscopy. Feeling the need for a similar acronym, and wanting to avoid the use of the ominous word "nuclear," we called the new technique NMR spectroscopy and used that term at every opportunity.

As quickly as possible, we moved from photographs to high-speed chart recordings that presented the NMR spectrum in a format closer to that of IR instruments. Whereas IR instruments displayed a wavenumber scale, NMR instruments displayed a magnetic field scan in parts per million. We were unprepared for the confusion created by that new meaning for a term previously used to quantify trace amounts of chemicals. Fortunately, the distinction soon became clear.

While highlighting the similarities between NMR and IR techniques, we still wanted to differentiate them. To that end, we established the practice of displaying NMR spectra as peaks with a positive deflection rather than as minima like IR spectra. The choice, we claimed, symbolized the vitality of the new technique. We referred to the fine structure arising from spin-spin coupling as a multiplet rather than an absorption band. It was years, however, before some organic chemists abandoned the term "NMR absorption band."

In July 1953 Rogers and I took a first step in a long-term effort to familiarize organic chemists with NMR spectroscopy. We circulated a report, on which we had collaborated, to the heads of the chemistry departments of major universities and the directors of research laboratories in large chemical companies. That report, which included our definition of NMR spectroscopy, a hypothetical experiment, and a series of our new spectra, was formally named "Technical Information from the Radio Frequency Laboratories of Varian Associates." It was popular, and our mailing list grew steadily. The "Technical Information Bulletin," as it came to be called, evolved into a series, always liberally illustrated with spectra, that appeared whenever new NMR developments occurred.

Varian's second step in introducing NMR spectroscopy, which began in April 1954, was more conventional: We began a monthly advertisement in ANALYTICAL CHEMISTRY (see box on p. 735 A). Even that ad was unique. Titled "This Is NMR at Work," the ad included a headline and some promotional copy on the top quarter of the page, but the box below rigorously described and illustrated a recent example of Applab work—exactly as if it had been submitted to a scientific journal. The advertising department was given some leeway with the top section but was strictly forbidden from altering



the material in the technical box. Scientists were colleagues before they were customers. Eventually that attitude became established as company policy: Varian scientists can be trusted to make objective assessments, not inflated claims.

A great deal of fine industrial research never sees the light of day because it is considered proprietary by the management. The opposite was true at the Applab: Papers were encouraged and supported. Between 1953 and 1956, I wrote or collaborated on 17 published papers conveying a variety of observations and applications of NMR spectroscopy.

We used technical bulletins, advertisements, and scientific papers to circulate information about the new technique, and we also spoke about it at every opportunity. Very few chemists were knowledgeable about NMR spectroscopy when the HR-30 was introduced, but chemists tend to be curious. We not only tried to be responsive to requests for a speaker; we actively sought out any interested parties. Once, in the early days when Rogers and I traveled to Albuquerque to speak to a section of the American Institute of Electrical Engineers, we outnumbered the audience. We really did work hard at taking the news to the scientific community.

There was one final hurdle, however, that we had not yet crossed. By mid-1954, chemical shifts and coupling constants had been measured for a wide range of known structures, and the effects of relaxation times and chemical exchange on the spectra were appreciated. But I had not yet found an example showing that NMR spectroscopy could be used to solve a significant problem that could not be solved by using other, more established techniques. I was certain that it could, but I wanted to be convinced.

E. J. Corey, then working at the University of Illinois, submitted the sample that proved to be the turning point (see Figure 2). He believed that the sample compound had one of two possible structures. IR or UV spectra could not be interpreted unequivocally in favor of one structure. But the spectrum produced on the Applab HR-30 showed that the ratio of areas of the two types of protons, olefinic and aliphatic, clearly supported one of the structures. With simplicity and directness, NMR spectroscopy had proved uniquely able to solve a chemical problem.

As time went on, more and more of the examples that appeared in "NMR

## UNLOCK the door to molecular secrets



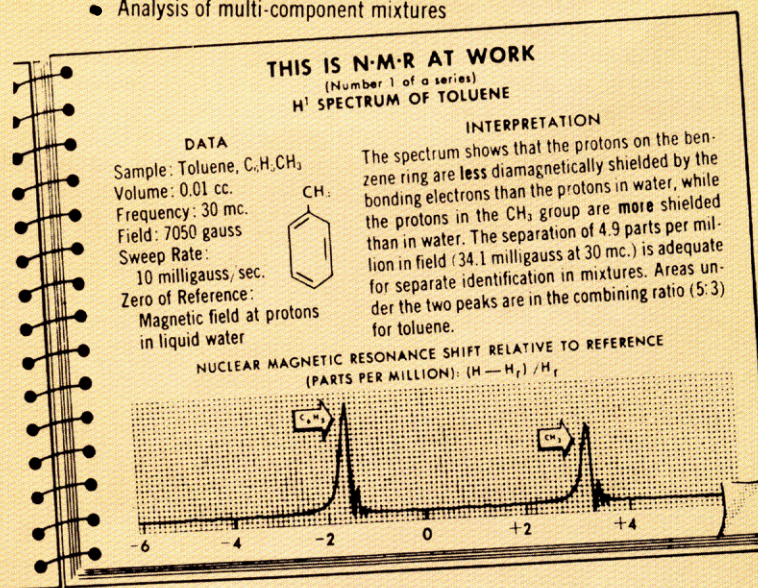
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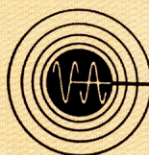
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at Work" reported solutions to problems—constituting original, publishable work. The Applab was occasionally accused of having an unfair advantage of running its own journal, whereas other NMR researchers had to await the usual delays of technical publication. I was familiar with such delays. I found it pleasant, occasionally, not having to deal with referees.

### Product improvement as a way of life: the HR-40

When a profitable instrument is produced in multiple quantities, innovation in design is often inhibited. In the case of the HR-30, which was difficult to operate and manufacture, improvement was necessary. With encouragement from Russ and Sig, we made product improvement our priority.

Things go faster if something is driving them. In this case, with my daily exposure to problems and my faith in the ability of electronic engineers (given time and money) to solve them, I slipped naturally into the role of product champion. Rogers generously characterized me as "a chemist with an antipathy to accepting horizons as they seem to be" (2). The more practical engineers saw me as "that chemist guy who won't take no for an answer." In any event, when I identified needed improvements or heard about good ideas, I coaxed, cajoled, wheedled, browbeat,

and pleaded for them. When management was persuaded to budget a generous percentage of sales income to R&D, the engineers and physicists could fully express their innovative thinking.

**Higher field strength.** We had to choose between an electromagnet and a permanent magnet for further development of an instrument. Both Gutowsky at the University of Illinois and Arnold and Anderson at Stanford were working successfully with permanent magnets, which had the advantage of great field stability but—because of the materials available at that time—field strengths of 7000 G or less. We decided we wanted the advantage of greater dispersion and sensitivity. Varian spectrometers would rely on electromagnets, and we would try to solve the stability problems.

Because chemical shift dispersion increases linearly with magnetic field and sensitivity increases as the  $3/2$  power, I welcomed the news that the power supply could deliver enough power to the magnet to operate continuously at a field strength of 9600 G, sufficient for operation at 40 MHz. That gave the new Varian spectrometer, which became available in 1955 and was christened the HR-40, the distinction of being the most powerful high-resolution NMR instrument.

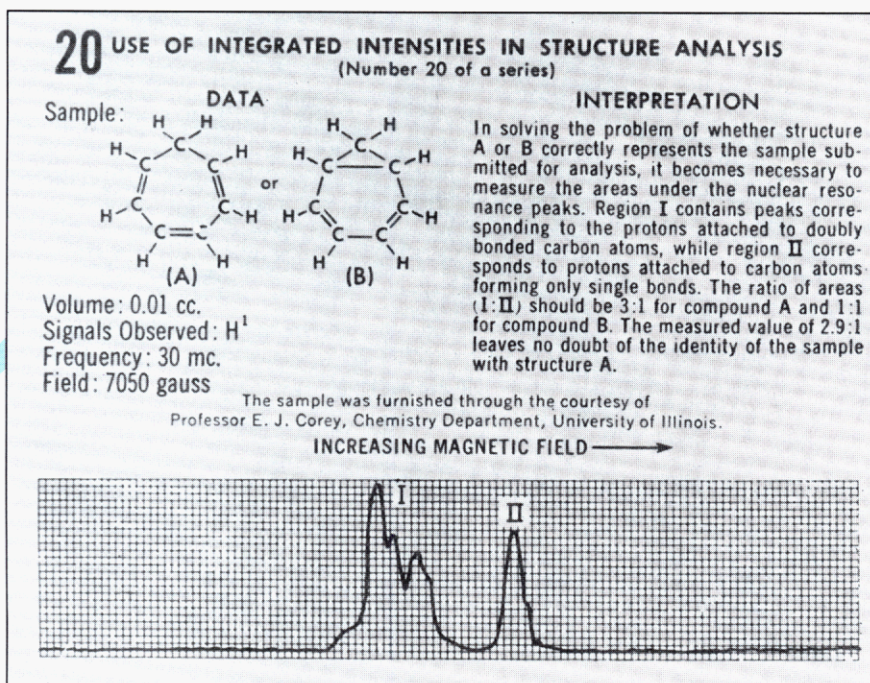
**Sample spinning.** The HR-40 was equipped with a simple device

that represented a major breakthrough: a sample spinner. Anderson and Arnold, working in Bloch's laboratory at Stanford, achieved previously unattained narrowing of the NMR lines in liquid samples by spinning the sample with a small air turbine (3). Spinning the sample produces a special case of "motional" averaging. All nuclei the same distance from the spinning axis of the tube at each point along that axis experience the same average magnetic field.

Sample spinning reduced the problem of optimizing the homogeneity of the field over the sample to a one-dimensional search for the minimum field gradient along the spinning axis. Previously, the operator had to search the homogeneous region of the magnet for a place where the  $x$ ,  $y$ , and  $z$  gradients were simultaneously small. Fortunately, the need to find only a place where the  $z$ -gradient was minimum made the search much easier. Sample spinning also improved resolution considerably. However, we knew that the full benefit of improved resolution could not be realized until the stability problem was solved.

**Field gradient shimming with electric currents.** The HR-30 and the HR-40 could not alter the distribution of field gradients unless their main bolts, which held the pole pieces to the yoke, were loosened and unless a thin metal "shim" was inserted or removed. The term "shimming" was applied to any process for adjusting homogeneity at the sample. An alternative to shimming was to search for a homogeneous spot by moving the sample probe around, but this assumed that there was such a spot. The group at Stanford had experimented with current-carrying coils on the pole faces to modify the distribution of magnetic flux. At Varian we realized that this approach was more sensible than searching, because it was possible to fix the sample in the center of the magnet and bring the corrective gradient to the sample.

The earliest electric shim sets were very difficult to adjust because they were highly interactive; adjusting one coil affected the settings of the others. Mathematical analysis was carried out, and soon a highly orthogonal set of coils was devised. Adjustment of homogeneity, although still requiring some expertise on the part of the operator, was reduced to a systematic procedure. Furthermore, it became possible to set a standard performance specifi-



**Figure 2.** First chemical problem solved by high-resolution NMR spectroscopy.

The work was completed in late 1954 at the Varian Applications Laboratory.



cation for the homogeneity over the sample volume.

**Magnetic flux stabilization.** Obtaining spectra from the HR-40 was like looking through binoculars at a row of birds on a telephone wire from the back of a truck bouncing over a rutted road. The regulation of the magnet current could not be made better than  $\sim 1$  in  $10^7$ , but we needed a field stable to 1 in  $10^8$  or better.

I believe the idea of applying degenerative feedback originated at Princeton and was communicated to us by our colleagues at Shell Development Laboratory. Once explained, it was so obvious a solution to the problem that we wondered why we had not thought about it sooner. A pickup coil containing hundreds of turns was fixed around one of the 12-in. magnet pole pieces. Any change in the field, even 1 in  $10^9$ , induced a few microvolts across the coil. That voltage resulted in a minute current in a galvanometer across the coil, and the deflection was amplified enormously by a light beam reflected off a mirror attached to the suspension. A split photocell gave an error signal indicating either an increase or a decrease in the field, and the signal was then passed to an operational amplifier that controlled an output current generating a magnetic flux opposed to the original change in the field.

I well remember adjusting the spectrometer for my first trial of the device and closing the switch. It was as if the truck had stopped and the binoculars were mounted on a tripod. I could easily see and count all the birds on the telephone wire. Better yet, I could even tell if their feathers were ruffled.

In a fit of marketing enthusiasm, we called the new device a Super Stabilizer. It was offered as an accessory that could be retrofitted to earlier spectrometers, thus establishing a precedent at Varian: Every effort would be made to make Varian spectrometers "living" instruments. It became a firm policy that once a customer purchased a spectrometer, new improvements to later models would be available as upgrade kits if technically feasible.

The Super Stabilizer had the same effect on the acceptance of high-resolution NMR spectroscopy as the double beam principle had on IR spectroscopy. Magnetic field jitter was eliminated, and slow drift could be balanced out by a small voltage. A perfectly linear sweep could be produced by injecting a controlled volt-

age at the input of the amplifier. The sweep could be slowed enough to allow the full resolving power to be achieved. At last the NMR spectrometer had everything needed to produce a precalibrated spectral chart except a precise, controlled reference point from which to start the chemical shift scale.

#### **A quantum leap: the HR-60**

Having committed ourselves to the electromagnet and solved the stability problems, it made sense to capitalize on its strong point: superior field strength. Tapering the pole caps and narrowing the gap would increase the field at a given current, whereas increasing the current to the limit of the power-handling ability of the power supply and cooling system would give still higher fields.

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A magnetic field of 14,096 G (corresponding to 60-MHz operation) was chosen, probably because we could get the magnet to reach this field without narrowing the gap and redesigning the sample probes. That represented a 50% increase in field (and chemical shifts) and a doubling of sensitivity. Many metallurgical problems had to be dealt with to manufacture pole caps that would give predictable high-resolution performance at 14,096 G. A curved profile was developed that produced a large homogeneous region in the magnet gap.

The resulting HR-60, announced in 1958, immediately showed that its problem-solving ability was vastly

superior to that of the HR-40. It was a commercial success but, more important, it was a vehicle for demonstrating what we so firmly believed at Varian: Overcoming sensitivity and spectral complexity problems would open up unlimited NMR applications in the fields of chemistry and biochemistry.

Large numbers of chemists began turning out at our presentations to ACS sections, Gordon Conferences, and analytical chemistry meetings. By 1960 I had described the principles of NMR spectroscopy and the potential of its chemical applications to  $\sim 20,000$  people. Many audiences were in other countries; Varian provided a generous travel budget, believing that it was a good investment in the market for the growing family of NMR spectrometers. That led to the rapid acceptance of the technique throughout the world.

In October 1957 the Instrument Division held the first of a series of annual workshops on NMR spectroscopy. The workshops provided a comprehensive picture of the current state of the art for chemists seriously considering the use of the new and still fairly mysterious technique. The faculty of Varian physicists, engineers, and chemists discovered that working together in that combined educational and promotional venture had a further value: It solidified mutual respect among the disciplines and gave the whole group a sense of direction.

As the interest in NMR spectroscopy increased, Rogers and I began considering various analytical meetings and instrument exhibits; we were planning to participate and, if possible, to operate a spectrometer in the midst of a crowd. In 1957 we decided to attend the Pittsburgh Conference, which was meeting for the ninth consecutive time on the eleventh floor of the William Penn Hotel in Pittsburgh. Our experiences there confirmed that the exhibitors at this meeting were indeed our kind of people and that the attendees represented an excellent cross section of potential NMR instrument users.

We asked about booking space for 1958 and were informed that the only remaining space suitable for a monster like a high-resolution NMR spectrometer was out in the hallway adjacent to the elevators, a corner booth about 15 ft. square. The booth was somewhat larger than most, but the location was deemed undesirable because of the traffic around the elevators, so the price was right. Having no other choice, we booked it and



the next year brought an HR-60 to display.

Taking a 5400-pound magnet to the eleventh floor in an elevator can be a challenging and exciting project. Providing it with cooling water and three-phase 220-V power in a hotel added to the excitement. We also had some problems with stability during our first attempt to operate the instrument, but those were resolved when our electronics wizard, Forest Nelson, realized that we had placed the magnet against the wall of the elevator shaft. The arrival and departure of the elevator did terrible things to the spectra, but because magnetic effects fall off rapidly with distance, the problem was solved by moving the magnet to the other side of the exhibit space.

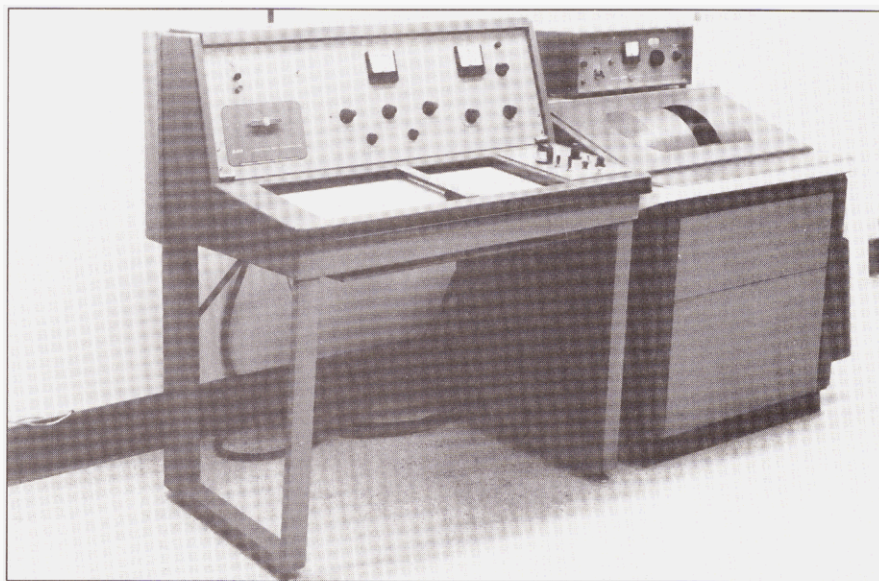
Far from being a problem, the traffic at the elevator was a great asset. Everyone who planned to enter the instrument exhibition was greeted by the sight of the Varian booth with its gargantuan magnet. It was like being at 42nd Street and Broadway; everyone passed by, and most of them stopped to look. The HR-60, successfully installed, proved to be a smash attraction. Over the years, other instrument exhibits claimed a share of the promotional budget, but none of them contributed as much as the Pittsburgh Conference to expanding chemists' awareness of this new kind of spectroscopy.

About the same time, seeking a wider readership for "NMR at Work," we explored the availability of advertising space in the *Journal of the American Chemical Society*. We found that the only full-page advertisement available was the magazine's back cover. We had misgivings but contracted for the space. The ad caught on. We were told on many occasions that the first thing our audience did was turn the magazine over and find out what was new in the NMR field. In all, nearly 100 different "NMR at Work" examples were published.

The wider readership brought hundreds of samples pouring into the Applab for analysis. We were forced to select those that would produce results that could be published and also pushed the limits of NMR techniques. It was an enormous and stimulating privilege for me to collaborate with leaders in many fields of chemistry throughout the world.

#### Pushing the limits: the HR-100

Once the magnet for the HR-60 was developed, we immediately set our sights on the highest field that the



*The A-60 spectrometer introduced in 1961 at the Pittsburgh Conference.*

magnet could reach while keeping constant the ratio of pole face diameter to gap, thereby maintaining a reasonably homogeneous volume. The narrower gap required a redesigned sample probe and stabilizer coils. Magnetic saturation of the iron set a practical limit of 23,490 G, corresponding to 100 MHz. The resolving power of the new instrument was better than 1 part in  $10^8$ ; astronomers, using a telescope with equal power, would be able to see two cats on the moon sitting a foot apart. The resulting product, the HR-100, was the world leader in chemical shift dispersion and sensitivity from the time it was introduced in 1959 until the first high-resolution superconducting magnet was built at Varian in 1962.

**Quantitation.** From the outset, NMR spectroscopy enjoyed a fundamental advantage for quantitative work: The various signals being compared all arise from the same spectroscopic transition. The protons in different parts of a molecule or in different molecules all have the same transition probability and therefore can be compared directly—unlike UV-vis and IR spectroscopy, which account for differing absorption coefficients. Assuming identical linewidths, all that was required was to compare the amplitudes of the peaks, or—for signals of different widths—the total area under the peaks. Unfortunately, whereas the electronic integration of peak areas was straightforward, the stability of the dc amplifiers was inadequate. The minute drifts in the baseline introduced large errors in the integrals.

The drift problem was solved by modulating the magnetic field at a fixed 2-kHz frequency and selecting the ac signal components while suppressing the sidebands with a balanced phase-sensitive detector. Amplification at this audio frequency was free of dc drift, the effects of probe balance, rf level, and stray pickup. In 1960 I wrote an article in which I showed, both theoretically and experimentally, that NMR signals from chemically shifted protons could be compared with an accuracy of 1% or better using this approach (4). The model 3521 NMR integrator became a valuable accessory for laboratories with HR-60 or HR-100 spectrometers.

**Spin decoupling.** The theory and experimental verification of various modes of spin decoupling were published in 1955 (5). This technique takes advantage of the long lifetimes of nuclear spin states, allowing the chemist to tamper with the energy levels of the coupled system and to deduce which nuclei share common energy levels. Those showing coupling must be located in atoms that are close neighbors in the molecular structure.

However, spin decoupling was not routinely applied in spectral analysis until 1961, when a minor modification of the NMR integrator and the addition of a variable-frequency audio-oscillator made it possible to irradiate a proton or group of protons strongly at any location in the spectrum while detection occurred for some other selected multiplet in the spectrum. Leroy Johnson wrote an article describing the modifica-



tions and how they worked, including an example of the application of spin decoupling to a structural problem (6). Earlier HR-60 and HR-100 spectrometers were retrofitted with integrator/decouplers, and organic chemists soon found that the analysis of complex spectra could be greatly facilitated with spin decoupling data.

### The end of the beginning: the A-60

There are times in the evolution of an instrumental technique when the necessary infrastructure is in place and a significant leap forward can be made. One of those times occurred in 1957, setting in motion events that transformed both high-resolution NMR techniques and the way in which chemists used them.

With help from the R&D group, Rogers and I developed a proposal to embark on a four-year project that would cost several million dollars. The end product would be an affordable, reliable, conveniently sized and shaped, proton-only spectrometer with high stability and sensitivity. Some specifications and features were so far from realization that it seemed a miracle had to occur in order to meet them. But we believed in miracles and had faith in ourselves and our co-workers. So did Varian Associates.

Our specifications called for a 6-in. electromagnet operating at 14,096 G (60 MHz) with resolution equal to that of the 12-in. electromagnet of the HR-60. But we wanted the new magnet styled to fit into a laboratory environment. The console would have an attractive, user-friendly cabinet for electronics, a control panel with logical groupings of controls, and a flatbed recorder for producing the NMR spectrum on a large precalibrated chart. The console also had to incorporate a method of locking the ratio of magnetic field and frequency.

The instrument would scan the entire proton NMR spectrum (a little less than a 10-ppm range) slowly enough to avoid distorting the NMR lineshapes (as long as 500 s) while reproducing the spectrum within the pen width on the chart. The sensitivity for a 5-mm sample had to be comparable to that of the HR-60. In addition, the instrument had to be simple enough that any organic chemist or graduate student could operate it with the aid of the manual. Its reliability would be one-year mean time to failure. And all of this was supposed to cost only a little

more than the better IR instruments and considerably less than a laboratory mass spectrometer.

The project was funded and manpower assigned in 1957. John Moran, the project engineer who coordinated the team of engineers, physicists, and artists, used a new method of critical path analysis to keep the project on schedule and within budget. An applications chemist was assigned to the project to see that prototype performance continued to meet the requirements when engineering compromises had to be made.

The code name for the project was ASP. That was not a symbol for a venomous attack on competitors, some of which had appeared by this time, but rather an acronym for the project schedule: As Soon as Possible. We thought long and hard about

the model designation, which we hoped would become a household word to chemists. We finally settled on the A-60, A for analytical, and 60 for the frequency and what we hoped would be the year of release.

The toughest technical challenge—to lock the frequency to the magnetic field—was solved in an ingenious way. A small sample of water in the probe near the analytical sample was irradiated at 60 MHz and modulated by an audio frequency generated by closing a loop to create a nuclear sideband oscillator, or NSBO. The audio circuit would oscillate only at a frequency that placed the sideband exactly at the water resonance line frequency. The very rapid response of the device made it easier to regulate the magnet, thus lessening the demands for

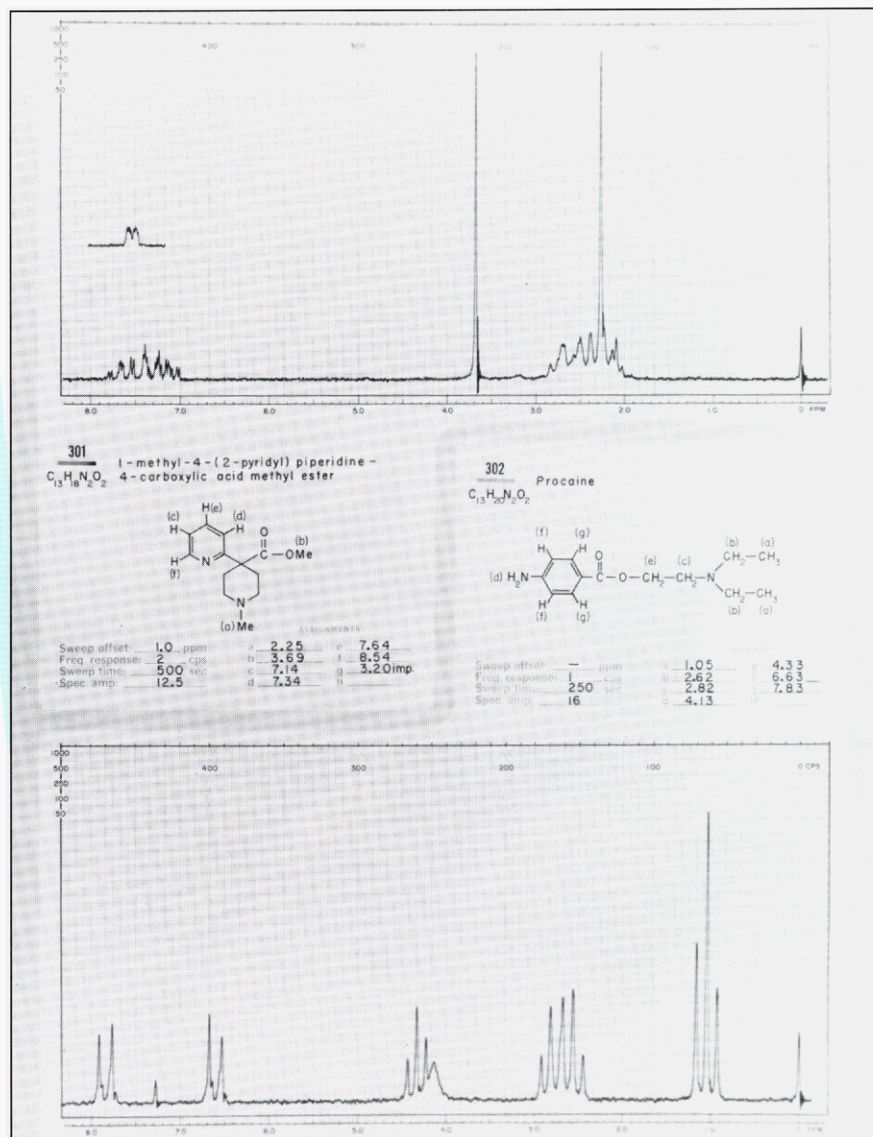


Figure 3. Two of the 700 spectra from the Varian spectra catalog, first distributed in 1961.



stability on both the power supply and the flux stabilizer.

The final test of the prototype (see photo on p. 738 A) that would be introduced at the 1961 Pittsburgh Conference is a particularly happy memory for me. I put a sample into the instrument, adjusted the resolution, and ran a spectrum on the pre-calibrated chart. It was perfect. But could the A-60 reproduce a spectrum with the fingerprint quality of the IR instrument? I moved the pen back to the start and restarted the scan. I was momentarily distracted, and when I looked back I saw only one line on the chart. "Why didn't the second scan run properly?" I asked. The answer came back, "It did!" Amazed and almost incredulous, I returned the pen three more times. It laid down five identical spectra with a single trace showing on the paper! At that instant, I knew that the field of organic chemistry would never be the same again.

We decided that if chemists became familiar with a standard format for the NMR spectrum, they would develop a feel for the interpretation. To that end, we prepared a two-volume

catalog containing 700 spectra of a carefully selected variety of chemical compounds (7). The catalog, which was shipped with each A-60, was available to anyone at a nominal cost. (Figure 3 shows a page from the catalog.) Over the years, it became the laboratory companion for numerous organic chemists.

During the late 1950s a controversy was brewing in the scientific community regarding the presentation of spectral data. One group favored establishing the reference peak, tetramethylsilane (TMS), at 10 ppm, with the 10-ppm spectral scan beginning at 0 ppm and increasing from left to right. At Varian we favored a system with TMS at 0 ppm, beginning at 10 ppm on the left and decreasing from left to right. Arguments could be made for both systems, and the NMR world was breaking into two camps. The design of the A-60 precalibrated, printed chart backed up by the catalog of 700 spectra made it easier to decide. The other system fell into disuse.

The A-60 met with overwhelming acceptance. More than 120 instruments were sold the first year, and

during its lifetime, more than 1000 were shipped. It proved exceptionally reliable and sturdy, and it became more than just an analytical tool; for many chemists it became the instrument of choice for following the progress of synthetic work and analyzing the structures of synthetic and natural products. NMR spectroscopy had come of age, and we had come to the end of the beginning.

By current standards, the A-60 looks like a primitive instrument, but its capabilities could hardly have been imagined a decade earlier. It clearly triggered an avalanche of acceptance of NMR spectroscopy. From the time it was introduced, improvements have continued at an accelerated rate. The 1960s saw the application of superconducting solenoids to high-resolution NMR spectroscopy, the invention of the pulsed FT-NMR spectrometer and its marriage to the digital computer, and the development of a vast body of data and solved problems. The 1970s brought polarization transfer experiments, laid the groundwork for multidimensional NMR spectroscopy, and sent problem-solving power soaring along

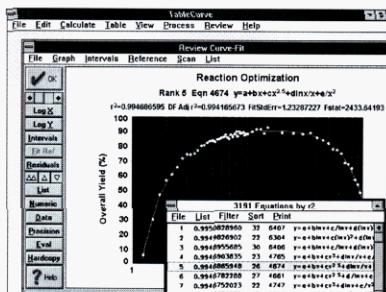


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Being part of the beginnings of NMR spectroscopy was a great privilege and the source of much personal satisfaction. Being asked to recount those experiences at the Pittsburgh Conference has enriched the pleasure of seeing our faith vindicated and our fondest dreams surpassed.

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*James N. Shoolery retired after working more than 35 years in the field of high-resolution NMR spectroscopy at Varian. He received his B.S. degree in chemistry from the University of California at Berkeley in 1948 and his Ph.D. in physical chemistry from the California Institute of Technology in 1952. Shoolery received the Sargent Award in Chemical Instrumentation in 1965, the Anachem Award in Analytical Chemistry in 1982, was named Scientist of the Year by Industrial Research Magazine in 1983, and was appointed a Varian fellow in 1989. He has authored or co-authored more than 160 papers in the field of NMR spectroscopy and holds several patents. He is active as a consultant on the application of NMR spectroscopy to chemical problems.*

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