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NMR's pivotal years: 1969–1972

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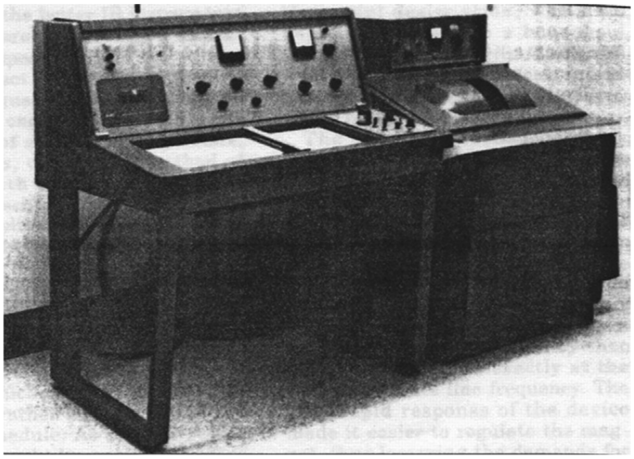
1. Prologue

Up to the late fifties' NMR was mainly in the hands of physicists. With the discovery of the chemical shift, chemists became increasingly interested in the technology and very soon NMR developed into a standard tool for chemists. The introduction of the first routine instrument on the market, the 'A 60' from Varian, was very important to facilitate this.



Varian NMR System 60 MHz early sixties

The introduction of 60 MHz was a vital step in corresponding field strength; before this system, 25 MHz or 30 MHz were the standards. Soon after the introduction of the 60 MHz the next increase of field strength for research instruments was 90 or 100 MHz, with the introduction of the HA 100 from Varian or with the Bruker HFX 90. This increase in frequency made spectra easier to interpret, improved sensitivity and started the race into higher and higher fields, which continues today.

Spectrospin (today Bruker BioSpin) was founded 1965 by Professor Günther Laukien. He decided that Spectrospin had to build a spectrometer – different from the systems available on the market – to compete successfully against Varian's overwhelming market presence.

The proposed HFX system had three independent channels, for measuring, lock and decoupling, the frequencies where generated by synthesizers, with power on each channel individually adjustable. It was equipped with modulation and time-sharing operation for base line stabilization. Furthermore, it was the first instrument on the market equipped with solid state technology. This improved system stability significantly and reduced service requirements considerably. In contrast, the Varian system was still using electronic tubes, one frequency source and was sweeping through the spectral range with the modulation side band also used for baseline stabilization.

This gave the HFX system significant advantages in complex NMR experiments, which then increasingly became the focus of scientists. Decoupling experiments on protons became routine; you just had to move the second frequency synthesizer to the peak you wanted to irradiate, adjust the power and sweep the measuring channel through the spectral range.

Homonuclear internuclear double resonance (INDOR) spectroscopy was also possible, as one put the measuring channel on top of a signal and then swept the decoupling channel through the measuring range indicating all interaction with the measuring signal.

The improved stability also enabled one to accumulate spectra with a CAT (computer of average transient), and thereby to improve sensitivity. This was useful for 1H NMR but even more important for heteronuclear spectroscopy, which was appearing on those days. With a third channel it was also possible to lock on fluorine or deuterium, while sweeping the measuring channel through a range of heteronuclei and while applying proton decoupling. All these new features made the Bruker product very com-

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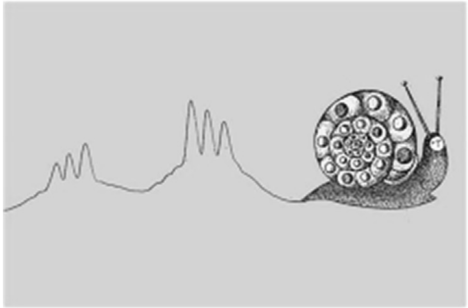
petitive against the dominant Varian one, and allowed Bruker to sell, not only in Europe, but also very successfully in a newly opened US market that began for Bruker in 1968.

Bruker HFX NMR spectrometer operating at 90 MHz, 1968

2. 1969–72: The game-changer

In the mid-sixties Professor Richard Ernst made first successful experiments with Fourier transformation at Varian. He accumulated free induction decays on a CAT, punched the results on cards, and sent them to IBM for Fourier transformation. Scientifically this was a very successful experiment for which, alongside other achievements, Professor Richard Ernst became a Nobel Laureate in 1991. However, as a routine operation this technique was far from being practical.

From CW to FT Spectroscopy



Up to 1964: Snail NMR

FT Spectroscopy
by Prof. Richard Ernst
Nobel Prize in Chemistry 1991

Courtesy of Prof Richard Ernst

Another development published by Ernst in those days was noise decoupling for C13 spectroscopy. With this decoupling, otherwise complex data was reduced to just shift spectra – with significant enhancement in signal strength; the method further improved C13 spectroscopy through the Overhauser effect. This was a big step forward in the measuring of C13 data. However, because the signal to noise achievable was still very low and the measuring took days to get signals barely above the noise level, the applications of C13 spectroscopy were limited to just a few specialists.

In 1969 Bruker entered in negotiations with the Fabri-Tek Instrument Corporation from Madison, Wisconsin – later known as Nicolet Instruments. Fabri-Tek, the producer of the CAT for the HFX 90, offered to modify the CAT by adding a PDP 8 computer, capable of performing FT transformations on-site. What a chance to have the entire FT NMR package right on the spectrometer! Right away a development project started in earnest at Bruker. Transmitter developments in Germany, preamplifiers in Switzerland and the system assembly and testing in America. I had the chance to co-ordinate this development.

My applications passion became C13 Spectroscopy, and therefore I wanted to try this first–although it was considered as not very promising because of the long relaxation times. For this relaxation time measurements enriched trimethyliodide was used. This compound has a really long relaxation time but an intense signal, allowing us to perform the relaxation time measurement in an acceptable timeframe. However, the assumption that ultra-long relaxation times where typically for C13, ended up being completely wrong.

The first step in my road to C13 NMR was to implement broadband decoupling. We considered noise modulation less efficient, and developed a system using a double modulation system with a swept frequency. This proved to be a correct route, and the lower power required to do full decoupling gave us an advantage for many years. Later this mode became less important with the composite pulse decoupling from Freeman et al.

The RF pulse amplifier, providing adequate power for decent 90° pulses, was a tube amplifier. Solid state devices where just not powerful and flexible enough to do the job. For NMR spectroscopy the first system just provided one pulse to stimulate the free induction decay. Finally, the power amplifiers, preamplifiers and the computers came to Billerica, the then Bruker headquarters in America.

A HFX system was modified with the Fabri-Tek computer for signal accumulation (4 K, 20 bit), the PDP 8 for Fourier transformation (16 bit, 8 K), two power amplifiers for pulse and decoupling, switchable preamplifiers, a time-shared lock and a quite elaborate cabling.

All this was disclosed in 1969, when the Journal of Magnetic Resonance was established, and in its first issue this set up was described as follows:

> *"A Fast Fourier Transform system has been introduced by Fabri-Tek, of Madison, Wisconsin. The system includes a 1070 signal averaging computer, a PDP-8/L general purpose computer, and all necessary software and interfacing. The 1070 collects data, which can have a maximum frequency content of 500 KHz, and the transformation is then an off-line process."*

Then came the great moment, the first experiment, a strong signal on the oscilloscope. I thought that it could not be real but must be some oscillation in the system, however I started the Fourier transform procedure anyway. After about 10 min, the transformation time for 4 K words in these days, I saw a spectrum, a spectrum over 100 to 1 on C13. Incredible!

Two weeks after this first spectrum was the Anaheim conference on C 13 spectroscopy. This was the place to show the results! Day and night I was measuring almost all the substances I had in the lab. The reception of the results in Anaheim was tremendous. Professor Thomas Farrar, University of Madison, found the data so spectacular that he gave me a part of his lecture to present my data, a unique event! One of the C13 gurus of this time came to look at the data he had heard of. After a first look he complained to me: 'I want to see C13 data, not protons'. I had a hard time convincing him this that he was seeing, was real C13 data.

After returning to Billerica, other low sensitivity nuclei's where measured. But C13 remained the big thing. I became a popular operator for quite a few NMR groups. For a short time producing the first C13 spectra of lower concentrations or even first temperature experiments were sufficient for a publication. But my main goal was to produce instruments with FT capability, so that we could deliver them to customers as fast as possible. The first deliveries were made in the beginning of 1970.

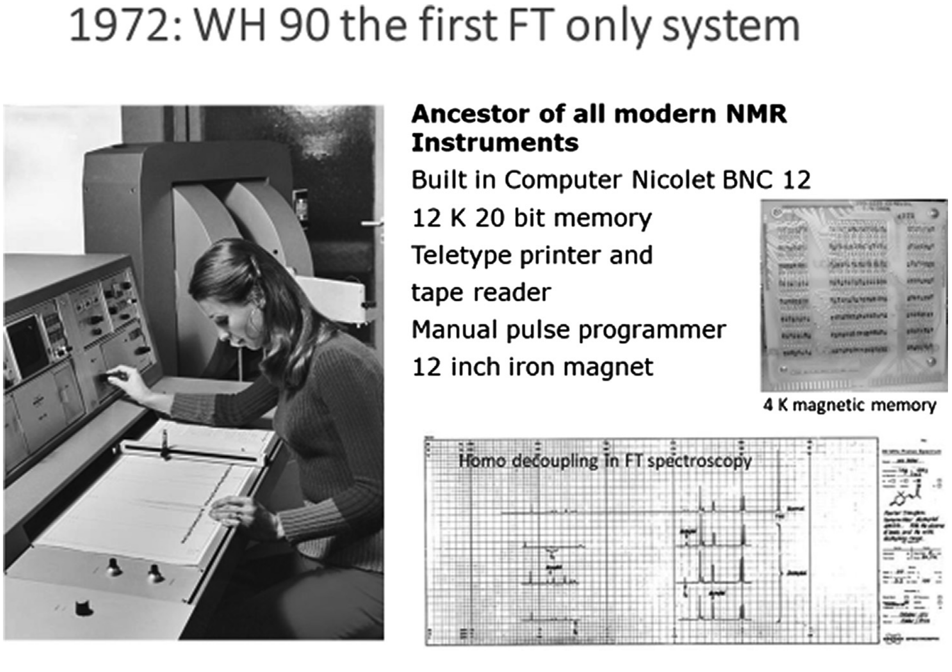
Varian introduced a system similar to our HFX Spectrometer around the same time. The XL 100, a system equipped with a receiver with two intermediate frequencies (IF). The second IF at a frequency of some KHz and therefore with a very narrow bandwidth. Excellent for CW spectroscopy but not for any kind of pulse spectroscopy. It had therefore taken quite some time and a major redesign before the competition could copy our results. This allowed Bruker to stabilize its position on the world market.

This was another announcement that appeared in JMR, Volume 1:

> *"Varian has developed a new solid-state 23.5-kG NMR spectrometer, the XL-100, available with either 12-in. or 15-in. magnet system. By means of a novel frequency division and phase comparator scheme, all rf signals in the lock, observing, and decoupling channels are derived from and synchronized with a deuterium master oscillator operating at 15.4 MHz. Built-in frequency synthesizers in the observing and decoupling channels mix with the rf signals for accurate digital frequency sweeps and offsets, and registration between the recorder arm and synthesizer frequency is obtained by an optical encoder. The system incorporates an all-purpose decoupler unit, both homo- and heteronuclear. In addition to the usual homonuclear internal lock, there are a variety of operating options, such as locking on deuterium while observing hydrogen, or locking on hydrogen while observing other nuclei. Up to five nuclei may be selected by push-button on the console, accompanied by change of several plug-ins on the probe, including a plug-in insert. External lock possibilities also exist by inserting suitable plug-ins into the probe. For more information, write: Varian, Analytical Instrument Division, 611 Hansen Way, Palo Alto, California 94303."*

The new Varian systems had some nice features, so our engineers designed an improved version of our HFX system, optimized for both FT and CW spectroscopy. I was able to try the new system at the Achema exhibition in Frankfurt. I was not impressed by the improvements and we decided not to bring this system to market but to stay with our original HFX design.

I was convinced by then that the CW time was over. One problem was proton homo decoupling, a very important experiment in this time – but we could solve this issue and apply for one of our best patents. Proton FT spectroscopy then became at least as flexible as CW mode, and ten times more sensitive. Therefore, we decided to use some of the inventions made for the improved HFX version and develop a radical new approach in NMR spectrometer design: the FT-only spectrometer. We introduced this



1972: WH 90 the first FT only system

Ancestor of all modern NMR Instruments

Built in Computer Nicolet BNC 12

12 K 20 bit memory

Teletype printer and

tape reader

Manual pulse programmer

12 inch iron magnet

4 K magnetic memory

Homo decoupling in FT spectroscopy

new design at the Pittsburg conference in 1972. We sold the first instrument at the exhibition – an excellent proof of concept!

This radical design was controversial, even inside Bruker; therefore I agreed to develop a CW timesharing attachment. Two customers of this spectrometer ordered this accessory and while we had to build it, it was never used!

This new system family was announced in JMR Volume 8:

> *"BRUKER has two recent additions to their line of high resolution NMR spectrometers. The WH-90 spectrometer is a dedicated Fourier transform instrument for routine analysis and research. The data system consists of a teletype and 20-bit computer with either an 8 K or a 12 K memory mounted directly in the console. Programs are supplied for Fourier transformation, phase correction, integration, peak print out, and basic computer programming. The spectrometer is supplied with a 15-in. magnet with power supply built into the base. The snap-on probe is factory tuned; to change nuclei one merely attaches a different probe head and preamplifier and exchanges plug-in modules on the console. A time-shared deuterium lock and broadband proton decoupler are provided. Accessories, such as a variable-temperature unit and a multi- pulse generator, are available. All rf frequencies are synthesized from a single crystal oscillator. The HX-270 spectrometer uses a superconducting magnet, manufactured in-house by Bruker, and operating at 63.42 kG. The room temperature bore is approximately 50 mm in diameter and permits spinning and variable temperature operation with sample tubes of up to 15 mm diameter. Sample changing can be accomplished completely from the top, eliminating the need to withdraw the probe from the bottom of the solenoid."*

In this instrument we used an improved version of the Nicolet computer the BNC 12. This was a compact version of the computer that we announced in JMR, Volume 7:

> *"NICOLET INSTRUMENTS announces the availability, as part of the 1080 Data System, of the Model SD-82 plug-in signal digitizer, which offers the user a choice of 21 different cut-off frequencies from 125 to 25 kHz. This active 4-pole Butterworth filter saves the expense of purchasing external filters and in addition is much easier to use. The 1080 System acquires and analyzes NMR spectral data using either Fourier or cw techniques. Its 20-bit word length eliminates time-consuming double-precision data storage. Data memory is expandable from 4 to 32 K in 4 K increments. Hardware multiply/-divide and bit-inversion are also standard. The 1080 is unique in that it performs both stored program and wired program computations using much of the same circuitry for both. Stored programs are used for complex arithmetic computations on stored data while wired programs facilitate high- speed signal averaging and data display functions. Complete 1080 Systems start at $29,300. For details contact Nicolet Instrument Corporation (formerly Fabri-Tek Instruments, Inc.), 5225 Verona Road, Madison, WI 53711."*

3. Magnet development

The iron magnets we were using had their physical limit around 100 MHz. We tried to go to higher fields but saturation of the iron made it impossible to reach resolution and stability required for NMR purposes. The only possibility to increase field strength was to go to superconducting magnets.

Varian was offering a 220 MHz system with a Westinghouse magnet, and the MPI in Heidelberg had a Siemens prototype with home build electronics. These systems where complicated to use, limited in resolution, stability and flexibility compared to the iron magnet systems.

In fall of 1970 we had a meeting at Oxford University with Sir Rex Richard and his team, Sir Martin Wood and John Woodgate of Oxford Instruments, and Günther Laukien and myself from Bruker. We discussed superconducting magnet designs. We agreed that the new magnet had to perform as well as the best iron magnet system, should be as easy to use and as flexible, and operate at significant higher fields. This brain storming did take a full day but, in the evening, we had the definition of the ideal magnet. The design was extremely successful and every magnet from every company ultimately followed the design we came up with. Bore diameter, access from top for the sample tube and from below the connections for cabling, the shim system and the variable temperature accessory is still exactly the same today. With the single filament SC wire available 1970 we decided for a spectrometer frequency of 270 MHz, three times the measuring frequency we could offer with an iron magnet system – the largest field increase ever!

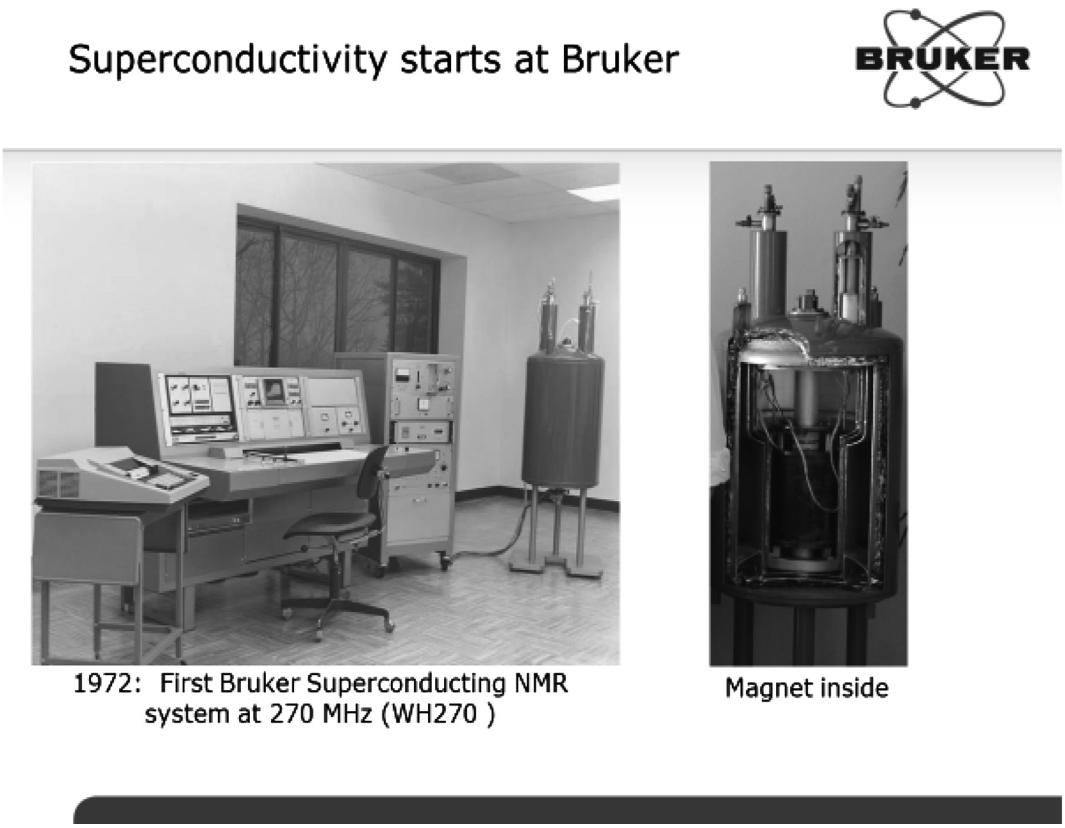
Both Oxford Instruments and Bruker in Burlington near Boston developed a system with these specifications. As early as 1972 we installed the first spectrometer with an Oxford magnet in Sir Rex Richards' lab. The announcement of the new magnet by Oxford Instruments came out in JMR, Volume 5

> *"The Oxford Instruments Company has announced the production of a high-homogeneity superconducting magnet system to be used at an operating frequency of 270 MHz for protons. The first system of this type is being delivered to the Department of Biochemistry at Oxford University, where it will operate with a Bruker HFX console as part of a Fourier-transform, multi-nuclei spectrometer. Initial tests with two sets of room temperature axial correction coils gave a measured line width of 2.5 parts in unspun and 1 part in* 10^8 *with sample spinning, using a 10 mm diameter sample. Additional correction coils are expected to permit reduction of field inhomogeneity to less than 1 part in* 10^9*. Design of the cryostat permits complete through access to the bore of the magnet, allowing changing of samples without moving the rf probe. Liquid-helium consumption is claimed to be only 100 cc/hr. Further information may be obtained from Dr. J.B. McKinnon, Head of Design and Development, Oxford Instrument Company, Osney Mead, Oxford OX2 ODX, England. American sales office is located at 100 Cathedral Street, Annapolis, MD."*

In the same issue Bruker announced its new facility in JMR as well

> *"Bruker Magnetics, Inc, has been established to distribute laboratory electro- magnet systems, DC power supplies, superconducting magnet systems, and magnetic susceptibility systems in the United States. Address is One Vine Brook Park, Burlington, Massachusetts 01803."*

The first Bruker NMR system produced in Boston was delivered to Chicago. It was the only superconducting spectrometer we delivered for CW spectroscopy, all other systems from then on where FT systems. That is how fast the new technology took over!



Superconductivity starts at Bruker

1972: First Bruker Superconducting NMR system at 270 MHz (WH270)

Magnet inside

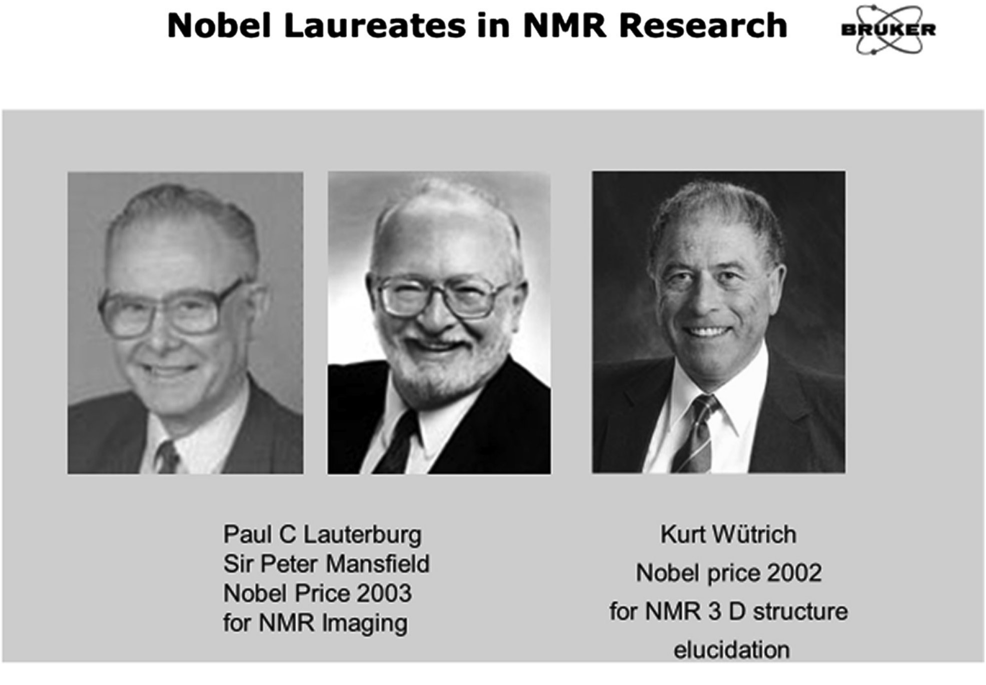
This magnet design was so revolutionary that all the other products where no longer saleable and it took Varian up to the end of the seventies to bring out a similar system: the XL 200. By this time we had broken the 400 MHz barrier, using multifilament wire technology!

In the mean time we had to close our operation in Burlington, as the building collapsed. The demand for these new magnets was very strong, and in a hurry, we transferred the production to Spectrospin in Switzerland.

4. Epilogue

I focused this account on 1969–1972; three years of major break throughs in NMR. But we were just on the edge of further major advances, which in the same seminal years included:

- The idea of Jean Jeener of 2D NMR, presented at the Ampere summer school in in 1971 in Basko Polje.
- The proposal of Paul Lauterbur at the ENC in the same year for imaging using gradients, which opened a new world of applications and two more Nobel prizes.

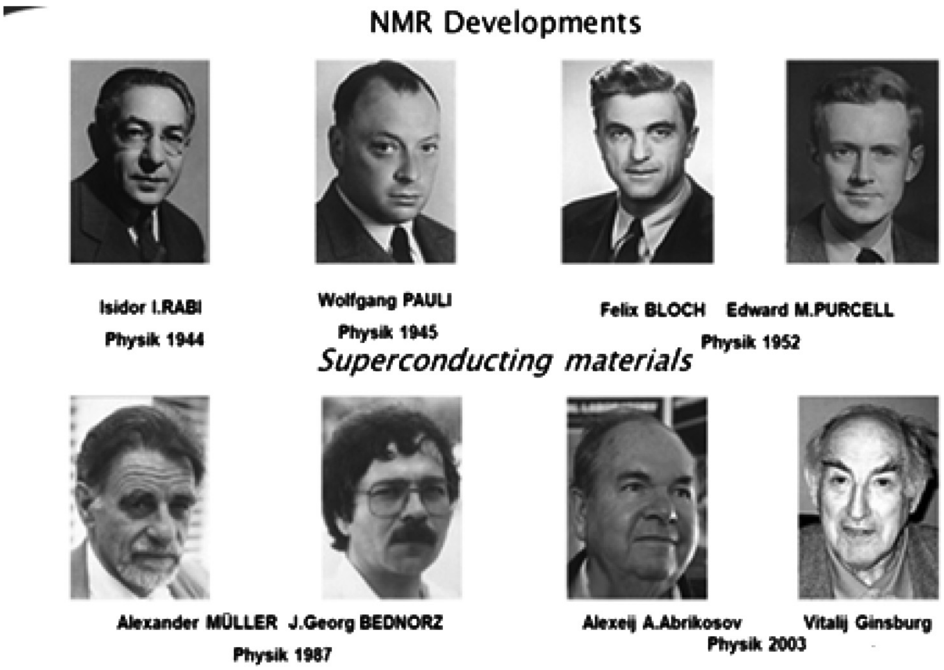


Nobel Laureates in NMR Research

Paul C Lauterburg
Sir Peter Mansfield
Nobel Price 2003
for NMR Imaging

Kurt Wütrich
Nobel price 2002
for NMR 3 D structure
elucidation

NMR and Superconductivity Laureates not yet mentioned:



To stay on top of these new applications was very challenging but also very rewarding for Bruker! The expanding field of NMR produced a continuous flow of inventions, to which Bruker contributed to and benefited from. It also produced a continuous flow of scientific contributions, which provided the base for the development of the Journal of Magnetic Resonance over the years. The developments in NMR continues at a strong pace, and I am sure there will be plenty of new materials and new contributions over the next 50 years! I therefore wish all the best to JMR and Bruker, in their drive of this extraordinary technology to further heights!