JOURNAL OF MAGNETIC RESONANCE IMAGING 20:177–179 (2004)

The next invited editorial comes from the immediate past President of the ISMRM, Dr. Chris Boesch. His overview provides a special perspective on the rapid development and application of MRI over a relatively short period of time, involving the award of 13 Nobel Prizes, including one to his own major professor. His overview of this process from his perspective as a recognized, elected ISMRM officer and as a Swiss physician-investigator follows below. The article includes 31 references that help to focus on the history of the development of MRI. Additional commentary for supportive or conflicting views is invited for consideration for publication in JMRI.

Invited Editorial Comment

Nobel Prizes for Nuclear Magnetic Resonance: 2003 and Historical Perspectives

Multiplied many times by emails and phone calls, a press release went around the globe in a few hours: *"The Nobel Assembly at Karolinska Institutet has today decided to award The Nobel Prize in Physiology or Medicine for 2003 jointly to Paul C. Lauterbur and Peter Mansfield for their discoveries concerning magnetic resonance imaging."* The MR community was speculating for years about a Nobel Prize that would be awarded to the developers of MRI. While it has been obvious that this discovery deserves recognition, it was a question of when and how the Nobel Prize Committee would select the laureates. While many contributed to the development of MRI in the early days, Paul C. Lauterbur and Sir Peter Mansfield unquestionably are the ones who had the fundamental ideas. While we celebrate happily these most recent laureates, their merits shall be put into a historic perspective of other Nobel Prizes in the field of NMR. In particular, I want to emphasize that four prizes were awarded for NMR in little more than a decade (Tables 1 and 2). Looking at the history of NMR (1–3) and at its applications in very different fields helps to recognize the enormous versatility of this physical effect and may explain why this field is so successful. It also gives an idea of how many applications are still hidden and waiting to be discovered in the future. In this respect, looking back may help to look forward.

There is no question that Paul C. Lauterbur's 1973 publication in *Nature* represents a milestone in the development of MR in medicine (4). He suggested that magnetic field gradients could be used to define the spatial distribution of protons in water by different frequencies. In this seminal paper, he showed a two-dimensional image of two tubes filled with water based on a "projection reconstruction" algorithm that was closely related to image generation by computed tomography (CT). While Lauterbur's publication was the most explicit and clear-cut suggestion of how NMR could be used to obtain images in macroscopic dimensions, Mansfield considered the use of magnetic field gradients for a spatial separation of NMR signals in a more theoretical description about "NMR diffraction in solids" (5). This approach dealt with crystals and was so sophisticated that it was overlooked for almost a decade before the MR community realized that Mansfield, in fact, had also suggested the use of gradients for spatial encoding, i.e., for imaging. While gradients had been used in earlier years to destroy spurious signals from imperfect radiofrequency pulses or as diffusion and flow sensitizing elements in a pulse sequence, Lauterbur and Mansfield introduced the unique idea to use gradients for spatial encoding, i.e., to generate a spectrum of spatially distributed frequencies.

Recently, Raymond Damadian claimed, in *The Washington Post*, his entitlement to the prize. It is unquestioned that he deserves recognition for his observation of relaxation time differences in malignant tissue (6). His suggestion motivated the application of MR in medicine, and, in that respect, it also fostered interest for the new imaging technology. However, his US patent on an "Apparatus and method for detecting cancer in tissue" (7) failed to show a feasible method to obtain spatially selected NMR signals. The described "beam of radiofrequency waves with a narrow cross-section, generated by helically moving transmitters" has, to the best of my knowledge, not been used so far to generate two-dimensional images. In particular, the later "Topical Magnetic Resonance" (8) and "FONAR" (9) are based on a spatial variation of the static magnetic field, not of the radiofrequency field. In contrast, two other ideas had a particular impact: "echo planar imaging," proposed again by Sir Peter Mansfield (10), and the application of Fourier techniques (11), suggested by Richard R. Ernst's group (Nobel Laureate 1991).

Tables 1 and 2 show nicely how NMR evolved from a physical tool (Prizes 1944 to 1989) to applications in chemistry (Prizes 1991 and 2002) and in medicine (Prizes 2003). Following the observation of Stern and Gerlach (12) in 1921, who observed the "spin" of silver atoms, Isidor Isaac Rabi published a one-page report on "A New Method of Measuring Nuclear Magnetic Moment" (13). He used oscillating fields to re-orient the nuclear spins and was awarded the Nobel Prize in Physics in 1944. At least two scientists contributed significantly to the field but failed in one or another way. It seems that E. K. Zavoisky, a scientist in Kazan/Russia, observed an NMR effect in 1941 (2), yet was not able to reproduce it, mainly due to World War II in his home country, the USSR. He was more successful in a related field, i.e., electron spin resonance (14). Another scientist, C. J. Gorter, attempted to measure nuclear paramagnetism. However, while he failed several times with his own measurements (15), he inspired Rabi's group to conduct their successful experiment (13). In the Western hemisphere, WWII promoted the development of radar and subsequently improved radio-transmitters and amplifiers, which were necessary for the discovery of magnetic resonance. At the end of the war, in 1946, Purcell, Torrey, and Pound (16) published a report on NMR effects in solids. At the same time, Bloch, Hansen, and Packard (17,18) made a similar and successful attempt to measure what they called "nuclear induction." It seems that it was not immediately clear that the two independent groups described the same effect. These reports were crucial for modern applications of NMR in solution and human tissue because they transferred knowledge about Rabi's work in molecular beams into an effect that had been observed in bulk matter. Bloch and Purcell were awarded the 1952 Nobel Prize in Physics. So far, NMR contributed almost exclusively to the development of nuclear physics, and research in this field continued to concentrate on characterizing materials and measuring nuclear parameters.

In his Nobel Lecture, Richard R. Ernst revealed an astonishing fact: quite a few scientists who contributed to the early development of NMR received a Noble Prize in Physics for their subsequent work in other areas. A. Kastler (Nobel Laureate 1966) was one of those who proposed the "double resonance method," combining optical with magnetic resonance (19). J.H. Van Vleck (Nobel Laureate 1977) developed the theory of dia- and paramagnetism and also published together with C.J. Gorter (20). Nicolaas Bloembergen (Nobel Laureate 1981) worked on relaxation effects ("BPP theory") and the influence of motion (21). K.A. Müller (Nobel Laureate 1987) contributed significantly to electron paramagnetic resonance (22). H.G. Dehmelt (Nobel Laureate 1989) developed pure nuclear quadrupole resonance (23). N.F. Ramsey (Nobel Laureate 1989) was I.I. Rabi's first graduate student and introduced the concept of the chemical shift (24) and J coupling.

In the early years of NMR, a spectrum was measured by continuous irradiation with radiofrequency waves (CW). Seminal publications by H.C. Torrey (25) and E. Hahn (26,27) showed that the signals "free induction decays" and "spin echoes" could also be detected after the excitation of the spins with a radiofrequency pulse. Ernst and Anderson (28) realized that these signals contain the whole information of a spectrum and thus introduced Fourier techniques into NMR. In the following years, the two subsequent Nobel Laureates, Richard R. Ernst (Chemistry 1991) and Kurt Wüthrich (Chemistry 2002), both worked at the ETH in Zurich, Switzerland. Amazingly, an old photograph shows two huts on the roof of the chemistry building where their offices had been installed. They used a common NMR system,

Table 1
Nobel Prizes Directly Related to MR

Name	Year	Category	Description	ISMRM opening lecture
Paul C. Lauterbur	2003	Medicine	"For their discoveries concerning magnetic resonance imaging"	Honolulu 2002
Sir Peter Mansfield	2003	Medicine	"For their discoveries concerning magnetic resonance imaging"	Glasgow 2001
Kurt Wüthrich	2002	Chemistry	"For his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution"	Kyoto 2004
Richard R. Ernst	1991	Chemistry	"For his contributions to the development of the methodology of high resolution nuclear magnetic resonance (NMR) spectroscopy"	Denver 2000
Felix Bloch	1952	Physics	"For their development of new methods for nuclear magnetic precision measurements and discoveries in connection therewith"	
Edward Mills Purcell	1952	Physics		
Isidor Isaac Rabi	1944	Physics	"For his resonance method for recording the magnetic properties of atomic nuclei"	See Table 2, Norman F. Ramsey

Table 2
Nobel Prizes in Other Fields, Awarded to Individuals Who Also Contributed to the Development of MR

Name	Year	Category	Description	ISMRM Opening Lecture
Norman F. Ramsey	1989	Physics	"For the invention of the separated oscillatory fields method and its use in the hydrogen maser and other atomic clocks"	Toronto 2003: Lecture on I. Rabi (see Table 1)
Hans G. Dehmelt	1989	Physics	"For the development of the ion trap technique"	
K. Alexander Müller	1987	Physics	"For their important break-through in the discovery of superconductivity in ceramic materials"	
Nicolaas Bloembergen	1981	Physics	"For their contribution to the development of laser spectroscopy"	
John H.Van Vleck	1977	Physics	"For their fundamental theoretical investigations of the electronic structure of magnetic and disordered systems"	
Alfred Kastler	1966	Physics	"Optical methods for studying Hertzian resonances"	

and Richard R. Ernst was desperate because it was equipped for CW only, though he had just invented the much more powerful Fourier technique. In the following years, an extremely successful collaboration started between the two groups; in contrast to the offices, the NMR equipment was always brand new and powerful.

After an oral presentation by Jean Jeener, Richard Ernst developed two-dimensional NMR spectroscopy (29,30), which is also the basis for modern imaging techniques (11) in medicine. While the paper on Fourier imaging had enormous impact on the development of MRI, Richard R. Ernst received his Nobel Prize 1991 particularly for his contribution to high-resolution NMR, where multi-dimensional Fourier techniques were increasingly used. Meanwhile, Kurt Wüthrich and his group applied NMR techniques for the elucidation of three-dimensional structures of biologic macromolecules (31). After decades of continuous improvements, NMR conformation analysis of molecules in solution became an essential tool in biochemistry and biophysics. When the Nobel Committee awarded the prize to Ernst in 1991, it was not immediately clear that Kurt Wüthrich would also be awarded some years later. However, when the committee decided to assign the 2002 Prize again to the field of high-resolution NMR, the message was clear: 1) high-resolution was so powerful in chemistry that it was appropriate to select this field again and 2) even if the scientific work of Ernst and Wüthrich was closely related, both contributions were so unique that they deserved an independent recognition.

As an interesting fact, the leftmost columns of Tables 1 and 2 illustrate how prophetic the ISMRM has been in selecting speakers for the opening sessions at the annual meetings. Also demonstrated are the success and impact of non-medical applications of magnetic resonance, in particular the physical roots and high-resolution NMR. This overview and the historic context of the 2003 Nobel Prizes in Medicine shall demonstrate how vital and vibrant NMR has been for several decades. Because high-resolution NMR and in vivo MR apply the same physical effect, I would speculate that many applications still wait to be transferred and that the already extremely successful history of medical MR is just the beginning of an ongoing progress. It is uncertain if this will result in additional Nobel Laureates in the field of MR in the near future; however, the field is so vital and sustaining that it will be a valuable candidate for the coming decades.

Chris Boesch, MD, PhD
University and Inselspital
Bern, Switzerland

DOI 10.1002/jmri.20120
Published online in Wiley InterScience (www.interscience.wiley.com).

REFERENCES

1. Andrew ER. A historical review of NMR and its clinical applications. Br Med Bull 1984;40:115–119.
2. Becker ED, Fisk C, Khetrapal CL. The development of NMR. In: Grant DM, Harris RK, editors. Encyclopedia of nuclear magnetic resonance. Chichester Sussex UK: Wiley; 1996. p 1–160.
3. Boesch C. Molecular aspects of magnetic resonance imaging and spectroscopy. Mol Aspects Med 1999;20:185–318.
4. Lauterbur PC. Image formation by induced local interactions: examples employing nuclear magnetic resonance. Nature 1973;242:190–191.
5. Mansfield P, Grannell PK. NMR 'diffraction' in solids. J Phys C: Solid State 1973;6:L422–L426.
6. Damadian R. Tumor detection by nuclear magnetic resonance. Science 1971;171:1151–1153.
7. Damadian RV. Apparatus and method for detecting cancer in tissue. US patent 3789832, 1972.
8. Gordon RE, Hanley PE, Shaw D. Topical magnetic resonance. Prog NMR Spectroscopy 1982;15:1–47.
9. Damadian R. Field focusing n.m.r. (FONAR) and the formation of chemical images in man. Phil Trans R Soc Lond Series B 1980;289: 489–500.
10. Mansfield P. Multi-planar image formation using NMR spin echoes. J Phys C: Solid State 1977;10:L55–L58.
11. Kumar A, Welti D, Ernst RR. NMR fourier zeugmatography. J Magn Reson 1975;18:69–83.
12. Gerlach W, Stern O. Der experimentelle Nachweis des magnetischen Moments des Silberatoms. Z Phys 1921;8:110–111.
13. Rabi II, Zacharias JR, Milman S, Kusch P. A new method of measuring nuclear magnetic moment. Phys Rev 1938;53:318.
14. Zavoisky EK. Spin-magnetic resonance in paramagnetics. J Phys USSR 1945;9:211–245.
15. Gorter CJ. Negative results of an attempt to detect nuclear magnetic spins. Physica (The Hague) 1936;3:995–998.
16. Purcell EM, Torrey HC, Pound RV. Resonance absorption by nuclear magnetic moments in solids. Phys Rev 1946;69:37–38.
17. Bloch F, Hansen WW, Packard ME. The nuclear induction experiment. Phys Rev 1946;70:474–485.
18. Bloch F. Nuclear induction. Phys Rev 1946;70:460–474.
19. Brossel J, Kastler A. La detection de la resonance magnetique des niveau excites—l'effect de depolarisation des radiations de resonance optique et de fluorescence. C R Hebd Acad Sci 1949;229: 1213–1215.
20. Gorter CJ, van Vleck JH. The role of exchange interaction in paramagnetic absorption. Phys Rev 1947;72:1128–1129.
21. Bloembergen N, Purcell EM, Pound RV. Relaxation effects in nuclear magnetic resonance absorption. Phys Rev 1948;73:679–712.
22. Shengelaya A, Reich S, Tsabba Y, Muller KA. Electron spin resonance and magnetic susceptibility suggest superconductivity in Na doped WO3 samples. Eur Phys J B 1999;12:13–15.
23. Dehmelt HG, Krüger H. Kernquadrupolfrequenzen in festem Dichloräthylen. Naturwissenschaften 1950;37:111–112.
24. Liddel U, Ramsey NF. Temperature dependent magnetic shielding in ethyl alcohol. J Chem Phys 1951;19:1608.
25. Torrey HC. Transient nutations in nuclear magnetic resonance. Phys Rev 1949;76:1059–1068.
26. Hahn EL. Spin echoes. Phys Rev 1950;80:580–594.
27. Hahn EL. An accurate nuclear magnetic resonance method for measuring spin-lattice relaxation times. Phys Rev 1949;76:145–146.
28. Ernst RR, Anderson WA. Application of Fourier transform spectroscopy to magnetic resonance. Rev Sci Instrum 1966;37:93–102.
29. Mueller L, Kumar A, Ernst RR. Two dimensional carbon-13 NMR spectroscopy. J Chem Phys 1975;63:5490–5491.
30. Aue WP, Bartholdi B, Ernst RR. Two-dimensional spectroscopy: application to nuclear magnetic resonance. J Chem Phys 1976;64: 2229–2246.
31. Wüthrich K. The second decade—into the third millenium. Nat Struct Biol 1998;5(suppl):492–495.