An Excursion into the History of Magnetic Resonance Imaging

An Offprint from

Peter A. Rinck

Magnetic Resonance in Medicine

A Critical Introduction

The Basic Textbook
of the European Magnetic Resonance Forum

13th edition • 2023
335 figures, 36 tables

Peter A. Rinck
Magnetic Resonance in Medicine • A Critical Introduction
The Basic Textbook of the European Magnetic Resonance Forum
13th edition 2022 – www.magnetic-resonance.org • www.trtf.eu • centralmaildesk@trtf.eu

European Magnetic Resonance Forum is an imprint of
THE ROUND TABLE
FOUNDATION

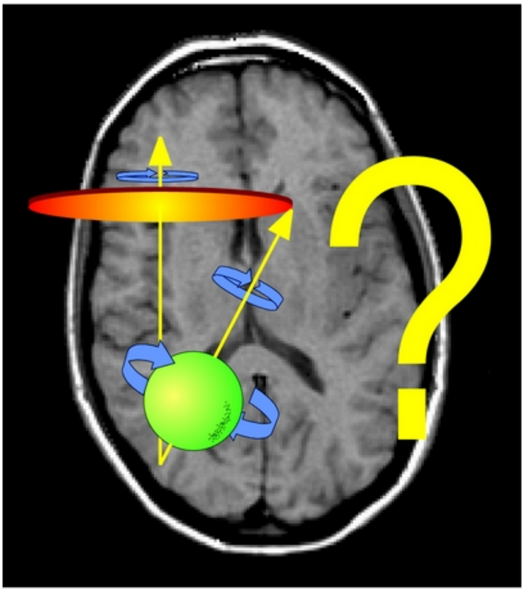
First English edition 1985
Eleventh English edition (e-book) 2017
Twelfth English edition (print) 2018
Thirteenth English edition (print) 2023

A bibliographic entry has been prepared for the Deutsche Nationalbibliographie. The German National Library (Deutsche Bibliothek) lists this publication in the German National Bibliography; detailed bibliographic data are available in the internet.

The interludes between the chapters were taken from Rinckside (ISSN 2364-3889). Rinckside is published at least six times per year both in an electronic (www.rinckside.org) and a printed version. Rinckside is listed by the German National Library.

Printing, binding and distribution in the DACH countries:
BoD Book on Demand, Norderstedt, Germany. Printed in Germany.
ISBN: to be announced – preprint – 22-VIII-08

Foreword



"Why, sometimes I've believed as many as six impossible things before breakfast."
The White Queen in Lewis Caroll's 'Alice Through the Looking Glass'.

We like books – printed on paper, if possible with a beautiful hard-cover binding. Thus, putting this standard textbook on the internet some years ago was a challenge. Now we return with a printed version of the magnetic resonance textbook. The reasons I have described elsewhere.[1]

Celebrating the 50th anniversary of MR imaging in 2021 was a good occasion to publish a new edition. The textbook-child has grown up, become an adult or, in our case – a rather successful standard textbook. The reviews and public reaction to the book were extremely positive.

The first version of this primer – a little booklet – was written at Paul C. Lauterbur's laboratories in the early 1980s. Lauterbur was the father of MR imaging and received the Nobel Prize twenty years later. The text was intended to be used as the Basic Textbook for EMRF, the European Magnetic Resonance Forum. After Lauterbur saw the first edition, he commented: "It looks like a fine book, especially for residents, nurses, and technicians."

Initially we thought this statement was not very encouraging, but in hindsight this was exactly what we had intended to write. We worked on it for another twenty years – and finally Lauterbur found the last edition he read before his death "gratifying". How-

1 Rinck PA. An expensive dilemma: Tablets versus textbooks. Rinckside 2015; 26,7: 17-19.

ever, the target audience today includes scientists and university professors. They should be able to acquire a basic knowledge which enables them to pursue studies of their own and to cope with some of the most common problems, among them tissue relaxation, image contrast and artifacts or questions concerning possible hazards to patients – and to become aware of how to perform reliable research, and to ask and be critical.

The main author and the contributors have not attempted to cover the field completely nor to be exhaustive in the topics discussed, as the field of magnetic resonance still is in a permanent stage of development and therefore changing year by year. Clinical MR machines and even equipment sold for scientific purposes have been increasingly altered into push-button black boxes with pre-fab, given and unchangeable protocols. We are not interested in certain gadgets or "apps" of commercial machines, and won't mention or describe them. We try to explain the fundamentals any user should know and understand.

As with everything in life, MR imaging does not only require knowledge of facts but also of background information and of the historical development of the field for critical decision making. Therefore we have interspersed some subjective, critical, and opinion-oriented sections – interludes – intended to offset the technical nature of the teaching sections and provide some insights into more practical questions faced by MR users.

Most of them were taken from *Rinckside* (www.rinckside.org), a collection of columns published since 1990.

Many of the recent developments concerning MR equipment and its medical and biological applications have turned away from magnetic resonance itself to novel engineering and software approaches in image processing including artificial intelligence. Techniques, ideas and algorithms were imported from fields outside medicine and adopted by software engineers with little or no background in MR and medicine nor insight into medical needs. We mention some of the prime approaches without going into details of signal or image processing – they are of no importance for the understanding of fundamental facts of magnetic resonance imaging.

There has been a long list of contributors to this and earlier versions (see page 418). Their support, ideas, dedication, and feedback have added much to the quality of this work. This book was peer-reviewed by a number of competent reviewers in different fields whom I thank for their efforts.

If you want to learn something about magnetic resonance imaging or its applications choose your topic of interest. If you want to learn it from scratch start with Chapter 1; and if you want to air your brain, read the interludes that are scattered in between.

If you find any mistakes in this book, rest assured that they were left intentionally so as not to provoke the gods with something which is perfect. Still, we would be happy about your feedback. We hope that this textbook will be useful for you and that you will enjoy it. If you have comments or suggestions, please write to us.

Peter A. Rinck, August 2022

Contents

Chapter Twenty

An Excursion into the History of MR Imaging

Figure 20-01:
After more than four hours: The first three-dimensional ECG-triggered images of the heart, 1982.
From left to right: Paul C. Lauterbur, Peter A. Rinck, and Robert N. Muller.

In the Mist of Time

Looking back at the main protagonists involved in MR imaging is vital for an understanding of the development of the modality. This chapter is a short, incomplete, but to our knowledge authoritative introduction to the topic of MR imaging in science and biomedicine – seen from a European perspective (Euro-American, that is: Figure 20-01).

The history of the little world of nuclear magnetic resonance and magnetic resonance imaging is a mirror of the big world: one meets good, honest, and straightforward people, and bad and dishonest people; true scientists and fake scientists; one learns that patents for discoveries are filed by people who have not even done research on the topic; one sees that different people at different places can get the same or similar ideas, independent from each other. And that money makes the world go round.

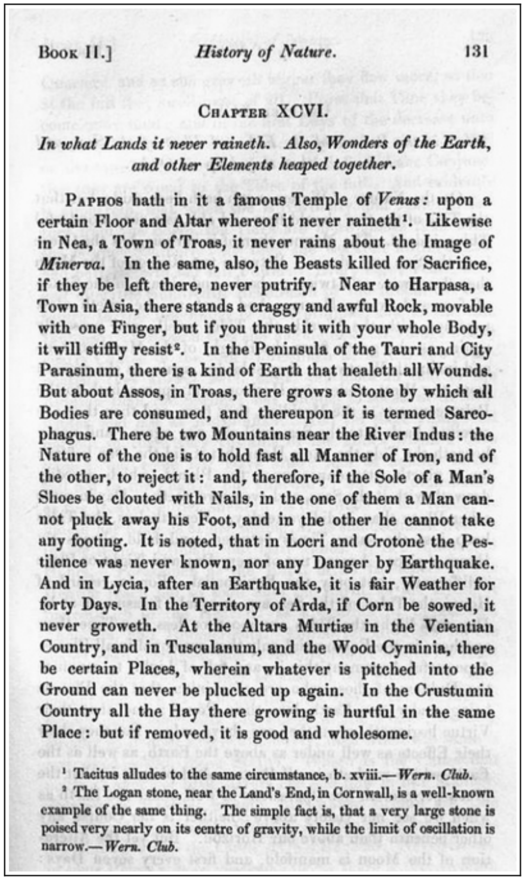
The history of MR imaging has no real beginning: *Everything flows and nothing stays,* as Heraklitos pointed out – and writing about history is a permanent Work-in-Progress.

Two of the most important scientists for the development of magnetic resonance imaging were Erik Odeblad who first described the differences of relaxation times in human tissue and Paul C. Lauterbur who invented MR imaging. Others liked to belittle their accomplishments.

There are a number of personal accounts tracing the development of NMR and MRI during the last eighty years, for instance those collected by Grant, Harris and collaborators.[482] A fine overview of magnetism and medicine was written by Manuel R. Mourino.[483]

Tales hinting to magnetism date back to the first centuries BC, among them the writings of Lucretius and Pliny the Elder.

Pliny (23-79 AD) wrote of a hill near the river Indus that was made entirely of a stone that attracted iron (Figure 20-02). He also mentioned the magical powers of magnetite that kept haunting mankind through the centuries.



BOOK II.] *History of Nature.* 131

CHAPTER XCVI.

In what Lands it never raineth. Also, Wonders of the Earth, and other Elements heaped together.

PAPHOS hath in it a famous Temple of *Venus:* upon a certain Floor and Altar whereof it never raineth[1]. Likewise in Nea, a Town of Troas, it never rains about the Image of *Minerva.* In the same, also, the Beasts killed for Sacrifice, if they be left there, never putrify. Near to Harpasa, a Town in Asia, there stands a craggy and awful Rock, movable with one Finger, but if you thrust it with your whole Body, it will stiffly resist[2]. In the Peninsula of the Tauri and City Parasinum, there is a kind of Earth that healeth all Wounds. But about Assos, in Troas, there grows a Stone by which all Bodies are consumed, and thereupon it is termed Sarcophagus. There be two Mountains near the River Indus: the Nature of the one is to hold fast all Manner of Iron, and of the other, to reject it: and, therefore, if the Sole of a Man's Shoes be clouted with Nails, in the one of them a Man cannot pluck away his Foot, and in the other he cannot take any footing. It is noted, that in Locri and Crotonè the Pestilence was never known, nor any Danger by Earthquake. And in Lycia, after an Earthquake, it is fair Weather for forty Days. In the Territory of Arda, if Corn be sowed, it never groweth. At the Altars Murtiæ in the Veientian Country, and in Tusculanum, and the Wood Cyminia, there be certain Places, wherein whatever is pitched into the Ground can never be plucked up again. In the Crustumin Country all the Hay there growing is hurtful in the same Place: but if removed, it is good and wholesome.

[1] Tacitus alludes to the same circumstance, b. xviii.—*Wern. Club.*

[2] The Logan stone, near the Land's End, in Cornwall, is a well-known example of the same thing. The simple fact is, that a very large stone is poised very nearly on its centre of gravity, while the limit of oscillation is narrow.—*Wern. Club.*

Figure 20-02:
Pliny the Elder's description of magnetism:
"There be two Mountains near the River Indus. the Nature of the one is to hold fast all Manner of Iron, and of the other, to reject it: and, therefore, if the Sole of a Man's Shoes be clouted with Nails, in the one of them a Man cannot pluck away his Foot, and in the other he cannot take any footing."
Translation into English by Philemon Holland. London: George Barclay Publishers, 1847.

The relation between electricity and magnetism was proved by Hans Christian Oersted (Figure 20-03) in 1820 when – during a university lecture – he deflected the needle of a magnetic compass by holding a charged wire next to it, thus producing a magnetic field. His finding influenced French physicist André-Marie Ampère's and British James Clerk Maxwell's research on electricity and magnetism.

A major contributor to – not only – magnetic resonance can be found in Napoleon's realm: Jean-Baptiste-Joseph Fourier (Figure 20-04). He served three years as the secretary of the Institut d'Egypte at the beginning of the nineteenth century, and later became prefect of the Isère département in France. However, the focus of his life was mathematics, and without his Fourier transform we would have difficulties to create MR images.

482 Grant DM, Harris RK. Encyclopedia of Nuclear Magnetic Resonance. Volume 1 – Historical perspectives. Chichester, New York: John Wiley and Sons. 1996.

483 Mourino MR. From Thales to Lauterbur, or from lodestone to MR imaging: magnetism and medicine, Radiology 1991; 180: 593-612.

Figure 20-03: Hans Christian Oersted (1777-1851)

Figure 20-04: Jean-Baptiste-Joseph Fourier (1768-1830)

Figure 20-05: Edward M. Purcell (1912-1997)

Figure 20-06: Felix Bloch (1905-1983)

Nuclear Magnetic Resonance

In 1946, two scientists in the United States, independently of each other, described a physico-chemical phenomenon which was based upon the magnetic properties of certain nuclei in the periodic system. This was *Nuclear Magnetic Resonance*, for short *NMR*. The two scientists, Edward M. Purcell and Felix Bloch, were awarded the Nobel Prize in Physics in 1952.[484, 485]

Purcell (Figure 20-05) was born in Illinois in the United States of America and studied at Purdue University in Indiana. After a research year at the Karlsruhe Technical University in Germany, he worked at the Massachusetts Institute of Technology.

The discovery of nuclear magnetic resonance absorption was made just after the end of the World War II when he became Professor of Physics at Harvard. As Bloch's paper on the subject, Purcell's was published in Physical Review in early 1946, (Figure 20-07).

Bloch (Figure 20-06) was born in Zurich and taught at the University of Leipzig until 1933; he then emigrated to the United States and was naturalized in 1939. He joined the faculty of Stanford University at Palo Alto in 1934 and became the first director of CERN in Geneva in 1962. In 1983 he died in Zurich.

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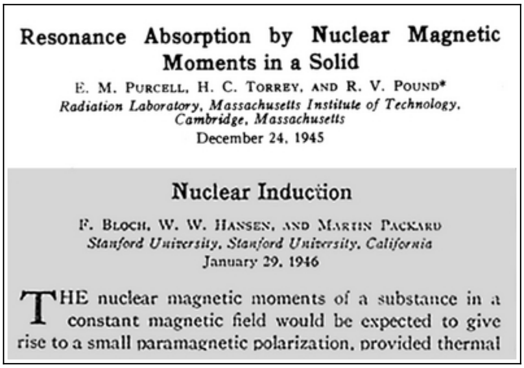
484 Bloch F, Hanson WW, Packard M. Nuclear induction. Phys Rev 1946; 69: 127.

485 Purcell EM, Torrey HC, Pound RV. Resonance absorption by nuclear magnetic moments in a solid. Phys Rev 1946; 69: 37-38.



Resonance Absorption by Nuclear Magnetic Moments in a Solid

E. M. PURCELL, H. C. TORREY, AND R. V. POUND*

Radiation Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts

December 24, 1945

Nuclear Induction

F. BLOCH, W. W. HANSEN, AND MARTIN PACKARD

Stanford University, Stanford University, California

January 29, 1946

THE nuclear magnetic moments of a substance in a constant magnetic field would be expected to give rise to a small paramagnetic polarization, provided thermal

Figure 20-07:
The headlines of Purcell's and Bloch's papers: Purcell's paper reached the Physical Review at Christmas Eve 1945, Bloch's short communication arrived four weeks later, in January 1946.

Both Purcell and Bloch were protagonists for the interaction between Europe and the United States.

They were not the only scientists working in the field. The 1920s had been roaring and inflationary, but also extremely fruitful in science.

In 1924, Wolfgang Pauli (1900-1958) suggested the possibility of an intrinsic nuclear spin. The year after, George Eugene Uhlenbeck (1900-1988) and Samuel A. Goudsmit (1902-1978) introduced the concept of the spinning electron.

Two years later Pauli and Charles Galton Darwin (1887-1962) developed a theoretical framework for grafting the concept of electron spin into the new quantum mechanics developed the year before by Erwin Schrödinger (1887-1961) and Werner Heisenberg (1901-1976).

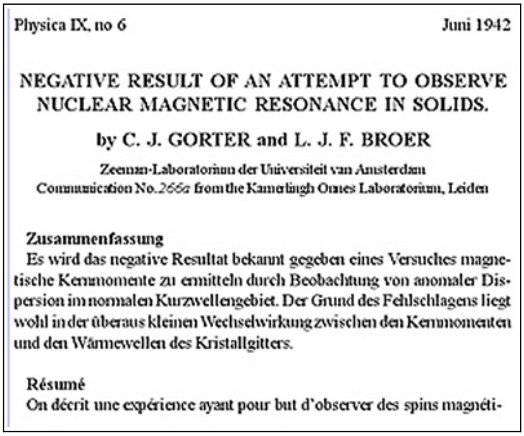
Pauli, Uhlenbeck, and Goudsmit went to the United States to work.

Figure 20-08:
Otto Stern
(1888-1969)

Figure 20-09:
Walther Gerlach
(1889-1979)

Figure 20-10:
Isidor Isaac Rabi
(1899-1989)

Figure 20-11:
Cornelis Jacobus Gorter
(1907-1980)



Physica IX, no 6 Juni 1942

NEGATIVE RESULT OF AN ATTEMPT TO OBSERVE NUCLEAR MAGNETIC RESONANCE IN SOLIDS.

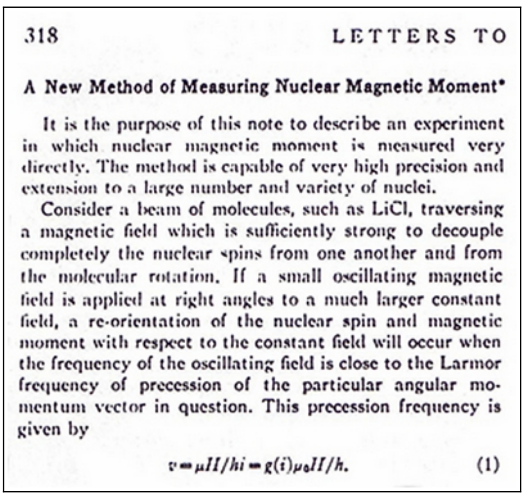
by C. J. GORTER and L. J. F. BROER

Zeeman-Laboratorium der Universiteit van Amsterdam
Communication No. 266a from the Kamerlingh Onnes Laboratorium, Leiden

Zusammenfassung
Es wird das negative Resultat bekannt gegeben eines Versuches magnetische Kernmomente zu ermitteln durch Beobachtung von anomaler Dispersion im normalen Kurzwellengebiet. Der Grund des Fehlschlagens liegt wohl in der überaus kleinen Wechselwirkung zwischen den Kernmomenten und den Wärmewellen des Kristallgitters.

Résumé
On décrit une expérience ayant pour but d'observer des spins magnéti-

Figure 20-12:
Beginning of Gorter's article (1942)



318 LETTERS TO

A New Method of Measuring Nuclear Magnetic Moment*

It is the purpose of this note to describe an experiment in which nuclear magnetic moment is measured very directly. The method is capable of very high precision and extension to a large number and variety of nuclei.

Consider a beam of molecules, such as LiCl, traversing a magnetic field which is sufficiently strong to decouple completely the nuclear spins from one another and from the molecular rotation. If a small oscillating magnetic field is applied at right angles to a much larger constant field, a re-orientation of the nuclear spin and magnetic moment with respect to the constant field will occur when the frequency of the oscillating field is close to the Larmor frequency of precession of the particular angular momentum vector in question. This precession frequency is given by

$$\nu = \mu H/hi = g(i)\mu_0 H/h. \quad (1)$$

Figure 20-13:
Beginning of Rabi's article about his first observation of nuclear magnetic resonance (1938). In a footnote he stated how indebted he was to Gorter and his idea of how to run the experiment.

After initial pacemaking work, in 1933, Otto Stern (Figure 20-08) – together with Walther Gerlach (Figure 20-09) – was able to measure the effect of the nuclear spin by deflection of a beam of hydrogen molecules (the so-called *Stern-Gerlach effect*).

Stern was awarded the Nobel Prize in Physics for 1943 "for his contribution to the development of the molecular-ray method and his discovery of the magnetic moment of the proton."

During the early 1930s, Isidor Isaac Rabi's (Figure 20-10) laboratory at Columbia University in New York became a major center for related studies.

Rabi's research was successful, but only with the visit by Cornelis Jacobus Gorter (Figure 20-11) from the Netherlands in September 1937 he was finally able to measure the nuclear magnetic moment. Gorter had tried similar experiments earlier and failed (Figure 20-12).

Several years later, Gorter was the first to use the term *nuclear magnetic resonance* in the publication about his failed experiments which appeared in the war-torn Netherlands in 1942, attributing the coining of the phrase to Rabi.[486] After Gorter's visit Rabi took up his suggestions concerning the experiments, changed them, and was able to observe resonance experimentally. This led to the publication of "A New Method of Measuring Nuclear Magnetic Moment" in 1938 (Figure 20-13).[487]

486 Gorter CJ, Broer LJF. Negative result of an attempt to observe nuclear magnetic resonance in solids. Physica (The Hague) 1942; 9: 591.

487 Rabi II, Zacharias JR, Millman S, Kusch P. A new method of measuring nuclear magnetic moment. Phys Rev 1938; 53: 318.

At some stage of their career, many European scientists contemplated – and still contemplate – working at academic facilities in the USA. Some stayed for good, others returned. There was hardly any movement in the other direction.

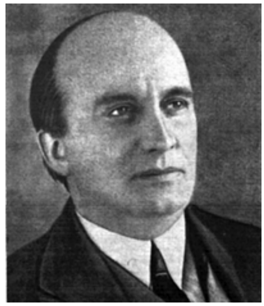


Figure 20-14:
Lev V. Shubnikov
Лев В. Шубников
(1902-1937)

Yet, far away, in the center of the East European Plain major contributions to nuclear magnetic resonance were made.

Figure 20-15:
Yevgeni K. Zavoisky
Евгений К. Завойский
(1907-1976)

One of the contributors was Lev Vasiljevich Shubnikov (Лев Васильевич Шубников – Figure 20-14), an experimental physicist. He studied physics at the Leningrad Polytechnical Institute, graduating in 1926.

He was then sent to the Leiden Cryogenic Laboratory in the Netherlands. At that time, Leiden Laboratory was the only laboratory in the world that had liquid helium. Shubnikov was first to observe the gradual penetration of a magnetic field in some superconductors: the hallmark of type-II superconductivity.

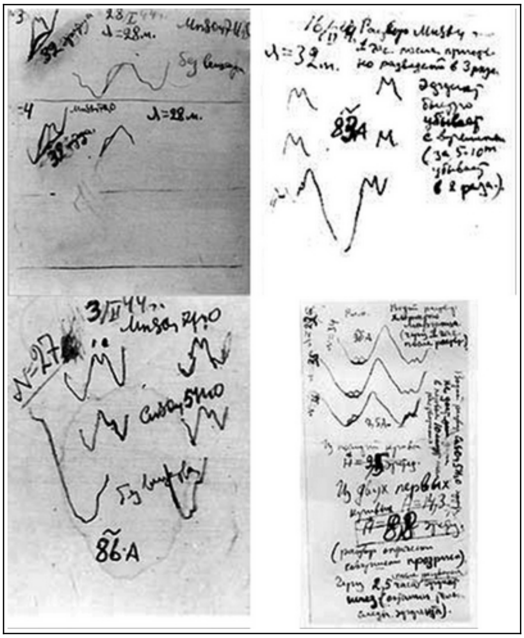
On his return in 1930, his experience in Leiden permitted him to head the Cryogenic Laboratory at the recently established Ukrainian Physico-Technical Institute in Kharkov.

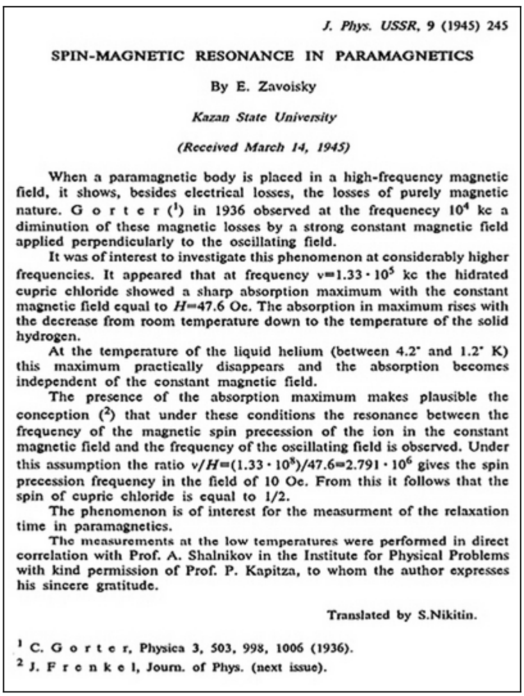
The Laboratory had liquid hydrogen in 1931 and liquid helium in 1933 which was partly made possible by the assistance of Wander de Haas from Leiden; he provided Shubnikov with the necessary material and devices unavailable in the USSR at that time. One of the central lines of activity of the Laboratory was research of superconductivity.[488] During these years Shubnikov in cooperation with Boris G. Lazarev also measured a proton magnetic moment.[489]

At the height of the Great Purge during the Stalin epoch, Shubnikov along with several colleagues was convicted of "crimes" and executed on 10 October 1937. In April 1957 he was posthumously rehabilitated by the Supreme Military Court.

488 Rjabinin JN, Shubnikow LW. Magnetic properties and critical currents of supra-conducting alloys. Nature. 1935; 135: 581-582.

489 Lazarev BG, Schubnikov LV. Das magnetische Moment des Protons. Physikalische Zeitschrift der Sowjetunion, 1936; 10: 117 (short communication), and 1937; 11: 445-457.





J. Phys. USSR, **9** (1945) 245

SPIN-MAGNETIC RESONANCE IN PARAMAGNETICS

By E. Zavoisky

Kazan State University

(Received March 14, 1945)

When a paramagnetic body is placed in a high-frequency magnetic field, it shows, besides electrical losses, the losses of purely magnetic nature. G o r t e r (1) in 1936 observed at the frequenecy 10^4 kc a diminution of these magnetic losses by a strong constant magnetic field applied perpendicularly to the oscillating field.

It was of interest to investigate this phenomenon at considerably higher frequencies. It appeared that at frequency $\nu = 1.33 \cdot 10^5$ kc the hidrated cupric chloride showed a sharp absorption maximum with the constant magnetic field equal to $H = 47.6$ Oe. The absorption in maximum rises with the decrease from room temperature down to the temperature of the solid hydrogen.

At the temperature of the liquid helium (between 4.2° and 1.2° K) this maximum practically disappears and the absorption becomes independent of the constant magnetic field.

The presence of the absorption maximum makes plausible the conception (2) that under these conditions the resonance between the frequency of the magnetic spin precession of the ion in the constant magnetic field and the frequency of the oscillating field is observed. Under this assumption the ratio $\nu/H = (1.33 \cdot 10^8)/47.6 = 2.791 \cdot 10^6$ gives the spin precession frequency in the field of 10 Oe. From this it follows that the spin of cupric chloride is equal to 1/2.

The phenomenon is of interest for the measurment of the relaxation time in paramagnetics.

The measurements at the low temperatures were performed in direct correlation with Prof. A. Shalnikov in the Institute for Physical Problems with kind permission of Prof. P. Kapitza, to whom the author expresses his sincere gratitude.

Translated by S.Nikitin.

1 C. G o r t e r, Physica 3, 503, 998, 1006 (1936).
2 J. F r e n k e l, Journ. of Phys. (next issue).

Figure 20-16a (left top):
Pictures of the first ESR signals as copied from the screen of Zavoisky's oscillograph into Zavoisky's laboratory notebook in 1944.
(Picture source: Memorial Laboratory of Yevgeni K. Zavoisky at Kazan State University).

Figure 20-16b (left bottom):
Zavoisky's publication from March 1945: "Spin-Magnetic Resonance in Paramagnetics" (English translation) in which he refers to Gorter.

Another famous contributor lived in Kazan in Tatarstan, which was part of the Soviet Union at that time and is now an independent republic within Russia.

Electron spin resonance (ESR) was discovered at Kazan's university by Yevgeni K. Zavoisky (Евгений Константинович Завойский – Figure 20-15) towards the end of the war.[490]

He had first attempted to detect NMR in 1941, but like Gorter he failed. Then, in January 1944, he was able to register ESR signals.

They were recorded on celluloid films and also copied by hand into the laboratory notebook (Figure 20-16a). He published his discovery first in his dissertation in 1944, then in a short paper early in 1945 (Figure 20-16b).

490 Zavoisky EK. Spin-magnetic resonance in paramagnetics. J Phys Acad Sci USSR 1945; 9: 245 (in Russian).

Early Applications in Medicine and Biology

Finding a relevant use of this new technique was difficult, and medicine and biology stayed somewhere backstage although *in vivo* NMR with a medical background has its roots in the early and mid-1950s.

In 1955 Erik Odeblad (Figure 20-17) and Gunnar Lindström from Stockholm published their first NMR studies, including relaxation time measurements of living cells and excised animal tissue.[491]

Figure 20-17:
Erik Odeblad (1922-2019), recalling his first NMR spectrometer – 57 years after his first publication about relaxation times and NMR in medicine.

Odeblad is the main pioneer in NMR in medicine and laid the foundations of NMR and MRI in biomedicine.

In 1952, while working at the University of California in Berkeley, Odeblad met Felix Bloch in Stanford. He asked him whether he could use Bloch's NMR spectrometer to study human samples, but the response was negative: NMR was a tool for physicists, not for research into physiology, medicine, or biology.

Odeblad returned to Sweden – and got his own machine. Around 1950 Gunnar Lindström of the Nobel Institute of Physics in Stockholm had built a spectrometer. Odeblad adapted and used it for his pioneering biomedical NMR applications, *in vivo* and *ex vivo*. In December 1954, they submitted their first NMR results (Figure 20-18a).

They had found out that different tissues had distinct relaxation times, most likely due to water content but also to different bindings to lipids – a phenomenon that explains tissue contrast in MR imaging.

Odeblad continued working on human fluids and tissues throughout the following decades and some sixty scientific papers on NMR in human tissues and secretions of mucous membranes followed between 1955 and 1968. The research for this publications was performed at the Department of Obstetrics and Gynecology at the Sabbatsberg

The Forgotten Pioneer

A short historical insight into Erik Odeblad's pioneering contributions to the application of relaxation times magnetic resonance in medicine and biology.

To be read on page 93.

491 Odeblad E, Lindström G. Some preliminary observations on the proton magnetic resonance in biological samples. Acta Radiol (Stockholm) 1955; 43: 469-476.

SOME PRELIMINARY OBSERVATIONS ON THE PROTON MAGNETIC RESONANCE IN BIOLOGIC SAMPLES.[1]

By

Erik Odeblad and *Gunnar Lindström*

If a sample containing atomic nuclei with a magnetic moment is placed in a magnetic field, the nuclei take up certain allowed directions with respect to the field. Transitions between these quantized directions can be induced if electromagnetic radiation with the appropriate quantum energy acts upon the sample. In a magnetic field of about 6,700 gauss the quantum energy for proton transitions is about $9 \cdot 10^{-20}$ erg, corresponding to a frequency of about 26.5 megacycles.

If this 'resonance frequency' is applied to the specimen, and the magnetic field is swept over a small interval less than a gauss, absorption of energy can be detected by the resonance absorption technique of PURCELL,

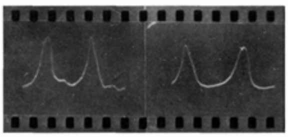


Fig. 1. Left: the proton signals from water. Right: the proton signals from living yeast cells. The same magnetic field and operating conditions were used in both cases. The magnetic field was swept sinusoidally so that two proton signals appear for each specimen, one at increasing, and one at decreasing, field. The proton signals in yeast were lower and somewhat broader than in pure water.

[1] Work supported in part by a grant from the Nobel funds of the Karolinska Institutet.

Submitted for publication, 16 December 1954.

Figure 20-18a (top):
The first paper on biological and medical NMR: "Some preliminary observations on the proton magnetic resonance in biological samples", by Erik Odeblad and Gunnar Lindström, submitted for publication to Acta Radiologica (Stockholm) in December 1954, published in 1955.

Odeblad, Erik, Acta Obst. et Gynec. Scandinav. *38*, 599, 1959.

From the Isotope Laboratory, Department of Obstetrics and Gynæcology (Prof. A. Ingelman-Sundberg), Sabbatsberg Hospital, Karolinska Institutet, and the Nobel Institute of Physics (Prof. M. Siegbahn), Stockholm, Sweden

RESEARCH IN OBSTETRICS AND GYNÆCOLOGY WITH NUCLEAR MAGNETIC RESONANCE

BY

ERIK ODEBLAD

One of the most fascinating physical methods, which has been applied in the study of the properties of matter, is nuclear magnetic resonance (NMR). Though NMR had been observed in atomic beams for several years before, the method was first successfully applied to bulk matter in the winter months of 1946 by Purcell, Torrey, and Pound (1946) and Bloch, Hansen, and Packard (1946). The discovery soon showed itself to be of very great importance for physics, because it allowed the measurement of nuclear magnetism with high precision and the two group leaders received the Nobel Prize in 1952 for their discovery.

NMR soon showed itself to be a powerful tool also in other fields than pure physics. In physical chemistry, organic chemistry, and metallurgy significant discoveries were rapidly made using this technique, and in the last few years biologists also have become interested in this field. Excellent books on NMR have been published, *e.g.* by Ramsey, 1953; Grivet, 1955; Andrew, 1955; Roberts, 1959, and Pople, Schneider, and Bernstein, 1959. NMR really seems to possess extensive possibilities to help us to study, in a non-destructive way, many problems in biology and medicine. In the special field of obstetrics and gynæcology there are many research problems, which can be extensively studied with this method. It seems certain, that in future the method will also be used for routine clinical diagnosis.

Figure 20-18b (bottom):
From Odeblad's 1959 paper on magnetic resonance in obstretrics and gynecology: "It seems certain that in future the method will also be used for routine clinical diagnosis."

Hospital, Karolinska Institute, and the Nobel Institute of Physics in Stockholm. It was partly supported by a grant given by the Nobel Funds.

He extended the range of possible applications further in the fields of obstetrics and gynecology[492] (his first medical discipline used to be gynecology and he became world-known for his research in fertility); later he also tried to localize cancerous tissue *in vivo,* but did not succeed.[493]

Odeblad finally left Karolinska for, what is claimed, reasons of conscience and became Professor of Medical Biophysics at the University of Umeå in North Sweden.

492 Odeblad E. Research in obstetrics and gynaecology with nuclear magnetic resonance. Acta Obstet Gynecol Scand. 1959; 38:599-617.

493 Ingelman-Sundberg A, Odeblad E. Attempts to localize a carcinoma of the endometrium with the use of short radio waves. Am J Obstet Gynecol. 1965; 92: 592-600.
In this paper the authors state: "... carcinoma of the uterus, which in all cases gave rise to significant RF absorption differences between contralateral symmetrical points. The results were fully confirmed at hysterectomy. By intrauterine RF scanning it appears, therefore, possible to determine the surface spread of an endometrial carcinoma." However, it was done solely by RF, not by NMR.

Soon others joined in this kind of research. In the late 1950s and early and mid-1960s the results of a very large amount of work on relaxation, diffusion, and chemical exchange of water in cells and tissues of all sorts appeared in the scientific literature.

Oleg Jardetzky and his collaborators performed sodium NMR studies in blood, plasma and red blood cells in 1956.[494]

T1- and T2-measurements of living frog skeletal muscle were published by Bratton in 1965 .[495]

In 1967, Ligon reported the measurement of NMR relaxation of water in the arms of living human subjects.[496]

In the late 1960s, James Hutchison at the University of Aberdeen in Scotland began working with magnetic resonance on *in vivo* electron spin resonance studies in mice.[497]

Hazlewood added to the work on NMR relaxation time measurements by studying developing muscle tissue.[498]

494 Jardetzky O. A study of interactions of aqueous sodium ion by nuclear spin resonance. Ph.D. thesis. Univ. of Minnesota. 1956.

495 Bratton CB, Hopkins AL, Weinberg JW. Nuclear magnetic resonance studies of living muscle. Science 1965; 147: 738-739.

496 Ligon TR. Coil design for low field NMR and NMR measurements on the human arm. MS thesis. Oklahoma State University. 1967.

497 Hutchison JMS, Mallard JR. Electron spin resonance spectrometry on the whole mouse in vivo: a 100 MHz spectrometer. J Phys E Sci Instrum. 1971; 4: 237-239.

498 Hazlewood CF, Nichols BL, Chamberlain NF. Evidence for the existence of a minimum of two phases of ordered water in skeletal muscle. Nature 1969; 222: 747-750.

– Hazlewood CF, Nichols BL, Chang DC, Brown B. On the state of water in developing muscle. Johns Hopkins Med J 1971; 128: 117.

Cooke and Wien worked on similar topics.[499] Hansen focussed upon NMR studies of brain tissue.[500]

Then, in the late 1960s and early 1970s research and dedicated science mushroomed in the field.

The first animal whole-body spectrometer was built in 1968. Jackson and Langham working at the Los Alamos Scientific Laboratory of the University of Los Angeles obtained the first NMR signal ever from a whole living animal, an anesthetized rat (Figure 20-19a and b).[501]

At this time medical doctors without prior background in NMR science joined in the research, curious about possible biological applications of relaxation times.

One of them was Raymond Damadian (1936-2022) at Downstate Medical Center in Brooklyn. He measured relaxation times of excised normal and cancerous rat tissue and stated that tumorous tissue had longer relaxation times than normal tissue.[502]

There was a lack of controls in his measurements and, as it turned out quickly, it was a fallacious assumption.

499 Cooke R, Wien R. The state of water in muscle tissue as determined by proton nuclear magnetic resonance. Biophys J 1971; 11: 1002-1017.

500 Hansen JR. Pulsed NMR study of water in muscle and brain tissue. Biochim Biophys Acta 1971; 230: 482-486.

501 Jackson JA, Langham WH. Whole-body NMR spectrometer. Rev Sci Instrum 1968; 39: 510-513.

502 Damadian RV. Tumor detection by nuclear magnetic resonance. Science 1971; 171: 1151-1153.

Donald P. Hollis and his colleagues from Johns Hopkins University in Baltimore repeated Damadian's studies – on the same pulsed NMR spectrometer Damadian had used – and Paul C. Lauterbur had provided. Hollis reached conflicting, contrary results and was more cautious and critical in his scientific conclusions. There was no verification of Damadian's claims that cancer pathology and their relaxation times possessed a numerical correlation.[503]

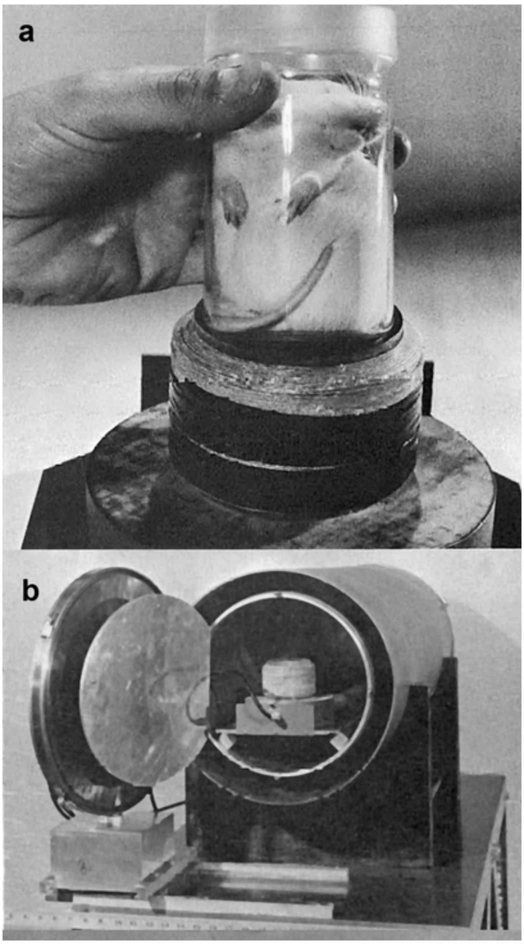


Figure 20-19 a and b:
The Los Alamos NMR spectrometer operating at 0.001 T (1968). **(a)** A rat being inserted into the sample coil. **(b)** End view of the solenoid and magnetic shield after assembly with sample coil.

Yet, Damadian promoted his findings as the ultimate technology to screen for ("to scan" – but not to image) cancer and patented the idea of a hypothetical relaxation time scanner similar to the Los Alamos spectrometer as "Apparatus and method for detecting cancer in tissue" (Figure 20-19e).[504]

Damadian was scientifically and medically wrong in his cancer-scanning patent and later his one-dimensional spot-by-spot spectrometric picture technique (once described as "the best advertised scientific scam of the 20th century"). However, his publicity stunts, exaggerated and colorful self-promotion, and massive advertising campaigns for his company made people curious and impacted research in NMR during the following decade.[505, 506]

He never mentioned Odeblad's original findings although he once admitted that he was well aware of them; he even put a private investigator on Odeblad.

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503 Hollis DP, Saryan LA, Morris HP. A nuclear magnetic resonance study of water in two Morris hepatomas. Johns Hopkins Med J 1972; 131(6): 441-444.
– Hollis DP, Economou JS, Parks LC, Eggleston JC, Saryan LA, Czeisler JL. Nuclear magnetic resonance studies of several experimental and human malignant tumors. Cancer Research 1973; 33: 2156-2160.
504 Damadian R. United States Patent no. 3789832. Filed 17 March 1972, awarded 5 February 1974. Apparatus and method for detecting cancer in tissue. Inventor: Raymond V. Damadian.
505 Hollis DP. Abusing cancer science. Chehalis, WA (USA): The Strawberry Fields Press 1987.
506 Kleinfeld S. A machine called Indomitable. New York: Times. Toronto: Random House. 1985

The New York Times pointed out major discrepancies between what he claimed and what he had actually accomplished, "discrepancies sufficient to make him appear a fool if not a fraud." (Figure 20-20).[507, 508]

In February 1973 Zenuemon Abe and his colleagues applied for a patent on a targeted NMR scanner (Figure 20-19d).[509] They published this technique in 1974.[510]

Damadian reported a technique derived from Abe's in a publication two years later, dubbed *field-focusing NMR (Fonar),* but his Fonar company that manufactured MRI equipment used the MR imaging method described by Paul Lauterbur.

Neither Abe's nor the Fonar techniques were suitable for medical imaging.

507 Altman LK. New York researcher asserts nuclear magnetic technique can detect cancer, but doubts are raised. The New York Times, 21 July 1977.

508 Fjermedal G. Book review of: Kleinfeld S. A machine called Indomitable. New York: Times Books, and Toronto: Random House, 1985. The New York Times, 9 February 1986.

509 Abe Zenuemon, Kunio Tanaka, Hotta Masao and Imai Masashi: [Patent] Application. Measurement method from the outside [to obtain] information in the inside applying nuclear magnetic resonance. Japanese patent application 48-13508, 1973 (application day: 02 February 1973. Patents pending in the United States, England, Germany, France, and the Soviet Union). and:

– Abe Z, Tanaka K, Hotta M, et al. Non-invasive measurements of biological information with application of NMR. in: Llaurado, Sances, Battocletti (eds). Biological and clinical effects of low-frequency electric and magnetic fields. Springfield, IL: Charles C. Thomas 1974. 295-315.

510 Tanaka K, Yamada T, Shimizu T, Sano F, Abe Z. Fundamental investigations (in vitro) for a non-invasive method of tumor detection by nuclear magnetic resonance. Biotelemetry 1974; 1: 337-350.

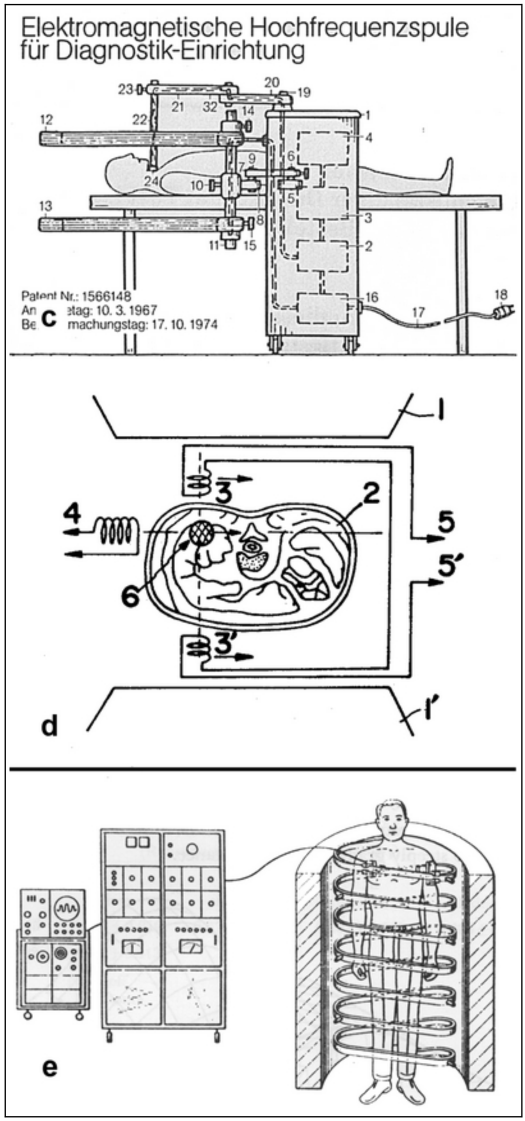

Figure 20-19 c, d,e:
As examples among others: Graphic designs of three patented though practically inapplicable magnetic-field-based diagnostic systems.
All systems were to deliver one-dimensional data and not conceived as imaging equipment.
(c) Ganssen 1967/1974; **(d)** Abe 1973/ 1973; **(e)** Damadian 1972/1974.

A18 THE NEW YORK TIMES, THURSDAY, JULY 21, 1977

New York Researcher Asserts Nuclear Magnetic Technique Can Detect Cancer, but Doubts Are Raised

By LAWRENCE K. ALTMAN

A New York City medical researcher announced yesterday at a news conference that he had developed "a new technique for the nonsurgical detection of cancer anywhere in the human body." However, in an interview later in the day, he retracted a contention that he had already used the technique on a cancer patient.

And other cancer experts expressed skepticism that the technique had reached the stage where it could be used in diagnosing cancer.

The researcher, Dr. Raymond V. Dama-

Cancer Institute to visit Dr. Damadian's Brooklyn laboratory.

Dr. Damadian said that he had applied for further Federal support.

A site visit from a group of scientific peers is a standard part of the process by which the National Cancer Institute, the National Institutes of Health and and other organizations review applications for Federal support.

Dr. Damadian said that the FONAR technique had been under development since 1971 with the ultimate aim of pinpointing cancers in the human body that could not be detected by X-ray or other techniques, and determining their chemical makeup. In 1974, Dr. Damadian

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Figure 20-20:
Headline in the New York Times, 21 July 1977.

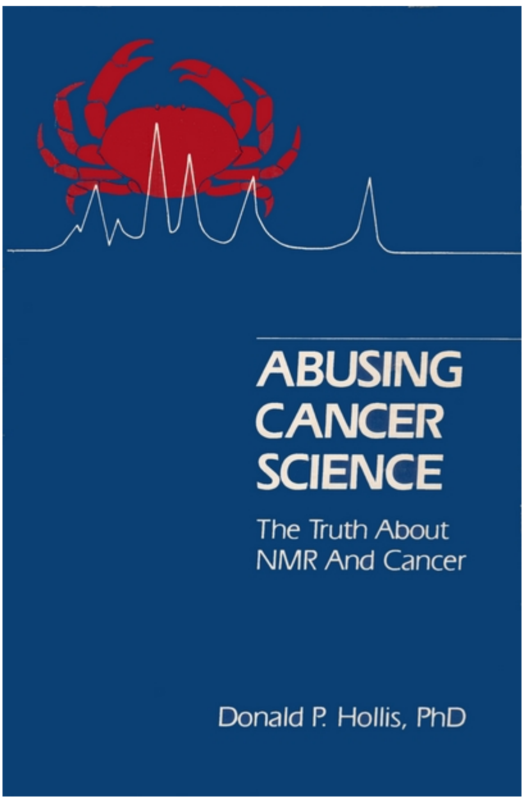


Figure 20-21:
The cover of Donald Hollis' book about Damadian's scientific scam.

The attribution that Damadian made the first proposal for an MR imaging device, repeated time and again, is historically not correct.

Ian Young wrote about Damadian's claims:

> "As is now well known, a huge variety of pathologic processes result in increases in the relaxation time constants, while some classes of tumor have shorter time constants than the normal tissues from which they have developed. Sadly, the many attempts that were made to correlate pathology and relaxation behavior have yielded none of the precise numerical relationships that were hoped for …
>
> "Raymond Damadian also produced a sketch of a possible NMR imaging system ... The method was, unfortunately for Damadian, one of those classic blind alleys that lead precisely nowhere.
>
> "Donald Hollis, in his book *Abusing Cancer Science: The Truth About NMR and Cancer*, published in 1987, has a great deal more to say, little of it complimentary to Damadian, about the various claims he has made about both cancer diagnosis and imaging." (Figure 20-21).[511, 512]

Still, Damadian was, as it happens so often in the history of inventions, one of the many who prepared the ground – even if his published results were conclusively disproved.

511 Young IR. Significant events in the development of MRI. J Magn Reson Imaging. 2004; 20: 183-186.

512 Hollis DP. Abusing cancer science. Chehalis, WA (USA): The Strawberry Fields Press 1987.

Spatial Encoding Leads to MR Imaging

In radiology, the times of conventional imaging ended in September 1971 when the world's first axial x-ray computer assisted tomograph (CT or CAT) was installed in England.

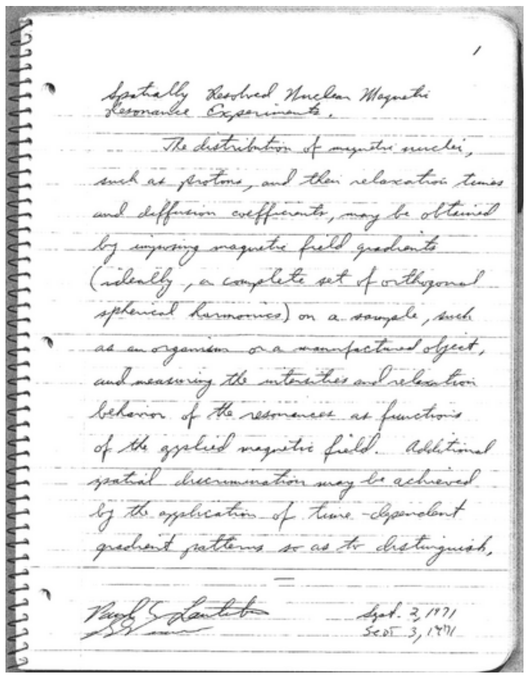
In the same month, on 2 September 1971, Paul C. Lauterbur, a professor of chemistry at the State University of New York at Stony Brook (Figure 20-22), recorded in his laboratory notebook the idea of applying magnetic field gradients in all three dimensions to create NMR images – and had his invention certified (Figure 20-23); yet, he was never able to patent it – the administrator and lawyers of the university did not believe that the technique would have any future.

Lauterbur once stated: "European scientists, physicians, governments and industries moved more confidently and thoughtfully into this new area than did their American counterparts." [513]

Already in the 1950s and 1960s Lauterbur had established his fame in the community of nuclear magnetic resonance scientists by showing carbon and silicon spectra which led to many publications on various classes of organic chemicals.[514]

However, all experiments before Lauterbur's invention of 1971 had been one-dimensional and lacked spatial information.

Figure 20-22:
Paul C. Lauterbur (1929-2007).



1

Spatially Resolved Nuclear Magnetic Resonance Experiments.

The distribution of magnetic nuclei, such as protons, and their relaxation times and diffusion coefficients, may be obtained by imposing magnetic field gradients (ideally, a complete set of orthogonal spherical harmonics) on a sample, such as an organism or a manufactured object, and measuring the intensities and relaxation behavior of the resonances as functions of the applied magnetic field. Additional spatial discrimination may be achieved by the application of time-dependent gradient patterns so as to distinguish,

Paul C Lauterbur Sept. 3, 1971

Sept. 3, 1971

Figure 20-23:
First page of Lauterbur's laboratory notebook describing his idea of "Spatially resolved nuclear magnetic resonance experiments," signed and witnessed on 3 September 1971.

513 Dawson MJ. Paul Lauterbur and the invention of MRI. Cambridge, MA (U.S.A.): MIT Press. 2013.

514 Lauterbur PC. 13-C nuclear magnetic resonance spectra. J Chem Phys 1957; 26: 217-218.

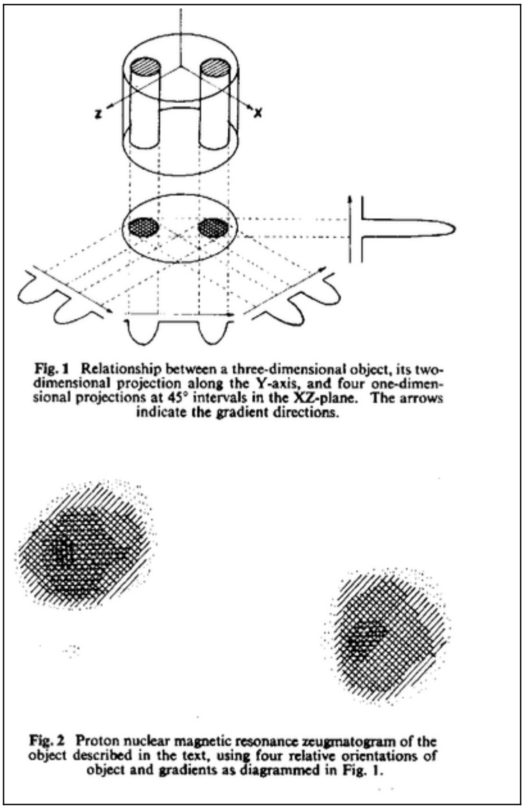


Figure 20-24:
Lauterbur's first published MR images acquired at the State University of New York at Stony Brook (from Nature 1973; 242: 190-191; reprinted with permission).

Nobody could determine exactly where the NMR signal originated within the sample. Lauterbur's idea changed this.

Lauterbur called his imaging method *zeugmatography*, combining the Greek words "zeugma" (ζεῦγμα = the bridge or the yoke that holds two animals together in front of a carriage) and "graphein" (γράφειν = to write, to depict) to describe the joining of chemical and spatial information. This term was later replaced by *(N)MR imaging* or *MRI*.

He published the first images of two tubes of water in March 1973 in Nature (Figure 20-24).[515] Later in the year the picture of a living animal, a clam, followed and in 1974 the image of the thoracic cavity of a mouse.[516]

Field gradients had been used before, though only in one dimension and without imaging in the mind of the researchers. They are an essential feature of the study of molecular diffusion in liquids by the spin-echo method developed by Erwin L. Hahn in 1950 (Figure 20-25);[517] his group also used a gradient approach to create a storage memory.[518]

Figure 20-25:
Erwin Louis Hahn (1921-2016)

515 Lauterbur PC. Image formation by induced local interactions: examples of employing nuclear magnetic resonance. Nature 1973; 242: 190-191.
516 Lauterbur PC. Magnetic resonance zeugmatography. Pure and Applied Chemistry 1974; 40: 149-157.
517 Hahn EL. Spin echoes. Phys Rev 1950; 80: 580-594.
518 Anderson AG, Garwin RL, Hahn EL, Horton JW, Tucker GL, Walker RM. Spin echo serial storage memory. J Appl Phys 1955; 26: 1324-1338.

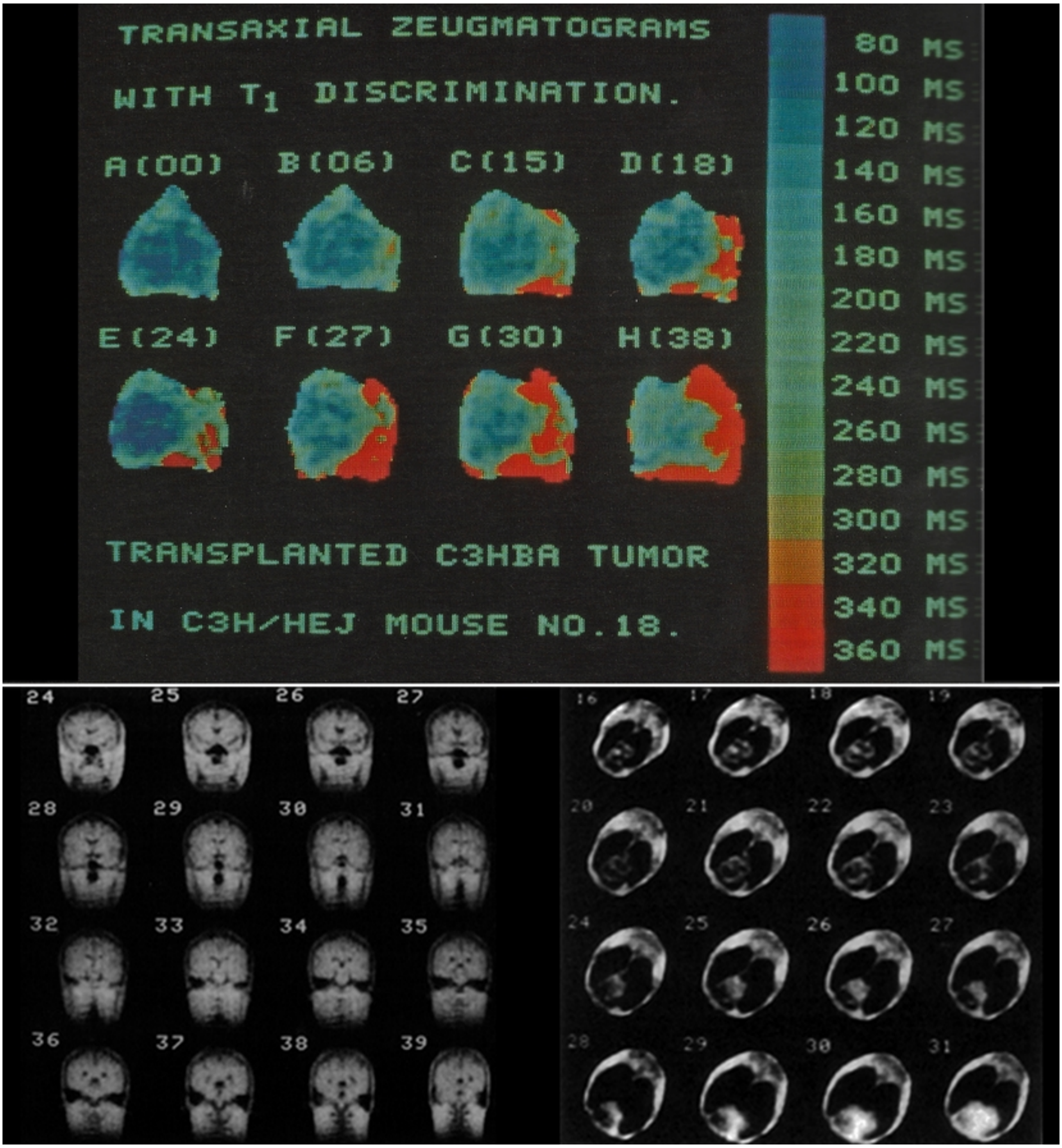


Figure 20-26:
Early examples of “zeugmatography”.
Top: Follow-up of the growth of an implanted tumor in a mouse for a period of 38 days. Each image was resonstructed from 12 projection, the slice thickness was about 3 cm.
Later, most images in Lauterbur's laboratory were acquired in three dimensions. These images were made in 1982. 3D- imaging with commercial systems became only possible some 10 years later.
Bottom left: Coronal images from a 3D human brain study. **Bottom right:** Transverse images from a 3D study of a dog's heart, synchronized with the ECG, 400 ms after the R-wave.

In 1951, Roger Gabillard from Lille in France had imposed one-dimensional gradients on samples.[519]

Carr and Purcell described the use of gradients in the determination of diffusion in 1954.[520]

Many of today's innovations were thought of and developed in Lauterbur's laboratory in the late 1970s and 1980s, from radio-frequency coil design,[521] magnetization transfer,[522] 3D-[523, 524] as well as chemical shift imaging, heart and lung imaging,[525] using elements different from hydrogen,[526] to NMR microscopy and contrast agents,[527] oblique and curved slice reconstructions, and flow imaging.

Some early examples are shown in Figure 20-26.

519 Gabillard R. Résonance nucléaire mesuré du temps de relaxation T2 en présence d'une inhomogenéité de champ magnétique supérieur à la largeur de raie. C R Acad Sci Paris 1951; 232: 1551-1553.
– Gabillard R. A steady state transient technique in nuclear resonance. Phys Rev 1952; 85: 694-695.
520 Carr HY, Purcell EM. Effects of diffusion on free precession in nuclear magnetic resonance experiments. Phys Rev 1954; 94: 630-638.
521 Bernardo ML, Cohen AJ, Lauterbur PC. Radiofrequency coil designs for nuclear magnetic resonance zeugmatography. IEEE Comp Soc 1982; 277-284.
522 Muller RN, Marsh MJ, Bernardo ML, Lauterbur PC. True 3-D imaging of limbs by NMR zeugmatography with off-resonance irradiation. Europ J Radiol 1983; 3: 286-290.
523 Simon HE. A whole body nuclear magnetic resonance (NMR) imaging system with full three-dimensional capabilities. SPIE Applications of Optical Instrumentation in Medicine IX 1981; 273: 41-49.
524 Lai C-M, Lauterbur PC. A gradient control device for complete three-dimensional nuclear magnetic resonance zeugmatographic imaging. J Phys E: Sci Instrum 1980; 13: 747-750.
525 Frank JA, Feiler MA, House WV, Lauterbur PC, Jacobson MJ. Measurement of proton nuclear magnetic longitudinal relaxation times and water content in infarcted myocardium and induced pulmonary injury. Abstract. Clinical Research. 1976; 24: 217A.
526 Rinck PA, Petersen SB, Heidelberger E, Acuff V, Reinders J, Bernardo ML, Hedges LK, Lauterbur PC: NMR ventilation imaging of the lungs using perfluorinated gases. Magn Reson Med 1984; 1:237 (abstract).
527 Lauterbur PC. Magnetic resonance zeugmatography. Pure and Applied Chemistry 1974; 40: 149-157.
– Lauterbur PC, Kramer DM, House WV, Chen C-N. Zeugmatographic high resolution nuclear magnetic resonance spectroscopy. Images of chemical inhomogeneity within microscopic objects. J Amer Chem Soc 1975; 97: 6866-6868.
– Lauterbur PC, Lai C-M, Frank JA, Dulcey Jr CS. In vivo zeugmatographic imaging of tumors. Abstract. Fourth International Conference on Medical Physics. Ottawa, Canada; 25-30 July, 1976.
– Lauterbur PC. Spatially-resolved studies of whole tissues, organs and organisms by NMR zeugmatography. in: Dweck RA, Campbell ID, Richards RE, Williams RJP. NMR in Biology. London: Academic Press, 1977. 323-335.
– Lauterbur PC, Mendonça Dias H, Rudin AM. Augmentation of tissue proton spin-lattice relaxation rates by in vivo addition of paramagnetic ions. in: Dutton PO, Leigh J, Scarpa A (eds). Frontiers of Biological Energetics. New York: Academic Press 1978. 752-759.

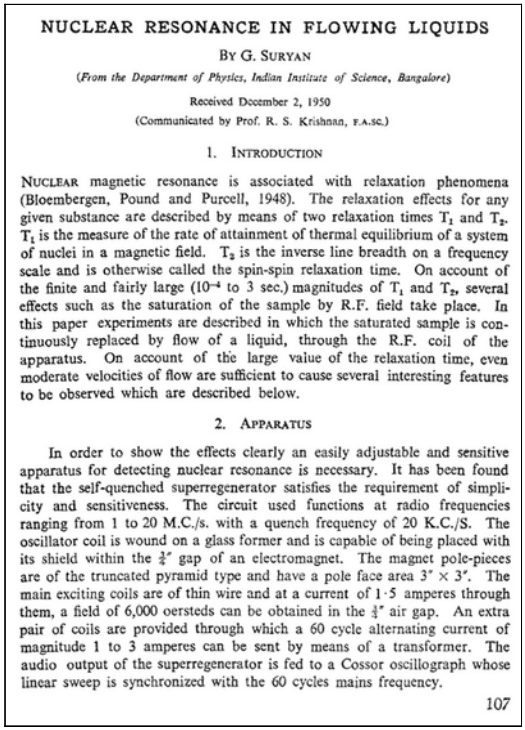
Flow measurements by NMR date back as far as 1951 when the first experiment using continuous wave (CW) NMR was described by Suryan (Figure 20-27).[528]

By 1959, Jerome R. Singer (Figure 20-28) had studied blood flow by NMR relaxation time measurements of blood in living humans.[529]

Such measurements were not introduced into common medical practice until the mid-1980s, although patents for similar ideas were filed earlier, for instance for an NMR machine to measure blood flow in the human body by Alexander Ganssen in early 1967.[530]

This machine was meant to measure the NMR signal of flowing blood at different locations of a vessel with a series of small coils, allowing to calculate the blood flow within that vessel. It could be described as an MR scanner (Figure 20-19c; page 386).

However, it was no MR imaging machine. Actual flow imaging became possible with Lauterbur's method.



NUCLEAR RESONANCE IN FLOWING LIQUIDS

By G. Suryan

(*From the Department of Physics, Indian Institute of Science, Bangalore*)

Received December 2, 1950

(Communicated by Prof. R. S. Krishnan, F.A.SC.)

1. Introduction

Nuclear magnetic resonance is associated with relaxation phenomena (Bloembergen, Pound and Purcell, 1948). The relaxation effects for any given substance are described by means of two relaxation times T_1 and T_2. T_1 is the measure of the rate of attainment of thermal equilibrium of a system of nuclei in a magnetic field. T_2 is the inverse line breadth on a frequency scale and is otherwise called the spin-spin relaxation time. On account of the finite and fairly large (10^{-4} to 3 sec.) magnitudes of T_1 and T_2, several effects such as the saturation of the sample by R.F. field take place. In this paper experiments are described in which the saturated sample is continuously replaced by flow of a liquid, through the R.F. coil of the apparatus. On account of the large value of the relaxation time, even moderate velocities of flow are sufficient to cause several interesting features to be observed which are described below.

2. Apparatus

In order to show the effects clearly an easily adjustable and sensitive apparatus for detecting nuclear resonance is necessary. It has been found that the self-quenched superregenerator satisfies the requirement of simplicity and sensitiveness. The circuit used functions at radio frequencies ranging from 1 to 20 M.C./s. with a quench frequency of 20 K.C./S. The oscillator coil is wound on a glass former and is capable of being placed with its shield within the $\frac{3}{4}''$ gap of an electromagnet. The magnet pole-pieces are of the truncated pyramid type and have a pole face area $3'' \times 3''$. The main exciting coils are of thin wire and at a current of 1·5 amperes through them, a field of 6,000 oersteds can be obtained in the $\frac{3}{4}''$ air gap. An extra pair of coils are provided through which a 60 cycle alternating current of magnitude 1 to 3 amperes can be sent by means of a transformer. The audio output of the superregenerator is fed to a Cossor oscillograph whose linear sweep is synchronized with the 60 cycles mains frequency.

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Figure 20-27:
The first page of G. Suryan's article in the Proceedings of the Indian Academy of Sciences, 1951.

Figure 20-28:
Jerome R. Singer (1921-2019)

528 Suryan G. Nuclear resonance in flowing liquids. Proc Ind Acad Sci, 1951; Section A33: 107-111.

529 Singer JR. Blood-flow rates by NMR measurements. Science 1959; 130: 1652-1653.

530 Ganssen A. Bundesrepublik Deutschland - Deutsches Patentamt: Patentschrift 1566 148. Elektromagnetische Hochfrequenzspule für Diagnostikeinrichtung. Patentiert für Siemens AG, Berlin und München. Erfinder: Alexander Ganssen. Anmeldetag 10.3.1967; Offenlegungstag 2.4.1970; Bekanntmachungstag: 17.10.1974.

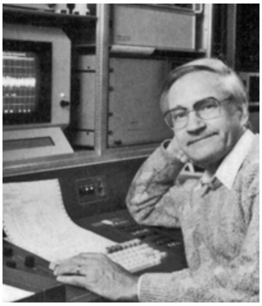

Figure 20-29:
Richard Ernst
(1933-2021)

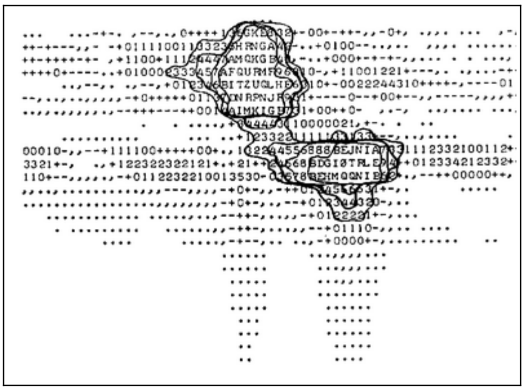

Figure 20-30:
One of the first 2D-FT MR images from the research group of Richard Ernst in Zurich, acquired by Anil Kumar in July 1974.

MR Imaging Strikes Roots

The news of Lauterbur's invention traveled slowly although he presented it at a number of scientific meetings between 1972 and 1975.

Some people listened, understood, and reacted. It's a tale of international conferences. Here are some examples:

In April 1974, Lauterbur gave a talk at a conference in Raleigh, North Carolina. This conference was attended by Richard Ernst from Zurich (Figure 20-29), who realized that instead of Lauterbur's back-projection one could use switched magnetic field gradients in the time domain.

This led to the 1975 publication, 'NMR Fourier Zeugmatography' by Anil Kumar, Dieter Welti, and Richard Ernst,[531] and to the universal reconstruction method for MR imaging today (Figure 20-30).

When Lauterbur presented his approach to NMR imaging at the International Society of Magnetic Resonance (ISMAR) meeting in January 1974 in Bombay, Raymond Andrew, William S. Moore, and Waldo Hinshaw from the University of Nottingham, England, were in the audience and took note. As a result, Hinshaw developed his own approach to MR imaging with their *sensitive point method*.[532]

531 Kumar A, Welti D, Ernst RR. NMR Fourier zeugmatography. J Magn Res 1975; 18: 69-83.

532 Hinshaw WS. Spin mapping: the application of moving gradients to NMR. Physics Letters 1974; 48A,2: 87-88.

– Hinshaw WS. Image formation by nuclear magnetic resonance: the sensitive-point method. J Appl Phys 1976; 8: 3709-3721.

At this time, several research groups in Nottingham worked in parallel on similar topics. The first group comprised E. Raymond Andrew, Waldo S. Hinshaw (Figure 20-31, William S. Moore, Neil Holland, and Paul Bottomley, all of them major contributors to the development of MR imaging. The second group included Peter Mansfield (Figure 20-32), Peter K. Grannell, Andrew Maudsley, Ian Pykett, and Peter Morris. They worked on studies of solid periodic objects, such as crystals.

At a Colloque Ampère conference in Cracow, Poland, in September 1973, Mansfield was told about Lauterbur's imaging method after he and his collaborator Peter K. Grannell had presented a one-dimensional interferogram of camphor/cardboard samples (Figure 20-35).[533]

For some time in 1974 a third research 'team' existed in Nottingham, consisting of Alan N. Garroway (Figure 20-33). He applied weak radiofrequency pulses in the presence of a field gradient in order to achieve spatial selectivity. Next door, Peter Mansfield and his postdoctoral students were developing a related method.

Garroway later joined the Mansfield group. A month before Garroway and Mansfield submitted their first imaging article to Journal of Physics in 1974[534] they applied together for a first patent.

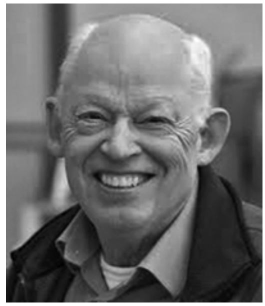

Figure 20-31: Waldo Hinshaw.

Figure 20-32: Peter Mansfield (1933-2017)

Figure 20-33: Alan N. Garroway.

Figure 20-34: Roger Ordidge.

533 Mansfield P, Grannell PK, Garroway AN, Stalker DC. Multi-pulse line narrowing experiments: NMR "diffraction" in solids? Proceedings. Colloque Ampère. Cracow, Poland. 1973. 16-27.

534 Garroway AN, Grannell PK, Mansfield P. Image formation in NMR by a selective irradiative process. J Phys C: Solid State Phys 1974; 7: L457-462.

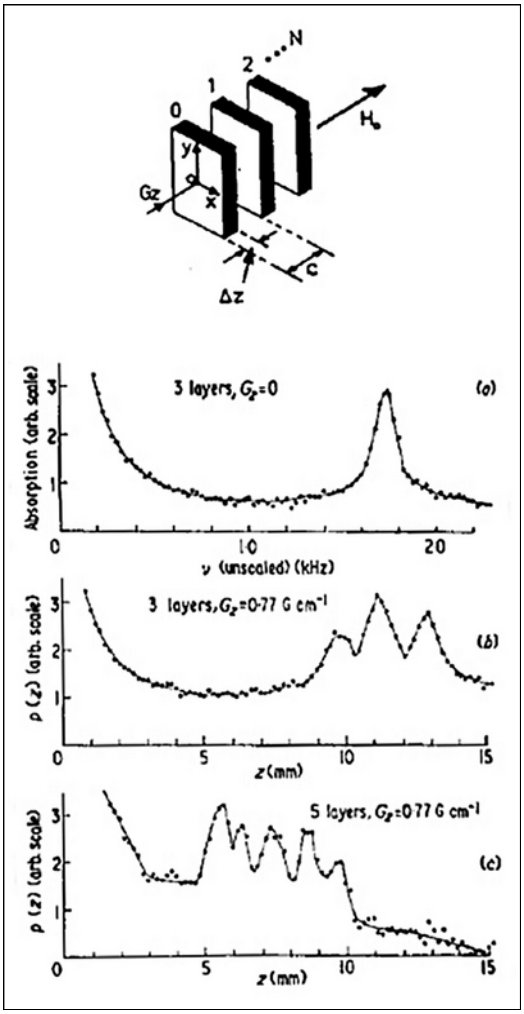

Figure 20-35:
Model of the one-dimensional lattice (camphor with cardboard spacers used for the experiment). Fourier cosine transforms of the transient response to a multiple pulse sequence from the layers of camphor. The result is a linear measurement in a single dimension, not an image.
(a) Three layers, no magnetic field gradient; **(b)** three layers, gradient of 0.77 G/cm; **(c)** five layers, same gradient.

Unfortunately, their method was unsuitable for practical application because it suffered from rapid loss of signal; the problem and its solution were explained by David Hoult from Oxford.[535]

By 1975, Mansfield and Andrew A. Maudsley proposed a line technique which, in 1977, led to the first image of *in vivo* human anatomy, a cross section through a finger. In 1978, Mansfield presented his first image through the abdomen.[536]

Echo-planar imaging (EPI), a real-time imaging technique, had been proposed by Mansfield's group in 1977, and the first crude images were shown by Mansfield and Ian Pykett in the same year. Roger Ordidge (Figure 20-34) presented the first EPI movie in 1981.[537]

The breakthrough of EPI came with manifold improvements in many aspects of the associated methodology and instrumentation – from gradient power supply and gradient coil design to pulse sequence development, presented by Pykett and Rzedzian in 1987.[538] However, it remains a niche technology in clinical MRI.

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535 Hoult DI. Zeugmatography: A criticism of the concept of a selective pulse in the presence of a field gradient. J Magn Reson 1977, 26: 165-167.

536 Mansfield P, Maudsley AA. Line scan proton spin imaging in biological structures by NMR. Phys Med Biol 1976; 21: 847-852.

– Mansfield P, Pykett IL, Morris PG. Human whole body line-scan imaging by NMR. Br J Radiol. 1978; 51: 921-922.

537 Ordidge RJ, Mansfield P, Coupland RE. Rapid biomedical imaging by NMR. Br J Radiol 1981; 54: 850-855.

538 Pykett IL, Rzedzian RR. Instant images of the body by magnetic resonance. Magn Reson Med 1987; 5: 563-571.

In 1977, Waldo Hinshaw, Paul Bottomley, and Neil Holland, succeeded with an image of the wrist.[539]

Hinshaw later went to Harvard and then joined the group at the Technicare company, at that time the most advanced scientific group with a commercial – and solid – medical applications background.

More human thoracic and abdominal images by different groups and several novel techniques followed, and by 1978, Hugh Clow and Ian R. Young, working at the British company EMI, reported the first transverse NMR image through a human head.[540]

The group around John Mallard at the University of Aberdeen also performed trailblazing research work. James Hutchison, a physicist, Margaret A. Foster, a biologist, and later Bill Edelstein, and their colleagues built their own whole-body MR imaging machine and developed the spin-warp technique. They published the first image through the body of a mouse in 1974 which was followed by a whole-body image in 1980 (Figure 20-36).[541, 542]

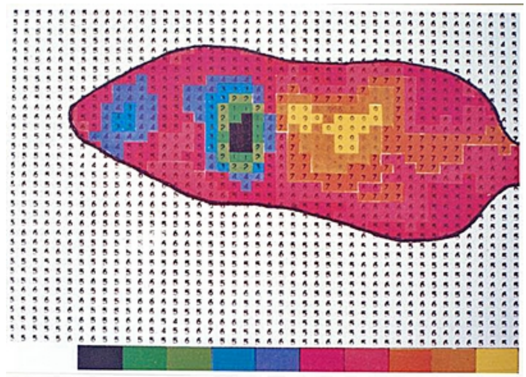


Figure 20-36:
(a) The first image of a whole mouse was obtained in Aberdeen, Scotland, in March 1974. **(b)** The prototype whole-body MR machine in Aberdeen. James Hutchison (1941-2018) lies in the magnet.

In the 1970s and 1980s Great Britain was a major contributor to the development of MRI equipment and software, but then a number of the researchers working in

539 Hinshaw DS, Bottomley PA, Holland GN. Radiographic thin-section image of the human wrist by nuclear magnetic resonance. Nature 1977; 270: 722-723.
540 Clow H, Young IR. Britain's brains produce first NMR scans. New Scientist 1978; 80: 588.
541 Hutchison JMS, Mallard JR, Goll CC. In-vivo imaging of body structures using proton resonance. Proceedings. 18th Ampère Congress. Magnetic resonance and related phenomena. Nottingham 9-14 September 1974. Amsterdam, Oxford: North-Holland Publishing Company. 283-284.
542 Edelstein WA, Hutchison JMS, Johnson G, Redpath TW. Spin-warp NMR imaging and applications to human whole-body imaging. Phys Med Biol 1980; 25: 751-756.

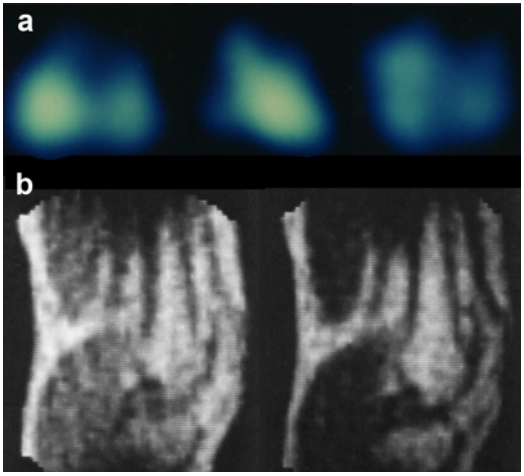


Figure 20-37:
(a) ^{19}F ventilation imaging of a dog's lung; coronal, sagittal and transverse images ("shadowgrams" of the entire lung). **(b)** Off-resonance (magnetization transfer) imaging of a knee joint.

Britain went to the United States. It was a major brain-drain for British universities, but there was little money in the British university system.

An excellent eyewitness report by some leading British researchers and scientists about the British work was given in the transcripts of a meeting at the Wellcome Institute for the History of Medicine, London, in 1996.[543]

Most of the British researchers stayed abroad, whereas many of the Continental Europeans who worked in the U.S.A. in the late 1970s and early 1980s returned to Europe.

Some of the Europeans had performed quite impressive research in the United States. Among them was Robert N. Muller who, in 1982, described off-resonance imaging, a technique later dubbed *magnetization transfer imaging*[544]; later he focused on relaxaometry and contrast agent research. Peter A. Rinck et al. described the first *in vivo* fluorine lung images (Figure 20-37a and b).[545]

Much of the research done in the early 1980s – for instance at Paul Lauterbur's lab – was not published, or only presented as abstracts because of the extremely rapid progress in the different research groups.

543 Christie DA, Tansey EM (eds). Making the human body transparent: The impact of nuclear magnetic resonance and magnetic resonance imaging. The transcript of a Witness Seminar held at the Wellcome Institute for the History of Medicine, London, on 2 July 1996. in: Tansey EM, Christie DA, Reynolds LA (eds). Wellcome Witnesses to Twentieth Century Medicine. Volume 2. London: The Wellcome Trust. 1998. ISBN 978 186983 5391.

544 Muller RN, Marsh MJ, Bernardo ML, Lauterbur PC. True 3-D imaging of limbs by NMR zeugmatography with off-resonance irradiation. Europ J Radiol 1983; 3: 286-290.

545 Rinck PA, Petersen SB, Heidelberger E, Acuff V, Reinders J, Bernardo ML, Hedges LK, Lauterbur PC: NMR ventilation imaging of the lungs using perfluorinated gases. Proceedings. The Society of Magnetic Resonance in Medicine. Second Annual Meeting. San Francisco 1983. 302-303. and in: Magn Reson Med 1984; 1:237 (abstract).

Clinical Applications

At about this time, MR imaging started being clinically evaluated. One of the most admirable research groups worked at Hammersmith Hospital in London. The head of the group was Robert E. Steiner, but Ian R. Young and Graeme M. Bydder were the moving forces. Among others, Frank H. Doyle and Jacqueline M. Pennock supplemented this group.

Because MR imaging is at the crossroads between medicine, biology and chemistry, physics, and computer science, research groups with strong interdisciplinary relationships and cross-fertilization became scientifically extremely fruitful, …

… which led to the 'odd couple' system, involving one physician and one scientist. At congresses, you would always see Ian Young (Figure 20-38) together with Graeme Bydder (Figure 20-39), a seemingly ideal combination.

There were other couples like them (e.g., Rinck and Muller, Figure 20-40), but apparently such an interdisciplinary relationship between radiologists and physicists or chemists does not fit into all European academic systems.

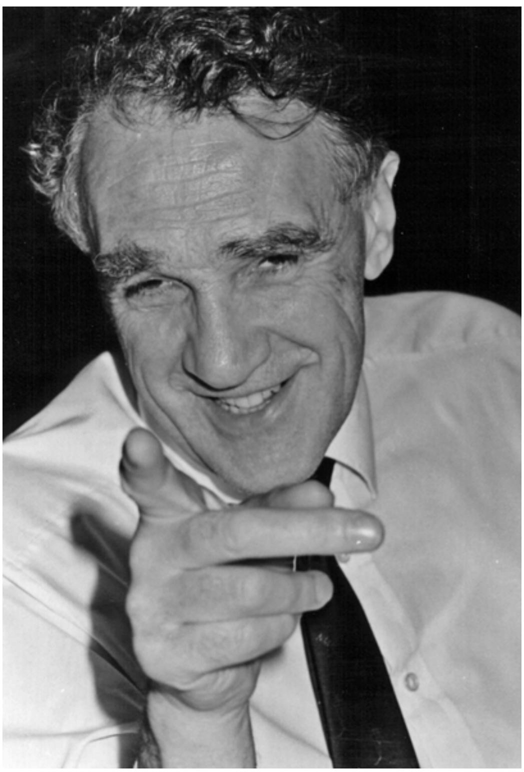


Figure 20-38:
Ian Young (1932-2019).

Figure 20-39 Graeme Bydder.

Figure 20-40: Peter A. Rinck and Robert N. Muller.

Early clinical imaging was extremely difficult, time-consuming, and often disappointing. Just taken as one example: spin-echo imaging, for instance, was a bigger step than many would imagine. Today it is taken for granted and mostly replaced by faster echo techniques; but it has helped MR imaging immensely to become a routine technique.

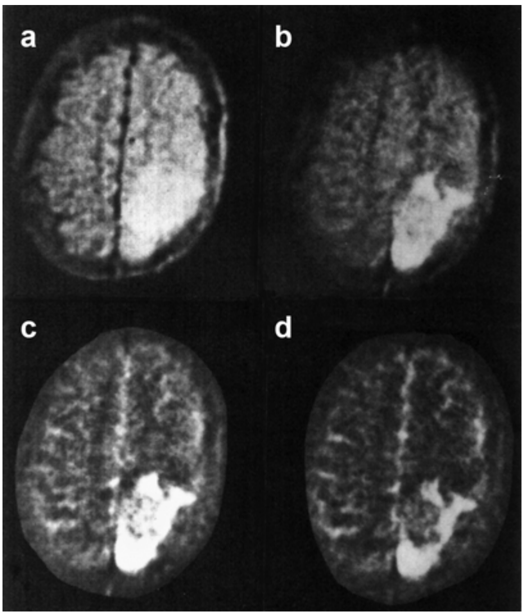


Figure 20-41:
Images of a recurrent brain tumor taken on a 0.14 Tesla system; TEs **(a-d)** between 20 and 300 ms.
Long echo times in multiecho CPMG sequences were a major leap forward in the first half of the 1980s. It took some years until T2-weighted images were generally accepted, mostly because many companies claimed that long TE was neither possible nor necessary.
The images were made five years before the introduction of Gd-based contrast agents; the tumor can be delineated on image d at a TE of 300 ms.
Illustration from: Rinck PA, Bydder GM, and Harms SE. Magnetic resonance imaging of the brain. Published in the first edition of this textbook in 1985.

The first MR images were based upon proton-density differences, later upon differences in T1-weighting.

By 1982-1983, the Hammersmith, Wiesbaden, and Freiburg groups pointed out that long heavily T2-weighted multiecho SE sequences were better at highlighting pathology (Figure 20-41).[546, 547]

There were similar groups in the United States, mostly in New England and California.

***In vivo* MR Spectroscopy.** Actual *in vivo* NMR spectroscopy took off in Oxford from 1974, with the group of Rex E. Richards and George K. Radda. Among others, David Hoult and David G. Gadian belonged to this group [more details can be found in Christie's Transcript; see above].

Unfortunately it is beyond the scope of this short introduction to mention all workers from around the world who can claim just credit for helping to advance the field – which is not meant to belittle their contributions to MR imaging.

We mention first and foremost our own work, that of our collaborators, students and colleagues because we are most familiar with it – and can assess and judge it.

546 Bydder GM, Steiner RE, Young IR, Hall AS, Thomas DJ, Marshall J, Pallis CA, Legg NJ. Clinical NMR imaging of the brain: 140 cases. AJR 1982; 139: 215-236.

547 Rinck PA, Bielke G, Meves M: Modified Spin-Echo Sequence in Tumor Diagnosis. Proceedings. The Society of Magnetic Resonance in Medicine. Second Annual Meeting. San Francisco 1983. 300-301. and in: Magn Reson Med 1984; 1: 236 (abstract).

Speeding up Clinial Imaging

In the 1980s, Continental Europe started to contribute intensively to MR imaging. Rapid imaging originated in European laboratories.

Jürgen Hennig (Figure 20-42), together with Arno Nauerth and Hartmut Friedburg, from the University of Freiburg introduced RARE (Rapid Acquisition with Relaxation Enhancement) imaging in 1986.[548] This technique is probably better known under the commercial names of *fast* or *turbo spin-echo*. The beginning of their article summarizes the problem to be solved:

> "Conventional imaging techniques used in MRI take several minutes for a multiple and/or multiecho 256×256 image. The use of these time-consuming methods causes several problems in routine clinical work. These well known problems include patient discomfort and positioning …"

At about the same time, FLASH (fast low angle shot) appeared, opening the way to similar gradient-echo sequences. FLASH had a completely different approach and, for non-scientifically reasons, was very rapidly adopted commercially.

The FLASH sequence was developed at Max Planck Institute, Göttingen, by Axel Haase (Figure 20-43), Jens Frahm (Figure 20-44), Dieter Matthaei, Wolfgang Hänicke, and Dietmar K. Merboldt.[549]

Figure 20-42: Jürgen Hennig.

Figure 20-43: Axel Haase.

Figure 20-44: Jens Frahm.

Figure 20-45: Richard A. Jones.

548 Hennig J, Nauerth A, Friedburg H. RARE imaging - a fast imaging method for clinical MR. Magn Reson Med 1986; 3: 823-833.

549 Haase A, Frahm J, Matthaei KD. FLASH imaging: rapid NMR imaging using low flip angles. J Magn Reson 1986: 67: 258-266.

Figure 20-46: Klaas Prüssmann.

Figure 20-47: Markus Weiger.

The inclusion of Hennig's RARE into the clinical imaging protocols was slower, and Mansfield's echo-planar imaging (EPI) – for technical reasons – took even more time to find its way into clinical imaging.

Acquiring images faster and with better quality remained one of the main goals in MR research. New ideas and distinct concepts were developed, for instance k-space substitution as proposed by Richard A. Jones (Figure 20-45).[550]

A combination of dedicated hardware and specific software led to *parallel imaging* which can reduce imaging time considerably. A first technique was described by Daniel K. Sodickson and Warren J. Manning but it required a particular coil configuration.[551]

In 1999 Klaas Prüssmann (Figure 20-46) and Markus Weiger (Figure 20-47) introduced SENSE and thus offered a more general solution.[552] Algorithms of the GRAPPA type, introduced a year later by Mark A. Griswold,[553] work better than the SENSE type for abdominal and thoracic or for echo planar imaging.

550 Jones RA, Haraldseth O, Müller TB, Rinck PA, Oksendal AN. k-Space substitution: a novel dynamic imaging technique. Magn Reson Med 1993; 29: 830-834.

551 Sodickson DK, Manning WJ. Simultaneous acquisition of spatial harmonics (SMASH): fast imaging with radiofrequency coil arrays. Magn Reson Med 1997; 38: 591-603.

552 Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. Magn Reson Med. 1999; 42: 952-962.

553 Griswold MA, Jakob PM, Heidemann RM, Nittka M, Jellus V, Wang J, Kiefer B, Haase A. Generalized autocalibrating partially parallel acquisitions (GRAPPA). Magn Reson Med. 2002; 47: 1202–1210.

Offsprings of MRI

The development of magnetic resonance imaging as a medical imaging technique opened the gates for several specialized imaging methods, highlighting different physical and chemical processes in the body – among them diffusion and neuronal activation. Both have become centers of attention in research.

Figure 20-48: Edward O. Stejskal (1932-2011).

Diffusion magnetic resonance imaging exploits the random diffusional motion of water molecules and is used in MR neuroimaging. During the recent years, additional research of numerous groups has turned this topic into one of the favorite research fields in MR imaging.

Some of the essential and fundamental work was published already in 1965 by Edward O. Stejskal (Figure 20-48) and John E. Tanner at the University of Wisconsin (cf. Chapter 11).[554]

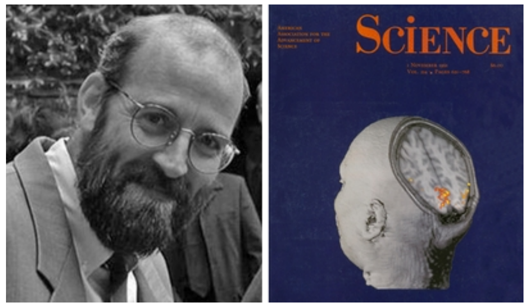


Figure 20-49: John W. Belliveau (1959-2014). **Right:** The cover page of Science (1 November 1991) featuring one of Belliveau's first functional images through the brain.

Functional brain imaging (fMRI) became similarly attractive to interdisciplinary research and to groups far outside conventional science.

Several research groups targeted neuronal activation, among them John W. Belliveau (Figure 20-49) and his collaborators from Boston[555] who observed the enhance-

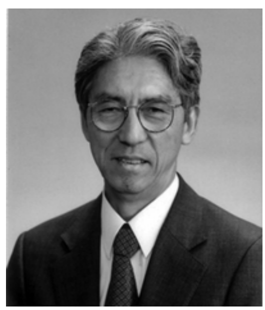


Figure 20-50: Seiji Ogawa.

554 Stejskal EO, Tanner JE. Spin diffusion measurements: spin echoes in the presence of time-dependent field gradient. J Chem Phys 1965; 42: 288-292.

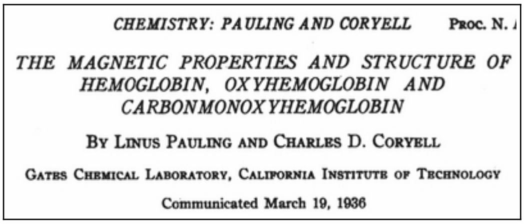
555 Belliveau JW, Kennedy DN Jr, McKinstry RC, Buchbinder BR, Weisskoff RM, Cohen MS, Vevea JM, Brady TJ, Rosen BR. Functional mapping of the human visual cortex by magnetic resonance imaging. Science. 1991; 254 (5032): 716-719.

– Belliveau JW, Rosen BR, Kantor HL, et al. Functional cerebral imaging by susceptibility-contrast NMR. Magn Res Med 1990; 14: 538-546.

I want to be a scientist too ...

How amateur researchers and scientist manqués abused and threw a bad light on a fundamentally brilliant discovery.

To be read on page 223.



CHEMISTRY: PAULING AND CORYELL PROC. N. A

THE MAGNETIC PROPERTIES AND STRUCTURE OF HEMOGLOBIN, OXYHEMOGLOBIN AND CARBONMONOXYHEMOGLOBIN

BY LINUS PAULING AND CHARLES D. CORYELL

GATES CHEMICAL LABORATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY

Communicated March 19, 1936

Figure 20-51: Pauling and Coryell paper (title page).

ment of stimulated regions of the human visual cortex by following the first pass of a contrast agent through the brain.

Other groups tried to exploit the differences in the magnetic properties of blood depending on its oxygenation state. The basis for this kind of contrast was described by Pauling and Coryell in 1936:[556]

> "Over ninety years ago, on November 8, 1845, Michael Faraday investigated the magnetic properties of dried blood and made a note 'Must try recent fluid blood.' If he had determined the magnetic susceptibilities of arterial and venous blood, he would have found them to differ by a large amount (as much as twenty per cent for completely oxygenated and completely deoxygenated blood) … " (Figure 20-51).

556 Pauling L, Coryell CD. The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. Proc Natl Acad Sci USA 1936; 22: 210–216.

At AT&T Bell Laboratories in New Jersey, Seiji Ogawa (Figure 20-50) and his collaborators compiled and elaborated upon these results and developed the idea of monitoring brain activity after stimulation with *Blood Oxygenation Level Dependent* (*BOLD*) contrast.[557] In the race (if there was a race) of who published the first BOLD image in an animal Ogawa came in first in 1990, Robert Turner second in 1991,[558] and third K.K. Kwong, John Belliveau and collaborators in 1992, but they came in with the first human image.[559] Kwong had successfully performed the first human experiment in May 1991, but his paper was rejected by *Science.*

Functional MRI using BOLD is now employed as one of the principal research techniques to map the visual, auditory and sensory regions for research in neurobiology and psychology. However, its validity is still very controversial.[560]

557 Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 1990; 87: 9868-9872.
– Ogawa S, Lee TM, Nayak AS, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. Magn Res Med 1990; 14: 68-78.

558 Turner R, Le Bihan D, Moonen CTW, Despres D, Frank J. Echo-planar time course MRI of cat brain oxygenation changes. Magn Res Med 1991; 22: 159-166.

559 Kwong KK, Belliveau JW, Chesler DA, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proceedings of the National Academy of Sciences USA, 1992; 89: 5675–5679.

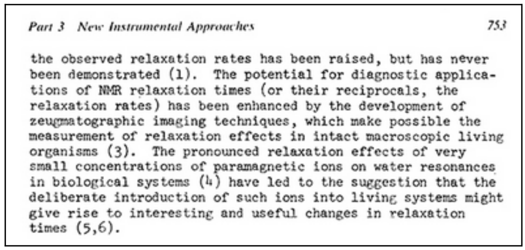
560 Kim SG, Ogawa S. Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals. J Cereb Blood Flow Metab 2012; 32: 1188-1206.

Contrast Agents

The concept of using paramagnetic contrast agents to enhance pathologies was described by Paul C. Lauterbur, Maria Helena Mendonça-Dias and Andrew M. Rudin in 1978 (Figure 20-52).[561] After injecting a manganese salt solution as contrast agent they imaged five dogs with myocardial infarctions and were able to highlight them.

In October 1983 Lauterbur's group published a major overview of paramagnetic contrast agents in MR imaging, explaining problems and questions involved in the development of possible contrast agents.[562]

In the period between the publication of these two articles, scientists in academia and industry took note and started their own research in the field. Several patents were taken and influenced the further progression of a hectic race, partly shrouded in secrecy.



Part 3 New Instrumental Approaches 753

the observed relaxation rates has been raised, but has never been demonstrated (1). The potential for diagnostic applications of NMR relaxation times (or their reciprocals, the relaxation rates) has been enhanced by the development of zeugmatographic imaging techniques, which make possible the measurement of relaxation effects in intact macroscopic living organisms (3). The pronounced relaxation effects of very small concentrations of paramagnetic ions on water resonances in biological systems (4) have led to the suggestion that the deliberate introduction of such ions into living systems might give rise to interesting and useful changes in relaxation times (5,6).

Figure 20-52:
Excerpt from Lauterbur's 1978 paper in "Frontiers of Biological Energetics" on the use of manganese to highlight myocardial infarctions in dogs; the first description of the use of contrast agents in MR imaging.

The former Schering company submitted a patent application for Gd-DTPA dimeglumine in July 1981 in a project involving Hanns-Joachim Weinmann (Figure 20-53) and Ulrich Speck.[563] In 1984, Dennis H. Carr from the Hammersmith and Wolfgang Schörner from Berlin published the first images in men.[564, 565] In 1988, Gd-DTPA (Magnevist) became commercially available, followed shortly afterwards in 1989 by Gd-DOTA (Dotarem) from Guerbet in Paris. A number of other agents entered the marketplace in the 1990s.

During the last decades, more than 800 potential MR contrast agents were described in the literature or been patented, but only a dozen are available on the market for clinical use. A number of those on the market had to be withdrawn because of possible side effects.

561 Lauterbur PC, Mendonça Dias H, Rudin AM. Augmentation of tissue proton spin-lattice relaxation rates by in vivo addition of paramagnetic ions. in: Dutton PO, Leigh J, Scarpa A (eds). Frontiers of Biological Energetics. New York: Academic Press 1978. 752-759.

562 Mendonça Dias MH, Gagelli E, Lauterbur PC. Paramagnetic contrast agents in nuclear magnetic resonance medical imaging. Sem Nuc Med; 1983; 13,4: 364-376.

563 Weinmann H-J, Gries H. Paramagnetic contrast media in NMR tomography – basic properties and experimental studies in animals. Proceedings. The Society of Magnetic Resonance in Medicine. Second Annual Meeting. San Francisco 1983.

564 Carr DH, Brown J, Bydder GM, Weinmann HJ, Speck U, Thomas DJ, and Young IR. Intravenous chelated gadolinium as a contrast agent in NMR imaging of cerebral tumours. Lancet 1984; March 3: 484-486.

565 Schörner W, Felix R, Laniado M, Lange L, Weinmann HJ, Claussen C, Fiegler W, Speck U, and Kazner E. Human testing of the nuclear spin tomographic contrast medium gadolinium-DTPA. RöFo - Fortschr Röntgenstr 1984; 140: 493-500 (in German).

The Contrast Agent Debacle

If physicians apply a drug outside the recommended and approved protocol, they bear the responsibility for the outcome ... or don't they?
A comment on page 257.

Figure 20-53:
Hanns-Joachim Weinmann (1949-2009)

Figure 20-54:
The Varian Associates site in San Carlos, CA, in 1948.

Figure 20-55:
A resistive Bruker whole-body MR machine from 1983. It operated at 0.15 T.

Magnetic Resonance Imaging Equipment

With the exception of the scientific instrument manufacturers, the medical hardware makers had no background in NMR.

Very early NMR attracted the attention of Russel and Sigurd Varian, two brothers who were involved in military technology development in World War II. The Californian company became, first and foremost, a major government contractor for highly sophisticated and classified military technologies. NMR equipment for research remained an important sideline for the next 50 years (Figure 20-54).

Other scientific manufacturers include JEOL in Japan and Bruker Spectrospin in Germany and Switzerland.

Most scientific developments connected to medical MR imaging were done on Bruker machines; even the competition used Bruker equipment inside their machines (Figure 20-55). Today Bruker is a US-American enterprise with a wide range of interests, from scientific equipment to military applications.

With few exceptions, most early magnets for MR machines were produced by Oxford Magnets. Still today many magnets stem from companies in the Oxford area, although nowadays most companies produce their own magnets.

The first hardware manufacturer to get involved in whole-body imaging was Electric and Musical Industries (EMI) in 1974. Later the company was taken over by Picker (later Marconi, today Philips).

Philips started research into MR imaging at the same time; P. Rob Locher, André Luiten (Figure 03-01b), and Piet van Dijk were seen at many scientific meetings.

Siemens got involved in 1977, with – among others – Arnulf Oppelt, Wilfried Loeffler and Andrew Maudsley working on the project. Johnson & Johnson's Technicare division began their development in 1978/79.

Others followed in the 1980s and 1990s, among them the big Japanese companies Hitachi and Toshiba, as well as the US-American General Electric company in 1983. To add to its competence and market in MR imaging, General Electric acquired Technicare from Johnson and Johnson in 1985, the French Compagnie Générale de Radiologie (CGR) in 1987, and the MR business of the Israeli company Elscint in 1998.

M&D Aberdeen was a company originating from the research group at Aberdeen University. It sold one machine to a private center Geneva, but the company disappeared a long time ago.

Another effort was the Finnish MR equipment in the late 1970s, produced by Instrumentarium in Helsinki. Raimo E. Sepponen (Figure 20-56), together with a number of other researchers, among them the surgeon Jorma T. Sipponen, aimed at developing a method and device for detection of internal hemorrhages.

Their first clinical MR imaging machine was installed at Helsinki University Central Hospital in June 1982 operating at a field strength of 0.17 T. The second unit operated at 0.02 T, and later units operating at 0.04 T,[566] which – at least at that time – was politico-commercially a step in the wrong direction. Nowadays, such intelligent and sophisticated approaches would be welcomed again.

Figure 20-56:
Raimo E. Sepponen.

Today there are numerous other companies producing MRI machines, many of them in Asia.

566 Sepponen RE, Sipponen JT, Sivula A. Low field (0.02 T) nuclear magnetic resonance imaging of the brain. J Comput Assist Tomogr 1985; 9: 237-241.

Prizes and Awards

Nobel Prizes. A number of Nobel Prizes were awarded for research results in NMR or neighboring disciplines. Among the recipients were:

- Otto Stern: Physics, 1943;
- Isidor I. Rabi: Physics, 1944;
- Felix Bloch and Edward M. Purcell: Physics, 1952;
- Nicolaas Bloembergen: Physics, 1981;
- Richard R. Ernst: Chemistry, 1991;
- Kurt Wüthrich: Chemistry, 2002.

Paul C. Lauterbur received the Nobel Prize in Physiology or Medicine in 2003 for the invention of magnetic resonance imaging (Figure 20-57). Peter Mansfield shared the Nobel Prize for his further development of MRI.

The Nobel Foundation's announcement read:

Figure 20-57:
Paul C. Lauterbur receiving the Nobel Prize in Physiology or Medicine from the King of Sweden in 2003.

> "Paul Lauterbur discovered the possibility to create a two-dimensional picture by introducing gradients in the magnetic field. By analysis of the characteristics of the emitted radio waves, he could determine their origin. This made it possible to build up two-dimensional pictures of structures that could not be visualized with other methods."

> "Peter Mansfield further developed the utilization of gradients in the magnetic field. He showed how the signals could be mathematically analysed, which made it possible to develop a useful imaging technique. He also showed how extremely fast imaging could be achievable. This became technically possible within medicine a decade later."

This was the first Nobel Prize in Physiology or Medicine awarded in the field.

Paul C. Lauterbur commented on this in a lecture given in Lund, Sweden, some days after the Prize Ceremony in Stockholm:

> "It has been noted that the Nobel Prize for the development of MRI was awarded to a chemist and a physicist. That is not accidental. The field developed from a discipline that was first the province of physicists, two of whom share a Nobel Prize for it, and then became most prominent in its applications to chemistry, so that chemists received the next two Nobel Prizes, for novel techniques and applications. Although the needs of medical diagnosis stimulated the development of MRI, it was firmly grounded in the knowledge and instruments of

physicists and chemists, as well as of those of mathematicians and engineers, all far from the knowledge and concerns of physicians, who became its greatest beneficiaries."

European Magnetic Resonance Award. Since the mid-1980s, the European Magnetic Resonance Forum (EMRF) and The Round Table Foundation (TRTF) confer the *European Magnetic Resonance Award* (Figure 20-58) upon those scientists without whom magnetic resonance imaging as a patient-friendly non-invasive diagnostic technology in medicine would not exist.

The European Magnetic Resonance Award is given to scientists irrespectively of their affiliation to a society or a company. Since 2014, the Award will only be given at special occasions.

Figure 20-58:
The European Magnetic Resonance Award is a crystal owl, representing Athena, the goddess of crafts and skilled peacetime pursuits. Paul C. Lauterbur smiles at her after he received the Prize. Sitting left to him Thomas Budinger (1986).

To date, the recipients of the European Magnetic Resonance Award are:

- Silvio Aime
- Jacques Bittoun
- Graeme M. Bydder
- Patrick J. Cozzone
- Jens Frahm
- Klaes Golman
- John Griffiths
- Axel Haase
- Anders Hemmingsson
- Jürgen Hennig
- Werner Kaiser
- Christiane Kuhl
- Gerhard Laub
- Paul C. Lauterbur
- Denis Le Bihan
- Donald Longmore
- Peter Luijten
- John Mallard
- Peter Mansfield
- Chrit T. Moonen
- Guy Marchal
- Luis Martí-Bonmatí
- Robert N. Muller
- Stefan Neubauer
- Erik Odeblad
- Roberto Passariello
- Klaas P. Prüssmann
- Peter A. Rinck
- Raimo E. Sepponen
- Thomas Vogl
- Gustav K. von Schulthess
- Hanns-Joachim Weinmann
- Ian Young

In addition, there are numerous research prizes by societies in the field of magnetic resonance imaging given to their members.

The Author

Peter A. Rinck is a University Professor of Radiology and Magnetic Resonance (*emeritus*) and has a Doctorate in History of Medicine.

After a classical school education he attended medical school in Berlin (Free University of Berlin) and served his internship and residency in radiology, nuclear medicine and radiation therapy at Charlottenburg University Hospital in Berlin.

Afterwards, until 1983, he was involved in the very early development of magnetic resonance imaging as Senior Research Associate at the State University of New York at Stony Brook where he worked in Paul C. Lauterbur's research group (Nobel Prize in Medicine 2003). The first version of this textbook was written at this time.

Subsequently Rinck worked as physician-in-charge of one of the first two German government sponsored MR machines in Wiesbaden, Germany.

Between 1987 and 1994 he was head of Europe's biggest clinical and research MR facility – at that time – at the University of Trondheim, Norway. Between 1986 and 2012 he was also Adjunct Professor at the School of Medicine and Pharmacy of the University of Mons-Hainaut in Belgium.

Since 1982 Rinck is Chairman of the European Magnetic Resonance Forum, EMRF, and since 2008 President of the Council of The Round Table Foundation, TRTF.

He is also Chairman of the Selection Committees of the the Pro Academia Prize and of the European Magnetic Resonance Award.

Visiting Professorships: The Neurological Institute of Colombia. Bogotá, Colombia (1986); Charité University Hospital, Medical Faculty of Humboldt University, Berlin, Germany (1991-1992); et al.

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Acknowledgements

There has been a long list of contributors to this and earlier versions, among them Atle Bjørnerud, Graeme Bydder, Patricia de Francisco, Jürgen Hennig, Richard A. Jones, Jørn Kværness, Willy Eidsaunet, Robert N. Muller, Gunvor Robertsen, Timothy E. Southon, and Geir Torheim.

Their support, ideas, dedication, and feedback have added much to the quality of this work.

We are also indebted to our friends who took care of some of the translations of the printed version – among them Andrea Giovagnoni for the Italian edition, Valentin Sinitsyn for the latest Russian edition, Luis Martí-Bonmatí and Ángel Alberich-Bayarri for a Spanish e-learning version; and Song Yingru for an earlier Chinese edition. The Editor-in-Charge of the current Chinese e-Learning and book editions is Qiuju Zhou.