

NUCLEAR MAGNETIC RESONANCE IMAGING (MRI)

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ABSTRACT

This article discusses the basic concepts of Magnetic Resonance Imaging (MRI) with the intention to introduce the subject to uninitiated. The MRI technique is a powerful noninvasive probe of the body's internal anatomy. In MRI, the images are produced not by X-rays, but through the use of non-ionizing radio waves that stimulate transitions between spin states of nuclei in a magnetic field when passed through the body. The time required for the nucleus to return to equilibrium gives information about the environment of that nucleus. In this way tissue abnormalities can be determined in vivo. This article covers the basis of MRI phenomena, the concept of magnetic moment of the sample, NMR excitation and emission and the equipment necessary to observe these NMR properties. The primary agents used to increase tissue contrast in MRI are also mentioned. Finally the importance and prospects of this technique in Pakistan have been discussed (JPMA 41: 259, 1991).

INTRODUCTION

Scientists prefer to examine the biochemical activity of living systems without disturbing its life and growth. MRI has transformed that dream into reality by which scientists can examine the metabolism of an intact cell, organ and even whole organism without disturbing, cutting or damaging the tissues. This new, exciting and non-invasive technique has enabled the diagnosis of a variety of muscular and vascular diseases, to identify cancerous tissues and to monitor the health of the transplant. The MRI also offers a new powerful probe of the body's internal anatomy and function. There are two major approaches, the first one is the generation of high resolution anatomical images which reflects the nuclear density distribution or spatial variation at the molecular level and chemical environments of the nuclei ^1H which is the most abundant in biological tissues and prominent in magnetic qualities. When a non-uniform magnetic field is applied across a section of body, the hydrogen nuclei present in varying concentration in the section are tagged with different frequencies, and are processed to give an image. The second major approach is an analytical. Scientists prefer to examine the biochemical activity of living systems without disturbing its life and growth. MRI has transformed that dream into reality by which scientists can examine the metabolism of an intact cell, organ and even whole organism without disturbing, cutting or damaging the tissues. This new, exciting and non-invasive technique has enabled the diagnosis of a variety of muscular and vascular diseases, to identify cancerous tissues and to monitor the health of the transplant. The MRI also offers a new powerful probe of the body's internal anatomy and function. There are two major approaches, the first one is the generation of high resolution anatomical images which reflects the nuclear density distribution or spatial variation at the molecular level and chemical environments of the nuclei ^1H which is the most abundant in biological tissues and prominent in magnetic qualities. When a non-uniform magnetic field is applied across a section of body, the hydrogen nuclei present in varying concentration in the section are tagged with different frequencies, and are processed to give an image. The second major approach is an analytical technique using ^{31}P NMR spectroscopy for identification and quantification of the most abundant metabolites in various tissues. Changes in the levels of these metabolites and intracellular cytoplasmic pH can be followed in various ischaemic and hypoxic conditions to monitor metabolic response to stress situation and to diagnose inborn errors of metabolism, The historical development, conceptual

basis and the application of various MM techniques are discussed.

PERSPECTIVE

NMR was first observed by Purcell¹ and Bloch² in 1946 who received the Nobel prize in 1952. They developed NMR studies of liquids and solids that have never been since used as powerful tools to identify and determine the structure, conformational and motional properties of the simplest to the most complex molecules and their phases. The possibility of obtaining pictures or images of spatial distribution of NMR signals was first demonstrated in 1973³. Bloch observed a strong NMR signals from his finger placed in the detector coil of the apparatus⁴. Gabillard investigated one dimensional distribution of NMR signals^{5,6} Singer conducted blood flow experiment⁷ using NMR in 1959 and Damadian observed elevated NMR relaxation time in cancerous tissues⁸ in vitro in 1971. Damadian's observation and the extensive in vitro studies of tissue relaxation times provided an early basis that MM can provide information of medical and biological importance. It should be noted that the use of pulsed and static magnetic field gradients in NMR is an essential ingredient of all MM techniques⁹⁻¹². After Lauterbur's work, individual groups led by Mansfield¹³⁻¹⁶, Hinshaw¹⁷⁻¹⁹, Hutchison²⁰ and Ernst²¹⁻²² devised and demonstrated several alternative MRI schemes. One of the first dedicated large scale imaging system was completed by Hinshaw in 1977, yielding promising proton imaging results of human forearm and live mammals upto 8cm in diameter²³⁻²⁸. Mansfield and coworkers also achieved improvements in images of finger in vivo MRI scans²⁹⁻³⁵, MM scan of human head and body were also produced³⁶⁻⁴⁴. Other groups were also actively involved with MRI⁴⁵⁻⁵². The imaging NMR parameters other than nuclear density and relaxation times have also received attention; schemes for imaging or generating chemical shift spectra have also been devised⁵³⁻⁵⁷. This technique can also be used to monitor metabolic state of intact biological tissues⁵⁸ and to image blood flow⁵⁹. The recent technological advances in MRI have proved it as a promising modality in children due to lack of radiation exposure, superior anatomic resolution and exquisite soft tissue contrast capability⁶⁰. MM seems to be advantageous over CT in a wide spectrum of central nervous system (CNS), abdomen, heart and urinary tract problems⁶¹.

Nuclear Magnetic Resonance Imaging technique

MM relies on atomic nuclei such as hydrogen with an odd number of protons or neutrons, which are electrically charged and act like a small magnet possessing a magnetic moment. An externally applied magnetic field rotates this magnetic moment towards the direction of the magnetic field and also aligns them. However, they wobble at a specific rate of frequency. The stronger the magnetic field, the greater the frequency. If a radiofrequency is aimed at these protons, it excites them and changes the alignment of their nuclei. When the radiofrequency is switched off the nuclei spiral back into place and realign themselves within milli seconds transmitting a small electric or radio signal of their own. A computer translates these faint signals into an image of the area scanned. The image reveals varying densities of the hydrogen atom and their interaction with surrounding tissues in a cross section of the body and also relaxation times (T1 = spin-lattice, T2 = spin-spin) which are different for different tissues depending on the biological state. Scientists chose hydrogen as basis for MM scanning because of its abundance in the body and its prominent magnetic qualities. Since hydrogen reflects water contents, doctors can use the image to make distinctions between tissues. Lauterbur pioneered^{3,62,63} the work that produced images from NMR specter by taking a series of projections at different gradient orientations and superimposing them- a two or three dimensional image can thus be produced^{37,38}. This technique is called zeugmatography where zeugma means to join together. A number of other methods of MIIT have

been suggested⁶⁴ some of which place more reliance on NMR spectra and less on computational power. These methods can be roughly grouped in terms of the way they build up cross-sectional images, such as point to point, line by line or a whole cross-section at one time. The point to point technique was explored early in the development of MM by Damadian and associates^{35,65,66} who used a static magnetic field distribution that was uniform only over a small, well localized region. The sample in question is moved step by step to cause a small homogeneous region to be scanned. Hinshaw's single sensitive point technique^{17,18,67} brought about three orthogonal oscillating field gradients which ensured that the detected signals came from the spatial region of time dependent field at the intersection of null planes of oscillating ingredients. The point by point technique has a double disadvantage; first it is very slow and dependent on weak signals arising from small volume, and second it requires much bigger detection coil. However, the technique is flexible to provide well localized measurements and it is also possible to obtain images without the help of a computer. The line by line scan technique^{23,29,46} has an advantage of both time and signal size over point to point method. The common feature of line scan method is that by means of various NMR maneuvers, it arranges for the only detectable signals to originate along unique line with the prescribed cross section of the sample. This will ensure NMR frequency spectrum, representing the density of resonant nuclei at each point along the line. Successive lines then generate the cross section in a manner similar to a television picture. Hutchison⁶⁸ also proposed an alternative selective irradiation line scan scheme. The construction of an image by this technique reduces the imaging time from the order of hours to several minutes. However, this technique must be differentiated from image reconstruction and projection⁶², which detects the signals from image generation. The technique of planar spin²⁹⁻³¹ imaging, multiple line scan method⁶⁹ or echo planner^{70,71} imaging, generate an image from a single shot of the planar response. More than twenty types of imaging techniques have been proposed and tested, some of them are mentioned below, but no method has proved universally acceptable.

1) Field Focusing Nuclear Magnetic Resonance (FONAR), 2) Image Reconstruction from ID Projections. 3) Direct 2D Projection Imaging, 4) Selective Irradiation, 5) Sensitive Region Method, 6) Inversion Recovery, 7) Echo-planar, 8) Spin Warp, 9) Fourier Zeugmatography, 10) Rotating Frame Zeugmatography, 11) Direct 3D Imaging. The diversity of potential imaging raises many questions for equipment manufacturers as well as for users⁷². The solution of these problems will involve testing clinical applications and situations and certainly some compromises. It is unlikely that any one machine will be able to provide all these solutions. In spite of this variability, there are some common elements in all Mill scanners which are discussed.

Nuclear Magnetic Resonance Imaging equipment

The imaging system consists of a number of elements and each plays an important role. The principal components are primary magnets, magnetic gradient, radio equipment, computer data storage and display system. In addition other components such as data manipulation systems, amplifiers, AD converter, computer memory system, magnetic tape unit, matrix camera and display unit are also involved. A schematic description of these major sub-systems of Mill scanners is shown in Figure.

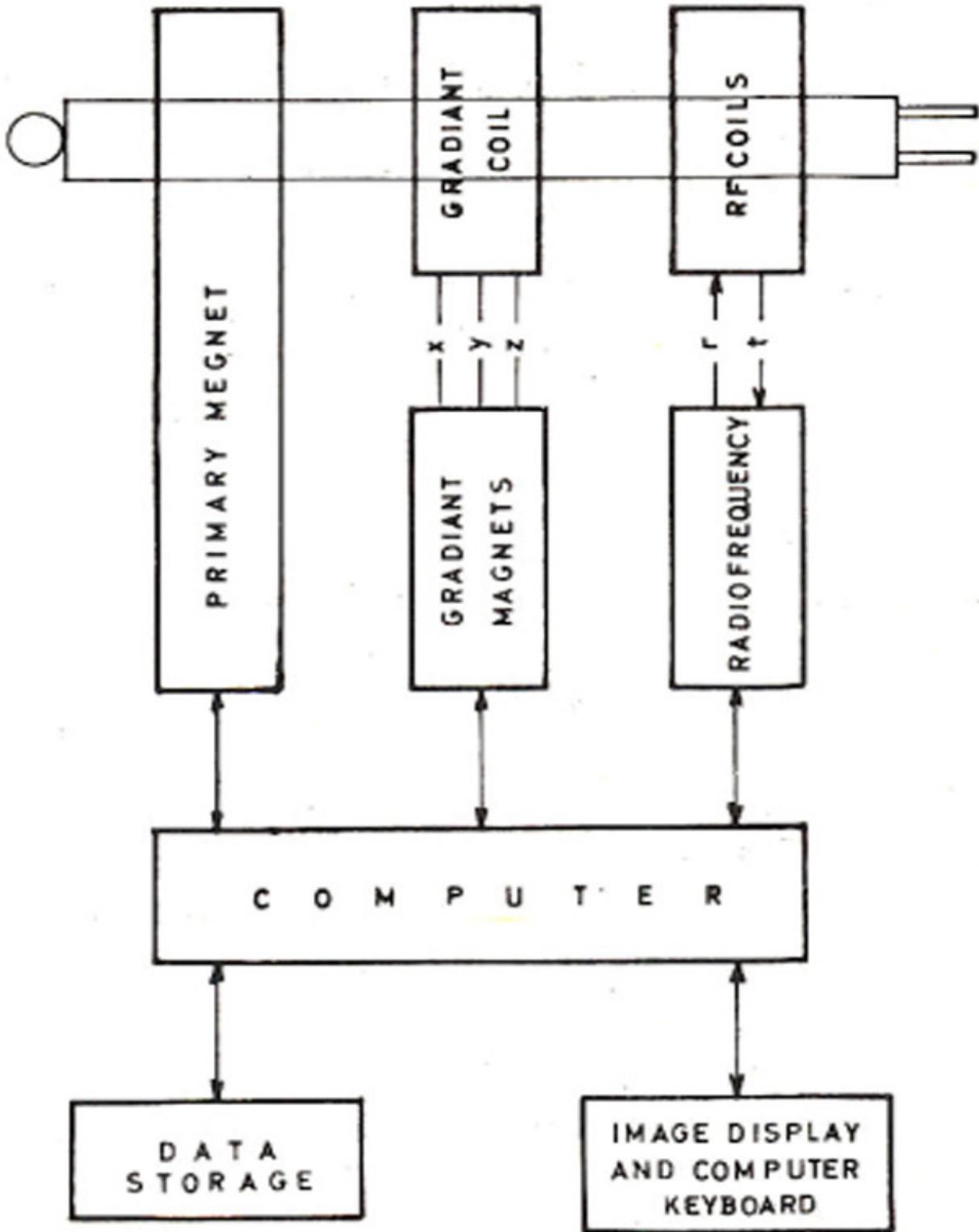


Figure. Block diagram of nuclear magnetic resonance scanner showing basic units.

The role of computer data storage and display sub-systems are identical as in CT imaging, therefore, these are familiar to most of the medical imaging personnel. Only the remaining sub-systems are discussed here.

1. Magnetic System - The magnet is definitely the key element in any MRI sub-systems as the

specifications required place great demands. The three types of magnets used in clinical MRI machines are electromagnet, permanent magnet and superconducting magnet.

2. Gradient Field Subsystem-The purpose of this subsystem is to create homogeneity and control gradients in the magnet field to allow spatial localization of the NMR signals.

3. Radio equipment subsystem - This consists of a radio transmitter, a power amplifier, transmitter-receiver coil, preamplifier and receiver. It also includes systems of converting the analog radio signal into digital form that can be processed and analyzed by the computer to form the final signal of the size and shape of RE energy from patients body.

Contrast agents In MRI

Contrast agents play an important role as their need arose due to overlapping of relaxation times in different pathological conditions (abscesses, malignant neoplasma, benign tumours) which do not provide absolute and specific diagnostic information^{73,74}. This low image intensity can be altered by the use of paramagnetic agents and thus increase the needed diagnostic specificity. These paramagnetic contrast agents alter the magnetic properties of the nuclei being observed in the image without being detected. The effectiveness of MRI contrast agents depends on its ability to change the NMR properties (nuclear spin density and relaxation time T1, and T2) of the nucleus being studied. The principal proton species used in MRI is H₂O, the contrast agents generally reduce T1, and T2. These contrast agents are paramagnetic, mostly metals in nature and usually possessing incomplete d and orbitals. Ions of these metals usually contains 1-7 unpaired electrons (Table)⁷⁵.

TABLE. Contrast agents (paramagnetic metal ions) used in MRI.

Ions	No of Unpaired Electrons	Magnetic Moments (Bohr Magnetons)
Ti ⁺³ , V ⁺⁴ , Cu ²	1	17-22
V ⁺³ , Ni ⁺²	2	26-28
Cr ⁺³ , V ⁺³	3	2.8-4.0
Co ⁺² , (high spin)	3	3.8
Mn ⁺³ , Cr ⁺² (high spin)	4	4.1-5.2
Fe ⁺² (high Spin)	4	4.9
Fe ⁺³ , Mn ⁺²	5	5.1-5.5
Ga ⁺³	7	5.9
		8.0

The strength of a magnetic moment is proportional to the number of these unpaired electrons which is one of the factors that determines relaxation time. Water molecules binds directly to these ions, leading to drastic decrease in H₂O relaxation time. Other paramagnetic species used include free radicals and oxygen⁷⁶⁻⁷⁷. These contrast agents have been reviewed in detail⁷⁸⁻⁸⁷. Clinical status of Magnetic Resonance Imaging in the world and its prospects in Pakistan. The growing awareness and

enthusiasm⁸⁸ in nuclear magnetic resonance imaging (Mill) led to the most momentous development in diagnostic imaging. Mill reflects on the behaviour of hydrogen atoms and focuses at water molecules, therefore the organs with water density higher than other tissues appear brighter. This allows Mill to do certain things better than CT scanners. This technique provides information at the cellular level and is very successful in the anatomical format and also appears to have appreciable promise in the physiological and metabolic areas. No definite imaging protocols have been established yet. Performing MR images demand multiple choice of protocols such as acquisition parameters, imaging plane orientation, type of coil, slice thickness, matrix size and number of excitations. These parameters can provide a foundation and practical basis for interpretation of Mill which generate a series of slices in the chosen plane (axial, sagittal, posterior). In practice the choice of plane and their order depends on the organ of the body. The examination of spinal cord begins with sagittal sections followed by axial slices. For the abdominal organs (liver, spleen, pancreas, kidney, adrenals) and the genitopelvic organs, two planes are often sufficient. In pathology such as an abnormality in craniocervical junction, such as Chiari malformation, can be imaged best in sagittal plane. The extent of a tumor in a long bone can be demonstrated by sections in a plane parallel to the diaphysis. Preoperative brain workup is an indication for assessment in all three orthogonal planes, in order to give the surgeon maximum number of anatomical indications. The fast imaging technique in Mill makes it possible to form primary scans within seconds. The work done and its clinical application to entire spectrum of medical disorders in the world is very exciting. In central nervous system Mill provides structural detail not attained by other modalities. The diagnostic significance of Mill is quite clearly evident in neurology⁸⁹, the head⁹⁰⁻⁹³ and in spinal column⁹⁴⁻⁹⁶. MRI is superior to CT in delineating the cortex such due to lack of beam hardening. Mill provides dramatic discrimination of grey and white matter and is more sensitive in detecting white matter hyperintensities⁹⁷. MRI provides excellent delineation of brain tumors of many varieties than CT due to better resolution, lack of beam hardening or streak artifacts and multiple imaging capabilities. In particular Mill is superior in evaluating cerebellum and brain stem while there may be severe artifacts on CT. Mill can distinctly demonstrate hemorrhagic infarcts, which may be missed on CT. MRI technique has proved to be ideally suited due to its ability to depict soft tissues in high contrast such as in spinal cord, thus reducing the painful procedure of injecting a contrast agent into the tissues for X-ray. The Mill also showed its worth in heart, mediastinum, liver, gallbladder, pancreas, kidney¹⁰⁸, adrenals¹⁰⁹⁻¹¹¹ and other disorders. In case of mediastinum it offers an advantage over CT in that the major blood vessels are easily identified and the thymus is clearly delineated over non-displaced mediastinal structures. MRI is also a promising modality for pediatric imaging¹¹² due to lack of radiation exposure, superior anatomic resolution and exquisite soft tissue contrast capability. Mill seems to be advantageous over CT in a wide spectrum of pediatric brain disorders, with the exception of acute head trauma and herpes encephalitis¹¹². MRI is superb for demonstrating Arnold-Chiari and Dandy-Walker malformations¹¹². Recent studies show that Mill may be more sensitive than CT for the early detection of avascular necrosis¹¹² and in non-invasive measurement of dynamics and elasticity of carotid artery¹¹³. Direct blood flow measurement is also accessible in MRI through variations in signal intensity of blood in the major vessels. The pulsatile nature of blood flow, and indeed the heart, can be observed in images collected synchronously with respect to the cardiac cycle. Sequence of such images show the dynamic function of the heart, potentially providing invaluable assistance in assessment of patients suffering from heart disease. MRI is very sensitive but has its limitation in not being specific since motion badly degrades the images¹¹⁴. Mill has some reservation in patients with medical prostheses of metal construction, particularly pacemakers whose operation could be affected by the pulses or movements within the static field¹¹⁵. Besides this, neurostimulators and ferromagnetic implants such as (intracranial vascular clips, metallic foreign bodies in soft tissues etc.) are likely to be displaced. Some metallic implants such as stainless steel dental hardware, hip

prosthesis, Harrington rod, etc. also cause image artifacts¹¹⁶. It can be assumed that the role of Mill in diagnostic radiology is very bright in future. This technique has already been adopted by all the big medical institutes in the USA, Canada and Europe. Currently more than 12 companies are building Mill systems and today more than 400 machines have been installed and are operating in the United States. This explosive growth reflects Mill's wonderful diagnostic results. The other developed and less developed countries are in the process of acquiring this technique. At present it costs more than 2.5 million US dollars for equipment plus half a million dollars for a room completely insulated from external radiofrequency. Mill can play very useful role in the health sector in Pakistan and its benefits would certainly outweigh its high cost. This technique will serve neurologists, oncologists and rheumatologists as a very powerful diagnostic tool.

REFERENCES

1. Purcell, E.M., Torrey, H.C. and Pound, LV. Resonance absorption by nuclear magnetic resonance in a solid. *Phys. Rev.*, 1946; 69:37.
2. Bloch, F., Hansen, W.W. and Packard, M. Nuclear Induction. *Phys. Rev.*, 1946; 69:127.
3. Lauterbur, P.C. Image formation by induced local interactions; examples employing nuclear magnetic resonance. *Nature*, 1959; 242:190.
4. Andrew, ER. N.M.R. imaging of intact biological systems. *Philos. Trans. R. Soc. Lond. (Biol.)*, 1980; 289:471.
5. Gabillard, R. Nuclear resonance: A simple apparatus for study of paramagnetic nuclear absorption. *Comp. Rend. Acad. Sci. Paris*, 1951; 232:324.
6. Gabillard, R. A study of a technique in nuclear resonance. *Phys. Rev.*, 1952; 85:694.
7. Singer, J.R. Blood flow rates by nuclear magnetic resonance measurements. *Science*, 1959; 130:1652.
8. Damadian, R. Tumour detection by nuclear magnetic resonance. *Science*, 1971; 171:1151.
9. Carr, H.Y. and Purcell, E.M. Effects of diffusion on free precession in nuclear magnetic resonance. *Phys. Rev.*, 1954; 94:630.
10. Stejskal, E.O. and Tanner, J.E. Spin diffusion measurements; spin echoes in the presence of a time dependent field gradient. *J. Chem. Phys.*, 1965; 42:288.
11. Packer, K.J. Study of a slow coherent molecular motion by pulsed NMR. *Mol. Phys.*, 1969; 17:355.
12. Grover, T. and Singer, J.R. NMR spin echo-flow measurement. *J. Appl. Phys.*, 1971; 42:938.
13. Mansfield, P. and Grannell, P.K. NMR "diffraction" in solids? 3. *Phys. Rev. Lett.*, 1973; 30:1422.
14. Allen, P.S., Andrew, ER. and Bates, CR. *Proceedings of 18th Congress Ampere*. North Holland, Amsterdam, 1974, p.431.
15. Garroway, A.N., Grannell, P.K. and Mansfield, P.J. Image formation in NMR by a selective radiation process. *J. Phys.*, 1974; C7:L457.
16. Mansfield, P. and Grannell, P.K. Diffraction and microscopy in solids and liquid by NMR. *Phys. Rev.*, 1975; B. 12:3618.
17. Hinshaw, W.S. Spin mapping; the application of moving gradients to NMR. *Phys. Lett.*, 1974; A48:87.
18. Hinshaw, W.S. Image formation by nuclear magnetic resonance; the sensitive point method. I. *Appl. Phys.*, 1976; 47:3709.
19. *Proceedings of 18th Congress Ampere*. Edited by Allen, P.S., Andrew, ER. and Bates, CA. North Holland, Amsterdam, 1975, p. 433.
20. *Proceedings of 18th Congress Ampere*. Edited by Allen, P.S., Andrew, ER. and Bates, CA. North Holland, Amsterdam, 1975, p.283.
21. Kumar, A., Welti, I. and Ernst, R.R. NMR Fourier spectroscopy. *Naturwissenschaften*, 1975;

62:34.

22. Kumar, A., Welti, D. and Ernst, R.R. NMR Fourierzeugmatogrphy. 3. Magn, Reson., 1975; 18:69.
23. Andrew, ER., Bottomly, PA., Hinshaw, W.S., Holland, G.N., Moore, W.S. and Simaraj, C. NMR image by the multiple sensitive point method; application to larger biological systems Phys. Med. Biol., 1977; 22:971.
24. Hinshaw, W.S., Bottomly, PA. and Holland, G.N. Radiographic thin-section image of the human wrist by nuclear magnetic resonance. Nature, 1977; 270:722.
25. Hinshaw, W.S., Andrew, E.R., Bottomly, PA., Holland, G.N., Moore, W.S. and Worthington, B.S. Display of cross-sectional anatomy by nuclear magnetic resonance imaging. Radiol., 1978; 51: 273.
26. Hinshaw, W.S., Andrew, R.R., Bottomly, P.A., Holland, G.N., Moore, W.S. and Worthington, B.S. An in vivo study of the fore- arm and hand by thin section NMR imaging. Br. J. Radiol., 1979; 52:36.
27. Bottomly, PA. In vivo tumor discrimination in a rat by proton nuclear magnetic resonance imaging. Cancer Res., 1979; 39:468.
28. Hinshaw, W.S., Bottomly, PA. and Holland, G.N. A demonstration of the resolution of NMR imaging in biological systems. Experientia, 1979; 35: 1268
29. Mansfield, P., Maudsley, A.A. and Baines, T. FastScan proton density imaging by NMR. J. Phys. (E), 1976; 9:271.
30. Mansfield, P. and Maudsley, A.A. Planar spin imaging by NMR. J. Magn. Res., 1977; 27:101-119.
31. Mansfield, P. and Maudsley, A.A. Planar spin imaging by NMR. J. Phys. (C), 1976; 9: L409.
32. Proceedings of the XIth Congress Ampere. Edited by Brunner, H., Hannsner, K.H. and Schwitzer, D. Heidelberg, Group Ampere, 1976; p.247.
33. Mansfield, P. and Maudsley, P.P. Medical imaging by NMR. Br. J. Radiol., 1977; 50:188.
34. Damadian, R., Goldsmith, M. and Minkoff, L. NMR in cancer. XVI. FONAR imaging of the live human body. Physiol. Chem. Phys. Med. NML, 1977; 9:97.
35. Damadian, R., Minkoff, L., Goldsmith, M. and Koutcher, J.A. Field-focusing nuclear magnetic resonance (FONAR); formation of images. Naturwissenschaften, 1978; 65:250.
36. Moore, W.S., Holland, G.N. and Kreel, L. The NMR CAT scanner: a new look at the brain. J. Comput. Assist. Tomogr., 1980; 4: 1-7.
37. Holland, G.N., Moore, W.S. and Hawkes, R.C. Nuclear magnetic resonance tomography of the brain. J. Comput. Assist. Tomogr., 1980; 4: 1.
38. Hawkes, R.C., Holland, G.N., Moore, W.S. and Worthington, B.S. Nuclear magnetic resonance (NMR) tomography of the brain; a preliminary clinical assessment with demonstration of pathology. J. Comput. Assist. Tomogr., 1980; 4:577.
39. Hawkes, R.C., Holland, G.N., Moore, W.S. Nuclear magnetic resonance (NMR) tomography of the normal heart. J. Comput. Assist. Tomogr., 1981; 5: 605.
40. Hawkes, R.C., Holland, G.N., Moore, W.S., Roebuck, E.J. and Worthington, B.S. Nuclear magnetic resonance (NMR) tomography of the normal abdomen. J. Comput. Assist. Tomogr., 1981; 5:613.
41. Doyle, R.H., Gore, J.C., Pennock, J.M., Bydder, G.M., Orr, G.S., Steiner, R.E., Young, I.R., Burl, M., Clow, H., Gilderdsle, D.J., Bailes, D.R. and Walters, P.R. Imaging of the brain by nuclear magnetic resonance. Lancet, 1981; 2:53.
42. Young, I.R., Burl, M., Clark, G.J., Hall, A.S., Patmore, T., Collins, A. and Smith, D. Magnetic resonance properties of hydrogen. Imaging the posterior fossa. AJR., 1987; 137:895-901.
43. Lai, C.M. and Lauterbur, P.C. True three dimensional image reconstruction by nuclear magnetic resonance tomography. Phys., 1980; E13:747.
44. Lauterbur, P.C. NMR in tomographic imaging of organs and organisms. J. Comput. Assist. Tomogr., 1981; 5:285.
45. Hansen, G., Crooks, L.E., Davis, P., DeGroot, S., Herfkens, R., Margulis, A.R., Goding, C., Kaufman, L., Hoenninger, S., Arakawa, M., McRee, R. and Watts, J. In vivo imaging of the rat anatomy with nuclear magnetic resonance. Radiology, 1980; 136:695.

46. Crooks, L., Hoenninger, 3., Arakawa, M., Kaufman, L., McRee, R., Watts, J.) and Singer, J.H. Tomography of the hydrogen with nuclear magnetic resonance. *Radiology*, 1980;136: 701.
47. Hoult, D.L Zeugmatography; a criticism of the concept of a selective pulse in the presence of a field gradient *J. Magn. Res.*, 1977; 26: 165.
48. Hoult, D.L. Rotating frame zeugmatography. *J. Magn. Res.*, 1979;33:183.
49. Hoult, D.L. NMR imaging rotation frame selective pulses. *Magn. Res.*, 1980; 38:369.
50. Tropper, M.M. NMR imaging. *Magn. Res.*, 1981; 42:193.
51. Feiner, L.F. and Locker, P.R. On NMR spin imaging by magnetic field. *App. Phys.*, 1980;22:257-271.
52. Tanaka, K., Yamada, Y., Yamamoto, E.R.Z., Abe. NMR relaxation data processing and a method for separation of multiple relaxation times. *Proc. IEE*, 1978; 66: 1582.
53. Lauterbur, P.C, Karner, D.M., House, W.V. and Chen, C.N. Zeugmatography high resolution NMR spectroscopy. Image of chemical inhomogeneity with microscopic objects. *Am. Chem. Soc.*, 1975; 97:6866.
54. Bendel, P., Lai, C.M. and Lauterbur, P.C. Phosphorus-31 spectroscopic zeugmatography of phosphorus metabolites. *Magn. Res.*, 1980; 38:343.
55. Ackerman, J.J.H., Grove, T.H., Wong G.G., Gadian, D.G. and Radda, G.K. Mapping of metabolites in whole animals by ³¹P NMR using surface coils. *Nature*, 1980; 283: 167.
56. Gordon, R.E., Hsien, P.E., Shaw, D., Gadian, D.G., Radda, G.K. Styles P., Bore, P.) and Chs, L. Localization of metabolites in animals using ³¹P topical magnetic resonance. *Nature*, 1980; 287:736.
57. Cox, S.) and Styles, P. Towards biochemical imaging. *Magn. Res.*, 1980; 40:209.
58. Nannally, R.L and Bottomley, P.A. Assessment of pharmacological treatment of myocardial infarction by phosphorus-31 NMR with surface coil. *Science*, 1981;211:177.
59. Singer, J.R. IEEE Blood flow measurements of the intact body. *Trans. Nucl. Sci.*, 1980; NS-27: 1245-1249.
60. Cohen, M.D. Pediatric magnetic resonance imaging. Philadelphia, Saunders 1986.
61. George, 3.C., Doyle, P.H. and Pennock, J.M. Relaxation rate enhancement observed, in vivo by NMR imaging. Edited by Partain, C.L and James, A.E. 2nd ed. Philadelphia. Saunders, 1988, p.194.
62. Lauterbur, P.C. Magnetic resonance zeugmatography. *Pure Appl. Chem.*, 1974; 40:149.
63. Lauterbur, P.C., Lai, C.M. Zeugmatography by reconstruction from projections. *IEEE Trans. Nucl. Sci.*, 1980; NS-27: 1227.
64. Mansfield, P., Morris, P.G., Waugh, J.S. Eds. Special Supplement in *Adv. Magn. Resonance*. New York, Academic Press, 1983.
65. Damadian, R. Field focussing n.m.r. (FONAR) and the formation of chemical images in man. *Philos. Trans. R. Soc. Lond. (Biol.)*, 1980; 289:489.
66. Goldsmith, M., Damadian, R., Stanford, M. and Lipkowitz M. NMR in cancer. XVIII. A superconductive NMR magnet for a human sample. *67. Physiol. Chem. Phys.* 1977; 9: 105. *Proceedings of 18th Congress Ampere*. Allen, P.S, Andrew, E.R and Bates, C.W. North Holland, Amsterdam, 1975; p.433.
68. Hutchison, J.M.S., Edelstein, W.A. and Johnson, G. A whole body NMR imaging machine. *J. Phys. (E)*, 1980 13: 947.
69. Maudsley, A.A. Multiple line scanning spin density imaging. *J. Magn. Res.*, 1980; 41:112
70. Mansfield, P. Multiplanar image formation using NMR spin echoes. *3. Phys.*, 1977; C10: L55.
71. Mansfield, P. and Pykett, I.L. Biological and medical imaging by NMR. *3. Magn. Res.* 1978; 29: 355.
72. Brown, P. NMR: Out of R&D and into radiology. *Disgn. Imaging*. 1981; 32-3K
73. Herf, J.C., It, Davis, P., Crooks, L., Kaufman, L., Price, D., Miller, T., Margullis, A.R., Watts, 3., Hoenninger, 3., Arakawa, M. and Mcree, R. Nuclear magnetic resonance imaging of the abnormal liver rat and correlation with tissue characteristics. *Radiology*, 1981; 141:211.
74. Brady, T.J., Buonanno, P.S., Pykett, I.L., New, P.P., Davis, K. R., Pohost, G.M. and Kistler, J.P.

- Preliminary clinical results of proton (^1H) imaging of cranial neoplasms; in vivo measurements of T1 and mobile proton density. *AJNR.*, 1983; 4:255.
75. Drago, R.S. Physical method in chemistry. Philadelphia, Saunders, 1977.
 76. Stone, T.J., Buckman, T., Nordio, P.L et al. Spin-labelled biomolecules. *Proc. Acad. Sci. USA.*, 1965; 54: 1010.
 77. Brasch, R.C. Work in progress; methods of contrast enhancement for NMR imaging and potential application. *Radiology*, 1983; 147: 781.
 78. Mendonca-Dias, M.H., Gaggelli, E. and Lauterbur, P. Paramagnetic contrast agents in nuclear magnetic resonance medical imaging. *Semin. Nucl. Med.*, 1983; 12: 364.
 79. Runge, V.M., Clanton, J.A., Lukehart, C.M., Partain, C.L. and James, A. E. Jr. Paramagnetic agents for contrast-enhanced NMR imaging. *APR.*, 1983; 141: 1209.
 80. Goldman, M.R., Brady, T., Pykett, I.L., Burt, C.T., Buonanno, P.S., Kiatler, J.P., Newhouse, J.H., Hinshaw, W. S. and Pohat, G.M. Quantification of experimental myocardial infarction using nuclear magnetic resonance imaging and paramagnetic ion contrast enhancement in excised canine hearts. *Circulation*, 1982; 66: 1011.
 81. Alfidi, R.J., Hasga, J.R., Elyovsef, S.J., Bryan, P.3., Fletcher, B.D., Lipuma, J.P., Morrison, S.C., Kaufman, B., Richey, J.B., Hinshaw, W.S., Karanrner, D.M., Yeung, H.N., Cohen, A.M., Butler, H.E., Ament, A.E. and Ueberman, J.M. Preliminary experimental results in humans and animals with a superconducting, whole-body nuclear magnetic resonance scanner. *Radiology*, 1981; 143: 175.
 82. Gore, J.C, Doyle, F.H. and Pennock, J.M. In *Nuclear Magnetic Resonance Imaging*. Partain, C.L., James, A.E. Jr. and Rollo, F.D. eda. Philadelphia, W.B. Saunders Co., 1983; pp. 44-106.
 83. Young, I.R., Clark, G., Bailes, D.R, Pennock, J.M., Doyle, P.H. and Bydder, G.M. Enhancement of relaxation rate with paramagnetic contrast agents in NMR imaging. *CF.*, 1981; 5:543.
 84. Wesbey, G.E., Braach, J.C, Engelstal, Bt, Moss, A.A., Crooks, L.E. and Brito, A.C Nuclear magnetic resonance contrast enhancement studies of the gastrointestinal tract of rats and a human volunteer using nontoxic oral iron solutions. *Radiology*, 1983; 149:175.
 85. Brasch, R.C., London, D.A., Wesbey, G.E., Tozer, T.N., Nitecki, D. B., Williams, R.D., Doemeny, J., Tuck, L.D. and Lallemand, D.P. Work in progress; nuclear magnetic resonance study of a paramagnetic nitroxide contrast agent for enhancement of renal structure in experimental animals. *Radiology*, 1983; 147: 773.
 86. Brasch, R.C, Nitecki, D.E., Brant-Zawadzki, M., Enzmann, D.R., Wesbey, G.E., Tozer, T.N., Thek, L.D., Cann, C.E., Pike, J.R and Shelden, P. Brain nuclear magnetic resonance imaging enhanced by a paramagnetic nitroxide contrast agent; preliminary report. *AJR.*, 1983; 141: 1019.
 87. Young, I.R., Baile, D.R. and Burt, M. Initial clinical evaluation of a whole body nuclear magnetic resonance (NMR) tomograph. *Comput. Asst. Tomogr.*, 1982; 6: 1.
 88. Stark, D.D. and Brady, W.W. eda. *Magnetic resonance imaging*. Saint Louis, Mosby, 1988.
 89. Anderson, M. Nuclear magnetic resonance imaging and neurology. *Br. Med. J.*, 1982; 284:1359.
 90. Tishler, J.M. and Partain, C.L Nuclear magnetic resonance of the central nervous system. *Ala. J. Med. Sci.*, 1984; 21: 190.
 91. Araki, T., Inouye, T., Suzuki, H., Machida, T. and Lio, M. Magnetic resonance imaging of brain tumors; measurement of T1. *Radiology*, 1984; 150:95.
 92. Young, I.R., Bydder, G.M., Hall, A.S., Steiner, R.E., Worthington, B.S., Hawkes, R.C., Holland, G.N. and Moore, W.S. The role of NMR imaging in the diagnosis and management of acoustic neuroma. *AINR.*, 1983; 4:233.
 93. Young, I.R., Randall, C.P., Kaplan, P.W., James, A., Bydder, G.M., and Steiner, R.E. Nuclear magnetic resonance (NMR) imaging in white matter disease of the brain using spin-echo sequences. *3. Comput. Asst. Tomogr.* 1983; 7:290.
 94. Modic, M.T. and Weinstein, M.A. Nuclear magnetic resonance of the spine. *Br. Med. Bull.*, 1984;

40: 183.

95. Normon, D. et al MRI of the spinal cord and canal. *AJNR*, 1984; 5:9.

96. Smith, F.W., Punge, V., Permezel, M., and Smith, CC Nuclear magnetic resonance imaging in the diagnosis of spinal osteomyelitis. *Magn. Resonan. Imag.*, 1984; 2:53.

97. George, A.E., deLeon, Mi. and Kalnin, A. Leukoencephalopathy in normal and pathological aging. 2. MRI of brain lucencies. *AJNR.*, 1986; 7:567.

98. Lanzer, P., Botvinick, BK., Schiller, N.B., Crooks, LE., Arakswa, M., Kaufman, L, Davis, P.L, Herfkens, It, Lipton, M.J. and Higgins, CB. Cardiac imaging using gated magnetic resonance. *Radiology*, 1984; 150: 121.

99. Leiberman, J.M., Alfidi, Ri., Nelson, A.D., Botti, R.E., Moir, T.W., Haaga, J.R., Kopiwada, S., Miraldi, PD., Cohen, AM., Butler, H.E. et al. Gated magnetic resonance imaging of the normal and diseased heart. *Radiology*, 1984; 152:465.

100. Pohost, G.M. and Ratner, A.V. Nuclear magnetic resonance potential applications in clinical cardiology. *JAMA.*, 1984; 251: 1304.

101. Steiner, R.E. Nuclear magnetic resonance imaging of heart and mediastinum. *Br. Med. Bull.*, 1984; 40: 191.

102. Vandijik, P. Direct cardiac NMR imaging of heart wall and blood flow velocity. *J. Compuc. Assist. Tomogr.*, 1984;8:429.

103. Cohen, SM. Application of Nuclear magnetic resonance to the study of liver physiology and disease. *Heptalogy*, 1983; 3: 738.

104. Moon, K.L. Jr., Hricak, H., Margulis, AR, Bernhoft, R., Way, LW., Filly, R.A, and Crooks, LE. Nuclear magnetic resonance imaging of characteristic of gallstone in vitro. *Radiology*, 1983; 148: 753.

105. Stark, D.D., Goldberg. Ul., Moss, A.A. and Bass, N.M. Chronic liver disease; evaluation by magnetic resonance. *Radiology*, 1984; 150: 149.

106. Hirack, H., Filly, RA., Margulis, A.R., Moon, K.L., Crooks, LB. and Kaufman, L Work in progress; nuclear magnetic resonance imaging of the gallbladder. *Radiology*, 1983; 147: 481.

107. Stark, D.D., Moss, A.A., Goldberg. H.I., Davis, P.L. and Fderle, M.P. Magnetic resonance and CT of the normal and diseased pancreas; a comparative study. *Radiology*, 1984; 150:153.

108. Hirack, U., Crooks, L, Sheldon, P. and Kaufman, L Nuclear magnetic resonance imaging of the kidney. *Radiology*, 1983; 146:425,

109. Smith, F.W., Hutchison, J.M.S., Millard, J.R, Reid, A., Johson, G., Redpath, T.W. and Sebie, RD. Renal cysts or tumors. Differentiation by whole-body nuclear magnetic resonance imaging. *Diag. Imaging*. 1981; 50:61.

110. Smith, P.W., Reid, A., Mallard, J.R., Hutchison, 3M., Power, D.A. and Catto, G. 111. Nuclear magnetic resonance tomographic imaging in renal disease. *Diag. Imaging*. 1982; 51: 209. 112. Steyn, J.H. and Smith, F.W. Nuclear magnetic resonance imaging of the prostate. *Br. J. Urol.*, 1982; 54: 726.

113. Grty. I., Delbeke, D. and SandIer, M.P. Correlative pediatric Imaging. 3. *Nucl. Med.*, 1989; 30:15.

114. Behling, R.W. and Tubba, U.K. Stroboscopic NMR microscopy of the carotid artery. *Nature*, 1989; 341: 321.

115. Bradly, W.G. Magnetic resonance appearance of flowing blood flow and cerebrospinal fluid, in brain magnetic resonance imaging of central nervous system. Edited by Zawadaski, M. and Norman, D. New York, Raven Press, 1987, p.83.

115. Pavlicek, W., Geisinger, M., Castle, L, Borkowski, G.P., Mesney, T.P., Brean, B.L and Gallagher, J.H. The effects of nuclear magnetic resonance on patients with cardiac pacemakers. *Radiology*, 1983; 147:149.

116. Bellon, E.M., Hascke, B. M., Coleman, P.E., Sacco, DC, Steiger, D.A. and Gangarosa, RE. MR. Artifacts; a review. *MR.*, 1986; 147: 1271.