RINCKSIDE

ISSN 2364-3889

Volumes 1 & 2 • 1990 & 1991

PRO ACADEMIA

EMRF

The Round Table Foundation

RINCKSIDE

ISSN 2364-3889 • VOLUMES 1 & 2 • 1990 & 1991

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Magnetic Resonance Imaging • How it all began

Peter A. Rinck

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In late 1972, a prospective contributor to the British scientific journal *Nature* received an apologizing letter from the editor of the journal that read as follows:

"With regret I am returning your manuscript which we feel is not of sufficiently wide significance for inclusion in Nature. This action should not in any way be regarded as an adverse criticism of your work, nor even an indication of editorial policies on studies in this field. A choice must inevitably be made from the many contributions received; it is not even possible to accommodate all those manuscripts which are recommended for publication by the referees."

The paper submitted was very short and described a new imaging technique dubbed *zeugmatography*. For those who did not study Greek at school, zeugma is the yoke, or as the author put it: "That what is used for joining."

The author did not mean that two horses were to be joined with a yoke; rather, he meant two magnetic fields were to be joined. His method was derived from an analytical technique that had been used in chemistry since the late 1940s, called nuclear magnetic resonance, or, for short, NMR.

The author of the paper was Paul C. Lauterbur, Professor of Chemistry at the State University of New York at Stony Brook. In early September 1971 he had the idea of how to create three-dimensional images using magnetic resonance and described a "Spatially Resolved Nuclear Magnetic Resonance Experiment." [1] A year later he had enough results to publish them. Lauterbur wanted this paper to be printed in *Nature* and wrote back to the editor proposing to change the style of the paper:

"Several of my colleagues have suggested that the style of the manuscript was too dry and spare, and that the more exuberant prose style of the grant application would have been more appropriate. If you should agree, after reconsideration, that the substance meets your standards, ... I would be willing to incorporate some of the material below in a revised manuscript ..."

The answer from the editor was short and positive: "Would it be possible to modify the manuscript so as to make the applications more clear?" [2] Finally, the paper was accepted and published in the 16 March 1973 issue of Nature under the title:

> *Image Formation by Induced Local Interaction: Examples Employing Magnetic Resonance* [3].

From reading this title, one would not think that a revolutionary idea in medical imaging was hidden behind it. However, this idea was the foundation of MR imaging, which has developed into one of the most outstanding medical innovations of the twentieth century, comparable with Wilhelm Conrad Roentgen's invention of the medical application of x-rays.

Magnetic resonance, or *nuclear magnetic resonance (NMR)* as natural scientists still call it, is a phenomenon that was first mentioned in the scientific literature before World War II. In 1946, independently of each other, two scientists in the United States described a physico-chemical phenomenon that was based upon the magnetic properties of certain nuclei in the periodic system.

They found that when these nuclei were placed in a magnetic field, they absorbed energy in the radiofrequency range and re-emitted this energy during the transition to their original orientation. Because the strength of the magnetic field and the radiofrequency must match each other, the phenomenon was called nuclear magnetic resonance: nuclear because it is only the nuclei of the atoms that react; magnetic because it happens in a magnetic field; and resonance because of the direct dependence of field strength and frequency.

The two scientists, Felix Bloch working at Stanford University and Edward M. Purcell working at Harvard, received the Nobel Prize in Physics in 1952 [4, 5]. In 1991, the Nobel Prize in Chemistry was awarded to Richard R. Ernst of Zurich for his contributions to the field of NMR spectroscopy.

The two most important scientists for the development of magnetic resonance in medicine and biology

were Erik Odeblad who in the early 1950s first described the differences of relaxation times in human tissue [6] and Paul C. Lauterbur.

In 2003, the Nobel Committee conferred their Prize in Medicine on Lauterbur for the invention of magnetic resonance imaging. He shared it with Peter Mansfield, a British physicist, who was awarded for the further development of the technique.

Shortly after the introduction of NMR to clinical imaging, the adjective *nuclear* was dropped by marketing people and radiologists because it sounded like *nuclear warfare* or *nuclear power plant*, words that for some people have a negative connotation – with which NMR has nothing in common at all. It was thought that the general public would be unable to distinguish between one nuclear and the other. Thus, today we talk about *MR imaging* or *MRI* and, e.g., *MR spectroscopy* – and the commercial people had taken over.

However, it should always be kept in mind that it is the nucleus we talk about because there is another kind of resonance that also can be used for imaging: *electron spin resonance (ESR)*. ESR involves the electrons of an atom.

NMR signals carry encoded information about the physical and chemical environment of the nuclei. Originally, NMR was used as an analytical method to study the composition of chemical compounds. Today, there are applications in a wide range of areas in chemistry, physics, biology, medicine, and food science.

However, before Lauterbur's discovery, nobody could determine from where within a sample the NMR signal stems. It could originate at the left or right end, at the top or at the bottom. Lauterbur's zeugmatography changed this. He joined the strong magnetic field and a second weaker field, the gradient field. Because the strength of the magnetic field is proportional to the radiofrequency, the frequency of, for instance, a hydrogen nucleus of a water molecule at one end of a sample differs from the signal of another hydrogen nucleus at the other end of the sample. Thus, the location of these nuclei can be calculated. Once their location is known, an image can be created of a slice through a human body, for example. Basically, therefore, MR imaging requires a strong static magnetic field produced by a large magnet, a second weaker magnetic field that varies across the sample, a radio transmitter and receiver, and a powerful computer to calculate an image.

Compared to x-ray and radioisotope methods, MR imaging uses energy on the opposite end of the electromagnetic spectrum, and to date, no permanent harmful side effects of MR imaging have been reported. The energy of MR imaging is nine orders of magnitude lower than that of x-rays and radioisotope techniques.

Although Lauterbur did not suggest distinct applications of the new technique in his paper, he did refer to the fact that it had been shown that cancer tissue had different signal properties compared to normal tissue, and he believed that zeugmatography could be used for medical imaging. Thus, he urged his university to file a patent application, but because neither the university patent lawyer nor the university administration itself believed in his idea, no patent application was filed and Lauterbur never obtained a patent on his invention. Others did – relatively fast.

Despite the nonbelievers within the university, it only took eight years for the first whole-body MR machines to appear in clinical settings, although these machines were crude prototypes compared to today's equipment. Ten years after the first description approximately a dozen research groups worked with whole-body imagers. Today, nobody knows exactly how many MR machines operate worldwide; more than 25,000 machines are a good guess – the majority of them in the United States and Japan, a quarter in Europe.

The hope that MR imaging, or other adaptations of MR in medicine, would be able to characterize cancerous cells in the body has not come true, but many other important applications of MR imaging have been found during the last decade. Today, MR imaging influences decisions in most areas of medicine, from neurology to orthopedics, from pediatrics to radiation therapy. MR imaging is even more interdisciplinary than roentgenology, although it is also complex and sophisticated.

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. Magnetic Resonance Imaging – How it all began. Rinckside 1990; 1,1: 1-3.
Reprinted and updated several times. Last update 2015.

Relaxation times blues

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Outstanding soft-tissue contrast is among the main characteristics of MR imaging that have enabled the technology to be developed so rapidly. This contrast is basically the result of the relaxation phenomena, T1 and T2.

Following the impulse a proton is given by a radiofrequency burst, the process of returning to a state of equilibrium from an excited state is called the *longitudinal* or *spin-lattice relaxation process*. It is characterized by the T1 relaxation time, which commonly lies in the range of several hundred milliseconds. The T2 relaxation time characterizes the dephasing of the spins (i.e., the separation of neighboring spins from each other), and therefore it is called the *spin-spin* or *the transverse relaxation process*. T2 times of tissues are much shorter than T1 times.

For example, at a magnetic-field strength of 0.5 T, human kidney tissue has a T1 relaxation time of approximately 500 ms and a T2 relaxation time of approximately 80 ms. Although other factors contribute to contrast on an MR image, the three dominant factors are T1 and T2 times and proton density, the latter reflecting the water content.

Peter Mansfield of the University of Nottingham stated in 1980 [5] that "NMR imaging of anatomical detail is feasible based purely on the measurement of water content."

He was wrong; however, he also pointed out that images could reflect a combination of water content and relaxation times.

Proton density does not change much between different tissues. For instance, its difference between gray and white brain matter in an adult is approximately 10%, and the difference between brain pathologies and surrounding uninvolved brain tissue may be even less. Thus, proton density or water-content imaging of the human body is not particularly useful.

Today, magnetic resonance pictures dubbed as proton density-weighted images always depict a combination of water content and the two relaxation times; nobody uses pure water-content pictures for medical diagnostics. Usually, T1- or T2-weighted images are acquired in MR imaging because the two main relaxation processes govern the contrast in medical MR imaging.

Tumors, as well as other brain pathologies such as multiple sclerosis (MS) or brain infarctions, are barely visible on water-content images. This was demonstrated in the early days of MR imaging when, in a number of cases, already known brain lesions could not be discovered.

The introduction of T2-weighted spin-echo pulse sequences changed this. On these images, many pathologies are seen easily. The importance of T2-influenced pictures was demonstrated at a magnetic resonance conference in San Francisco in 1983 [9]. Soon afterwards, all manufacturers started offering this feature with their machines, and now it is part of any MR examination.

The use of relaxation times for medical applications was introduced in 1955/1956 by Erik Odeblad and Gunnar Lindström [7, 8]. Since then, this idea has occupied the minds of many researchers because the ultimate goals of diagnostic medicine are noninvasive tissue characterization and the external identification of cell structures within the human body, without even touching the body.

In 1974 Raymond Damadian and his collaborators attempted and patented a method for relaxation time measurements in malignant diseases [1]. At that time, Damadian was a medical doctor at the State University of New York at Brooklyn.

Originally, he did not intend to use the relaxation times for imaging but for malignant tissue characterization. The method, for which he gained a U.S. patent, was aimed at screening humans for cancer cells. He had to retract his assertion that he could non-invasively diagnose cancer tissue during a press conference in 1977. It didn't work – and was not an imaging method as he claimed later.

Damadian's claim that relaxation-time changes highlight cancer cells seemed to be the pivotal step in

medical progress. Thus, it is understandable that relaxation has been described as the Holy Grail of magnetic resonance – one of the many Holy Grails.

Damadian was a colorful and controversial figure in magnetic resonance circles. He had antagonistic and cynical articles written about him in all major US newspapers, mostly because he was more of his time businessman than medical doctor. However, he didn't bother because – as the Wall Street Journal finally pointed out – "Raymond Damadian is, according to an old friend, 'the most egotistical person I've ever met.'" [4] His friend and other people who know him certainly agree – egotism is a severely unpleasant and injurious personal trait.

Damadian invested massively in public relations and sponsored several books written about him [3, 6] – even, as painful as it sounds, a children's book [2]. He had many opponents, not only because of his exuberant character and unrestrained behavior at conferences but also because of his (un-) scientific publications. Immediately after his first publication, his opponents showed that his claims were only founded on particular cases and not on any specific disease; his claim was a fallacy. However, this did not stop him continuing to propose his hypotheses.

In spite of Damadian's critics and his deceit, nobody can deny that his description of relaxation-time changes in cancer tissue was one of the main motivations for the introduction of magnetic resonance into medicine. His assertion that this method can detect cancer has proved to be partly true, but in a completely different way: MR imaging with pictures influenced by relaxation times has become one of the main medical technologies applied in cancer diagnosis and follow-up.

However, the basic idea of obviating the need for hospital pathology departments and replacing them with MR imaging did not materialize.

In vivo relaxation time measurements based on MR imaging have been tried out over the years by a large number of people, who have used relaxation-time values for tissue characterization in the brain, body, muscles, and bones. The task proved to be in vain because all efforts to characterize or even type tissue largely failed.

The reasons are manifold and include systematic measurement errors, inaccuracy of two-point plotting methods of relaxation curves, inherent variability of tissue composition, partial volume effects, and inter-observer variability. Researchers realized that it is futile to measure a point or a region of interest within a tumor because too many different components such as tumor and necrotic cells, small vessels, calcifications, and other structures can be found within a volume of interest. In addition, T1 and T2 values overlap with those of other pathologies and sometimes normal tissue: T1 and T2 of normal tissue change with age and hormonal cycles, breast tissue being a good example.

Already several months after Damadian's publication, Donald P. Hollis and his collaborators showed that the T1 relaxation times of tumors are not necessarily longer than those of other diseased or normal tissues [10, 11]. In 1985, it was realized that even very carefully performed *in vivo* T2 measurements cannot be used as a diagnostic method in cancer detection, characterization, or typing [12].

After absolute T1 or T2 values had been used unsuccessfully by researchers, combinations of T1 and T2, histogram techniques, and more sophisticated 3-D display techniques of factor representations were applied. However, the heterogeneity of normal tissues as well as of pathological benign and malignant tissues did not allow the pathologist's view through the microscope to be replaced with MR techniques.

Damadian also claimed that T1 values of tumorous tissue are always higher than those of normal tissue. His dream of MR being the perfect screening method for cancer tissue in the human body was finally shattered when this claim was refuted. T1 values depend on the magnetic field strength (i.e., they increase with the magnetic field). Some tumor values can be lower than the values of normal tissue in certain fields while others are the same in certain fields, and therefore they cannot be distinguished.

Every year, the literature reports new attempts to change the relaxation-times blues into something more swinging. There are some positive stories about the successful use of relaxation-time measurements *in vivo.*

Among the many studies is the measurement of apparently uninvolved white brain matter in MS patients. MS plaques in the brain have longer T2 relaxation times than surrounding tissue, which enables them to be visualized on T2-weighted spin-echo im-

ages. However, the inconspicuous-looking white matter in the rest of the brain is also changed by the disease. Relaxation-time measurements revealed longer T2 values than in normal subjects. This is not enough to diagnose MS, but it might be of use in follow-up therapy or in helping with the differential diagnosis [13].

Since I am the first author of the latter paper I am allowed to say: I wouldn't rely on such measurements if I were the patient.

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. Relaxation times blues. Rinckside 1991; 2,1: 5-7.
Reprinted and updated several times. Last update 2015.

The field-strength war

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Like almost everything in this world, MR machines come in different sizes: extra-small, small, medium, large, and extra-large. The technical terms in MR lingo for these sizes are *ultralow, low, medium, high,* and *ultrahigh field* machines.

These terms refer to the magnetic field strength of the respective machine. The field strength is measured in Tesla (T), a unit that replaced the former unit of Gauss (G) some years ago, although Gauss is still used sometimes (10,000 G = 1 T).

Ultralow-field machines operate at a field strength below 0.1 T, low field between 0.1 and 0.5 T, medium field between 0.5 and 1 T, high field between 1 and 2 T, and ultrahigh field machines above 2 T.

In clinical surroundings, the national radiological protection boards used to allow machines as high as 2.0-2.5 T. Everything above this limit was considered potentially hazardous and thus should only be admitted to research facilities – particularly if fast gradient-switching was used. Today, ultrahigh fields are considered safe for research and, partly, for clinical routine – at least in some countries.

In describing MR machines, natural scientists prefer to talk about frequencies instead of field strengths. This is because different nuclei in the periodic system possess different resonance frequencies. At 1 T, for instance, protons resonate at 42.58 MHz, whereas at the same field strength, phosphorus nuclei resonate at 17.23 MHz. For clinical imaging purposes in medicine, this is of no importance because only proton MR imaging is used.

Strolling down the aisles of the world's biggest commercial exhibition of medical imaging equipment at the annual meeting of the Radiological Society of North America, one could find small machines operating at 0.06 T and huge machines operating at 4.0 T or even higher fields. Their magnets are different: below approximately 0.3 T, the magnets are permanent and resistive or electromagnetic, but above this field the magnets are superconductive. All these magnet types have their pros and cons.

Why does one find small ultralow field MR imagers and high field machines operating at fields 100 times stronger? Why are there not only low or high field machines?

The field-strength question has divided the MR community since the early 1980s. At that time, all MR machines operated at low fields, and many of the prototypes had strengths of approximately 0.15 T. Researchers did not believe that imaging at higher field would be possible because higher radio frequencies would not be able to penetrate the human body. Like many other predictions in MR imaging, this prediction was wrong.

MR images at that time were crude, blurry, and generally worse than CT images. Scientists working for the R&D divisions of companies producing MR equipment were asked:

"How do you get better image quality?" They had a simple answer: "Increase field strength."

From analytical applications of chemical MR spectroscopy it was known that the signal-to-noise ratio increases when field strength is increased. The better your signal-to-noise, the better your image will be. Higher fields also require higher gradient strength to reduce the chemical-shift artifacts created by these fields. In turn, this led to better spatial resolution. So some manufacturers, driven by their research and marketing people, moved to high-field superconductive magnet systems. These systems were (and in some instances still are) huge, dinosaurlike machines. They were expensive, difficult to produce, and costly to maintain, but image quality suddenly became better.

Another argument supported the development of high field machines; only these machines are able to produce *in vivo* MR spectra for phosphorus or proton spectroscopy. At this time, one of the aims in the development of MR in medicine was to combine imaging and spectroscopy to acquire morphological and metabolic information about the human body. The higher the field, the more detailed spectroscopic information will be.

However, *in vivo* spectroscopy did not take off, whereas the popularity of MR imaging exploded. Dedicated imaging machines became the rule, combined imaging and spectroscopy the exception.

Even for imaging, it became an ideology to plead for high fields. There is no rational scientific reason for this development; image quality and spatial resolution of low and medium field machines became as good as, and in some instances even better than, that of high or ultrahigh field equipment. Additional research revealed that the most important factor in medical imaging, tissue contrast, at least for certain diagnostic questions in the central nervous system, seems to be best at medium fields and, in some instances, even decreases with higher fields [2,3].

There was still no rational approach to the problem. At a 1983 magnetic resonance conference in San Francisco, a debate on field strength that had started on the platform was continued in the corridor of the conference center. The discussion nearly ended in a fist fight between the proponent of the high field ideology, whose company had put all its efforts into 1.5 T machines, and the proponent of low fields, whose company advocated MRI systems at 0.35 T.

The front lines in this war were mighty and the trenches deep. You were either part of one camp or the other. All large companies jumped on the high field side and promoted high fields with all the ammunition their marketing departments could provide. In some countries, millions of dollars of taxpayers' money were channelled into subsidies for the development of high field systems.

However, one morning in the early 1990s MR customers woke up and found that a gap was emerging. One company had decided to enter the mid-field market, another followed suit, and a third decided to compromise by offering an MR machine operating at a field strength in between the others.

The reasons for these steps were never publicly discussed, but people had realized that the signal-to-noise increase expected from the results in analytical NMR did not occur in the same way in whole-body MR imaging.

In whole-body MR imaging, signal-to-noise increased to a certain extent, and then the human body created additional noise that led to a flattening of the signal-to-noise curve at high fields. In addition, nobody had foreseen the new problems faced by users at higher fields, among them being the worsening of motion and susceptibility artifacts. Cost and hazards also increased with higher fields. At the same time, low and medium field machines became smaller, the quality of their diagnostic output better, and interventional MR became feasible.

A new generation of buyers, the smaller hospitals and private practices, preferred cost-efficient MR systems that they could use for most of the daily routine examinations. Bigger hospitals, and in particular those interested in spectroscopy and research in functional imaging, went for high field systems, but for them also the second and third system usually was medium or low field. Today, the market for 1.5 T high field equipment is nearly unbroken because they are good diagnostic machines.

Definitions always seem to be in the eye of the beholder.

The marketing department of the biggest US-American manufacturer pushed for high field (1.5 Tesla) in the 1980s. Fifteen years later, they postulated that their new mid-field equipment (0.7 Tesla) was also high field. Another 15 years later, 3 Tesla was the *non-plus-ultra* and "high field". Definitions always seem to be in the eye of the beholder. If all of this had been known or taken into consideration 15-20 years ago, more patients would have had access to MR imaging, and medical MR equipment might have been less expensive than it is today.

Derek Shaw worked for Varian, later for Oxford Instruments, and since 1983 until his retirement for General Electric Medical Systems. He is one of the leading MR scientists in Europe. In 1996, he wrote the following statement in a book chapter:

"The early period of MRI ... was dominated by the 'field-strength war'. What was the best field strength for MRI? These battles were essentially commercial, science being used to justify the company's competitive position ...

"Our pawn in the field strength battle was in vivo spectroscopy... As it became apparent that there was not going to be sufficient specificity available via T1 and T2 determinations, MRS ... was seen as a potential alternative ... MRS needed the highest field possible ...

"This need, along with the higher signal-to-noise ratios achievable at higher field strengths ... led, despite their extra costs, to the use of 1.5 T magnets ... Without this push to high field, MRI systems might be quite different today, probably lower down on the cost/performance scale."[4]

Thus, the trend went towards high field. High field made higher profit, which is a recurrent theme not only in medical technology. This is reflected in equipment sales worldwide and in the sales revenue of MR equipment according to field strength.

Recently the field strength quarrel has flared up again. This time it is 1.5 Tesla versus 3.0 Tesla. However, this time it is not MR spectroscopy, but functional MR imaging pushing up field strength. The results are the same. In research – and in some places even in routine imaging – 3-Tesla system have become the *sine qua non*. It has become fashionable to buy them.

They also have some advantages over low field equipment; for instance, ultrafast imaging, where scan time is reduced at the expense of signal-to-noise ratio, is generally more effective at higher fields. This facilitates another 'sexy' research area: functional imaging of the brain.

Once again, people claim that the signal-to-noise ratio in MR imaging increases linearly with field strength. Some researchers state that signal-to-noise between 1.5 T and 3.0 T increases by 200%, even 300%. There are papers indicating that this might be correct for functional MR imaging using the BOLD technique. However, comparing the BOLD technique and MR imaging is like comparing apples and oranges. On the other hand, for MR spectroscopy a 20% increase in sensitivity, but the same signal-to-noise ratio has been shown in comparative studies between 1.5 Tesla and 3.0 Tesla [1].

For MR imaging itself, reliable comparative studies do not exist – to make a valuable comparison, the total amount of signal acquired during the same time should be taken into account and this is not in favor of ultahigh fields since T1 increases.

Without any doubt, signal-to-noise and spatial resolution can be better at 3 Tesla, coronary arteries are better seen, small brain structures better delineated. However, the cost/benefit ratio remains unknown ... and adverse effects might threaten both patients and staff.

Next stop: 7 Tesla, perhaps 9.

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. The field-strength war. Rinckside 1991; 2,2: 9-11.
Reprinted and updated several times. Last update 2015.

The slow life of clinical spectroscopy

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Magnetic resonance imaging has taken off like a rocket and become the diagnostic runner of the last twenty years, but MR spectroscopy has stayed in the back rooms of the researchers. There are two main reasons for this development: there are not many clinical applications for MR spectroscopy, and there is no reimbursement for such examinations in most countries. This makes the method unattractive for physicians, hospitals, and in particular for private practices.

One of the first papers on medical MR spectroscopy applications was published in the New England Journal of Medicine in 1981 by Ross and his collaborators. They described spectroscopic changes of phosphorus in McArdle's syndrome [3].

McArdle's syndrome is not a major global disease, nor are other muscular diseases in which MR spectroscopy has shown changes of phosphorus or proton spectra.

Thus, it is understandable that both the clinical users and the manufacturers of MR machines have reduced or even ceased to use whole-body MR spectroscopy machines. In 1990, a spokesman for one of the major manufacturers of whole-body MRI/MRS equipment stated that there are no clinically efficient applications for MR spectroscopy. Therefore, his company and other producers of high-field equipment have limited their investments in whole-body MR machines below 2 Tesla although in recent years some higher field machines have reached the market.

However, this trend is not reflected by the research output – MR spectroscopy research is thriving. In 1982, at the first meeting of the Society of Magnetic Resonance in Medicine in Boston only two papers dealt with MRS. In 1983 less than 100 papers were published about MRS, in 1991 MedLine counted 500, and in 1999 700 publications. As well as there being more papers, there was also an increase in complexity.

The following statement is typical of many articles dealing with MR spectroscopy and its applications:

"It is hoped that the new information provided by (in this case) multidimensional spectroscopic imaging of metabolites in vivo will further enhance the clinical and scientific value of this technology [1]."

The overwhelming majority of publications about MRS either focus on anecdotal clinical cases, in which some changes in spectra were (or were not) seen, or they discuss improvements of MRS technology. It is always 'hoped' that one day MRS will enhance the horizons of medicine.

MR spectroscopists sometimes claim that whole-body MRS is not accepted by clinicians because the latter cannot read and interpret the spectra. They postulate that:

"The arrogance of the ignorants hinders the development of spectroscopy."

This might be partly true because radiologists are not trained in biochemistry or in reading and recalculating spectra.

However, the ball is played back into the spectroscopists' court by the physicians. The latter underline that spectroscopists, with a background in chemistry or physics, have no idea of the possible medical relevance of spectra and are, by and large, only interested in playing scientific games. They also claim that spectroscopists create a sea of irrelevant data in which potentially useful information is drowned.

Another important argument is that spectroscopy is insensitive. Phosphorus spectroscopy is sometimes dubbed 'the Twin Peaks of MR', although in reality there are three main peaks in *in vivo* phosphorus spectra.

The technique of phosphorus spectroscopy suffers because of the large volumes (50-100 ccm) that are necessary to acquire decent spectra within the time period a patient can remain motionless in the magnet. However, tissue volumes of 50-100 ccm are of no relevance to clinical diagnosis. When examining brain tumors, an MRS examination volume usually includes vital tumor tissue, the necrotic tumor center,

edema, perhaps hemorrhage, and also normal non-involved tissue. This type of volume is too inhomogeneous to clarify or even grade such a tumor. Follow-up examinations may reveal whether a tumor responds to therapy, but even this is doubtful.

However, proton spectroscopy has a greater sensitivity and possesses a wider range of metabolic information than phosphorus MRS. It saves between a half and two-thirds of the time necessary to acquire a similar phosphorus spectrum at 1.5 T.

Spectroscopic data usually require spectral analysis to indicate the metabolite concentration, ratios, and tissue pH. These data give a momentary picture of macroscopic local metabolism and the distribution of metabolites. To date, both time and space resolution are restricting factors of MRS, and therefore MRS examinations cannot compete directly with single photon emission computed tomography (SPECT) or positron emission tomography (PET). However, MRI can now begin to compete with these radioisotope technologies.

It is also possible to convert the spectroscopic result into metabolic maps. Thus, images can be created that reflect the concentrations of certain metabolites on an anatomical background.

Maps of phosphates or other metabolites can deliver spectroscopic information as pictures that can be more easily understood by radiologists. Proton spectra might become the solution for creating such maps because numerous metabolites such as creatine, choline, and lactate can be depicted.

The interpretation of such maps still requires considerable knowledge of diagnostic biochemistry. Because today's radiologists are not trained in this field, this is a job for skilled spectroscopists. Worldwide, there are few scientists with such knowledge, and training is limited because of financial restrictions.

■ The question remains as to how MRS can be accepted by clinicians using whole-body MR machines.

First, relevant clinical and diagnostic applications have to be found. These applications must be better than competing techniques, and if possible, the MRS examinations must become faster and cheaper than comparable diagnostic methods. In addition, for its implementation in clinical routine, there should be a therapy for the patient's disease. MRS must be able to exclude certain differential diagnoses better than other diagnostic techniques, and/or MRS must be superior to other diagnostic methods in the follow-up period.

Second, MR spectroscopy must be easy-to-use and accepted by radiologists, otherwise it will stay a research tool.

On the other hand, there is no doubt that MRS has already contributed greatly to the furtherance of medical knowledge and the understanding of certain aspects of human physiology and pathophysiology. MRS examinations of muscle metabolism, tumors, tissue damage caused by ischemia and infarction, and transplant rejection have added to the understanding of these diseases.

■ Still, to date, most examinations have not proved useful for daily medical routine. And, what makes it even more difficult for medical spectroscopy, functional and dynamic magnetic resonance imaging have become possible during the last few years. Functional imaging allows users to depict some of the working mechanisms in the body such as the response of the visual cortex of the brain upon light, enabling almost direct assessment of neuronal function.

However, unrelated events can influence and boost medical techniques – such as diseases of presidents or monarchs or wars. MR spectroscopy of the brain, for instance, hit the frontpages of newspapers when a research group was able to show brain abnormalities in veteran military personnel after the Gulf War [2].

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. The slow life of clinical spectroscopy. Rinckside 1991; 2,3: 13-14.
Reprinted and updated several times. Last update 2015.