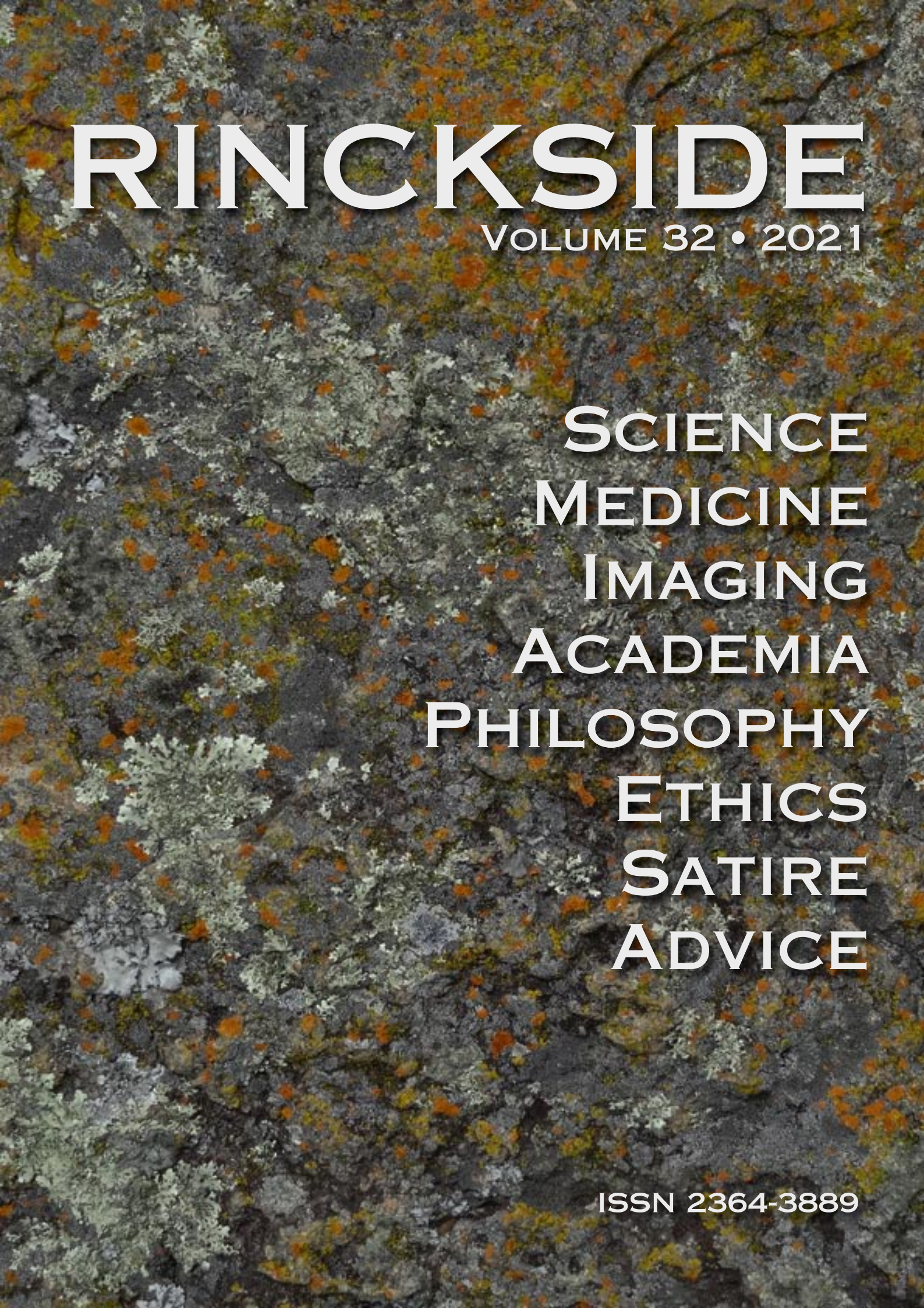

ISSN 2364-3889

RINCKSIDE

ISSN 2364-3889 • VOLUME 32, 2021

CONTENTS

RINCKSIDE is published by The Round Table Foundation (www.trtf.eu).
It is listed by the German National Library.

Smashing the magnetic field strength dogma • MRI: an unexpected change

Peter A. Rinck

Some years ago, I concluded an article about field strength of MRI equipment with the words: "Next stop: 7 Tesla, perhaps 9 or 11 – for nerds. Or, perhaps and less wasteful, routine imaging at 0.5 Tesla for down-to-earth clinical applications with new wire and coil technologies."

Quietly, without much fuss, it seems that the high-field nerds will wake up to a downward trend. After several decades, low (<0.5T) and medium (0.5T—<1.5T) field MR machines [1] push their way up on the markets.

The field-strength question has divided the MR community since the early 1980s. At that time, all MR machines operated at low fields; many of the prototypes of that time had strengths of approximately 0.15T. Their image quality was poor. It improved at 0.5T and 0.7T.

Then, some manufacturers, prompted by their research and marketing people, drove MRI up to 1.5 T with high-field superconductive magnet systems: "Increase field strength and you'll have more beautiful images."

These systems were and still are huge, dinosaur-like machines. They were expensive, difficult to produce, cumbersome to install, and costly to maintain, but image quality suddenly became better and more patients could be examined per day. *Faster imaging* became one of the catchphrases of the day.

"Without the push to high field, MRI systems might be quite different today, probably lower down on the cost/performance scale."

At that time, Derek Shaw was one of the leading MR scientists in Europe. He worked for several of the main MR manufacturers, among them General Electric. In 1996, he wrote in a book chapter:

> "Without the push to high field, MRI systems might be quite different today, probably lower down on the cost/performance scale [2]."

For the manufacturers, health insurance companies, and MRI owners high field meant higher profit, which is a recurrent theme not only in medical technology. After the introduction of 1.5-Tesla machines competition between different companies brought the clinical 3T MRI equipment.

The high and ultrahigh field dogma was born and established. In some countries low and medium field equipment was even banned by tricky regulations imposed by the reimbursement agencies, although there was strong evidence that low and medium field systems possess some major advantages [3, 4].

The medium-field antithesis

Meanwhile, it seems, the US-American, European and Asian markets with money à gogo are creamed off. Times have changed. Competition is tough. Intricate and complicated equipment doesn't necessarily find uncritical users any more. New customers have to be found, for all one knows new demands have to be created, even if one has to return from extravagance to thriftiness – and use common and scientific sense.

Low and medium field had the disadvantage of lower image quality which meanwhile has been overcome by the improvements made in soft- and hardware in general and, for instance, noise reduction. Here, phased array coils and parallel imaging have helped to make substantial headway. Since the T1 relaxation is longer at higher fields (e.g., T1 of gray matter at 3.0T more than three times longer than at 0.3T), data averaging to increase signal strength is practicable at low and medium fields.

Inherent advantages of low and medium field machines include ease of installation and operation, and general patient friendliness. Low and medium fields are ideal for open MRI systems which drastically re-

duces claustrophobia. Open systems are convenient for interventional MRI. More so, there is minimal noise of gradient switching compared to the high and ultra-high machines (no danger of auditory damages to patients), and no perturbation of the vestibular apparatus leading to vertigo.

Since there is hardly any magnetic fringe field, no heavy shielding is necessary to protect the environment from the magnetic field emanating from the system. These systems are also less artifact prone: there are fewer metal and chemical shift artifacts, reduced susceptibility and dielectric effects. Tissue penetration is better, and there is less radiofrequency power deposition.

On the financial side, the prices of low and medium field equipment are more convenient than those for high and ultra-high field apparatuses. Maintenance and energy costs are also lower. With the latest technology, helium replenishment is unnecessary, eliminating the need of buying and refilling of liquid helium at permanently higher costs.

MgB_2 superconductive wires and coils

A major step to achieve superior diagnostic quality at low and medium fields was the invention of wires and coils using magnesium diboride (MgB_2). For some years now they can be commercially created, eliminating the need for liquid helium and possible quenches [5]. MgB_2 machines require one liter of helium to keep its superconducting magnet cold, compared with hundreds of liters for old-type high-field machines.

They allow, for instance, the production of superconducting easy-access open MR systems operating at low field with an imaging performance equal to high-field equipment. This development is a major challenge for existing high field equipment, in particular because the diagnostic quality of low and mid field systems was already described competing with high field even before the introduction of high-temperature superconductive coils.

The science behind the image contrast at different magnetic fields

While in the 1980s the commercial battles of the field strength war flared up, one of the most sophisticated research projects on the behavior of tissue relaxation by creating nuclear magnetic resonance dispersion (NMRD) was carried out. This huge scientific effort remained unique, the coordination and logistics were intricate, nobody has ever repeated it.

The results did not overlap with the commercial ideas, and were deliberately overlooked in the race for higher fields.

It was an interdisciplinary project involving several universities and taking more than two years, using an IBM Field Cycling Spectrometer, a machine of which only a handful were built by the IBM Research Laboratories in upstate New York. This machine could change its magnetic field strength within seconds between ultra-low fields and high fields to measure T1 relaxation times which change with field strength.

For brain studies, for instance, normal human brain gray and white matter samples from various anatomical locations of the brain were excised, within 24h after death, from patients who died of other than neurological causes. Tissue samples weighing between 200 and 600 mg were transferred to sample tubes directly after dissection, quickly deep frozen, transported to the NMR laboratory on dry ice (-78.5°C), and stored in a deep freezer until rapid examination. The samples were thawed at room temperature shortly before the measurements.

Measurements up to 1.5 Tesla were performed on the NMRD relaxometer. The advantages of relaxometric measurements of ex vivo samples are the extreme high accuracy of the measurements, the selection of tissue that looks homogeneous with the ability to reject mixed tissue samples, and the detailed histology available after the measurements. Compared to NMRD data, T1 computations with MRI systems are rough estimations.

Relaxometry permitted the determination of longitudinal relaxation rates of numerous tissues and chemical compounds. The resulting nuclear magnetic relaxation dispersion profiles allowed the prediction of tissue contrast and efficacy of contrast agents at any field strength [6-11].

The T1 of tissues does not show a monotonic increase with field strength. Characteristic transverse decay data and longitudinal relaxation dispersions were observed for the main constituents of human brain, i.e., gray and white matter. White matter exhibits a dispersion not encountered in any other tissue. This is most probably caused by an additional

relaxation process occurring in myelin and involving the, themselves MR-invisible, membrane lipids. Due to this fact, pure T1 contrast of normal brain tissue and pathologic lesions (multiple sclerosis, astrocytoma) increases from low field strengths to a maximum between 0.3T and 0.5T MHz and decreases afterwards.

Thus, optimum T1 contrast for brain examinations with decent signal-to-noise can be best reached around 0.5 Tesla. As we wrote in a publication more than 30 years ago:

> "It is felt that consequences of this particular behavior will be important for neurological MRI, adding a new element to the sometimes controversial question of optimal field strength."

Suddenly these scientific results seem to make commercial sense too.

References

1. EMRF (European Magnetic Resonance Forum Foundation). Definition of field strength. in: Rinck PA. An Introduction to magnetic resonance in medicine. 2nd ed. New York: Thieme Medical Publishers. 1990. 12. | Rinck PA. Magnetic field strength. in: Rinck PA. Magnetic Resonance in Medicine. A Critical Introduction. 12th ed. BoD, Norderstedt, Germany. 2018. ISBN 978-3-7460-9518-9. 38.
2. Shaw D. From 5-mm tubes to man. The objects studied by NMR continue to grow. In: Grant DM, Harris RK. Encyclopedia of nuclear magnetic resonance. Volume 1, Historical perspective. Chichester: John Wiley and Sons. 1996, 623-624.
3. Hoult DI, Chen C-N, Sank VJ. The field dependence of MRI II. Arguments concerning optimal field strength. Magn Reson Med 1986; 3: 730-746.
4. Posin JP, Arakawa M, Crooks LE, Feinberg DA, Hoenninger JC, Watts JC, Mills CM, Kaufman L. Hydrogen MR imaging of the head at 0.35 T and 0.7 T: effects of magnetic field strength. Radiology. 1985;157: 679-683.
5. Bertora L. MRI magnets based on MgB2. in: Flückiger R (ed). MgB2 superconducting wires. Basics and applications. Hackensack, NJ, U.S.A.: World Scientific Publishing. 2016. 485-536.
6. Rinck PA, Muller RN, Fischer H. Field and temperature dependence of contrast in magnetic resonance imaging. RöFo Fortschr Röntgenstr 1987; 147: 200-206 (in German).
7. Rinck PA, Fischer HW, Vander Elst L, Van Haverbeke Y, Muller RN. Field-cycling relaxometry: medical applications. Radiology 1988; 168: 843-849.
8. Fischer HW, Van Haverbeke Y, Rinck PA, Schmitz-Feuerhake I, Muller RN. The effect of aging and storage conditions on excised tissues as monitored by longitudinal relaxation dispersion profiles. Magn Reson Med 1989; 9: 315-324.
9. Fischer HW, Rinck PA, Van Haverbeke Y, Muller RN. Nuclear relaxation of human brain gray and white matter: analysis of field dependence and implications for MRI. Magn Reson Med 1990; 16: 317-334.
10. Muller RN, Vander Elst L, Rinck PA, Vallet P, Maton F, Fischer H, Roch A, Van Haverbeke Y. The importance of nuclear magnetic relaxation dispersion (NMRD) profiles in MRI contrast media development. Invest Radiol 1988; 23, Suppl 1: S229-231.
11. Rinck PA, Muller RN. Field strength and dose dependence of contrast enhancement by gadolinium-based MR contrast agents. Eur Radiol 1999; 9: 998-1004.

Rinckside, ISSN 2364-3889

Citation: Rinck PA. Smashing the magnetic field strength dogma • MRI: an unexpected change. Rinckside 2021; 32,1. 1-3.

New realities in medical imaging

Peter A. Rinck

The organization and logistics of medical imaging are changing rapidly in some countries. Independent small private practices disappear – Germany and Switzerland being good examples. The legal introduction of medical care centers (MVZs) in Germany some fifteen years ago has redefined the framework of radiological care.

To many patients the radiologists' offices might look the same, a thriving medical business, but what was formerly owned by one, perhaps two radiologists who had set themselves up, today is part of one of the specialist chains with branch offices in the region or all over the country.

We are watching the end of the epoch of the single, independent "universal" medical imaging specialist.

We are watching the end of the epoch of the single, independent "universal" medical imaging specialist.

The German radiology market consists of over 1,000 imaging centers and 800 radiology hospital departments with more than 6,800 radiologists. That's approximately 83 radiologists per one million inhabitants – compared to 68 in Great Britain [1].

Outside the hospitals, one sees a trend towards centralization: buying, advertising on their home pages and, e.g., Google adverts, bringing everything and everybody in one line, and adjusting manpower to the radiological overkill. This overkill is due to a dramatic increase of examinations for diagnostic questions that were not considered necessary some years ago. This also means a rise in specialized and subspecialized radiologists required for the new spectrum of indications. General radiologists have problems to survive on their own.

During the past 15 years, for example, more and more imaging centers have been expanded, the number of salaried physicians working for the owner or owners of them has risen sharply, and many practices are organized in networks or purchasing associations.

Similar endeavors of independent radiology communities were launched in other European countries, for instance in France with VIDI, a network of private radiology. By creating an independent association, the founders intended to protect the quality of medical imaging for all patients and facilitate access throughout France to excellent diagnostics and care.

They stated: "We accompany our patients throughout their medical imaging journey, from screening to interventional procedures, from diagnosis to care. The strength of our network is also to give our patients access to a group of radiologists who are highly specialized in all areas of expertise. The radiologists in the Vidi network share values of responsibility, commitment, accessibility and human relations [2]."

The network was created in January 2017, comprising 14 imaging centers with 207 radiologists; in December 2020 the VIDI cooperative network consisted of 50 medical imaging centers in France and included nearly 900 radiologists working alongside nearly 3600 employees to examine more than 5 million patients per year.

In a completely different approach, radiologists turned businessmen and started acquiring imaging practices or entire centers from colleagues and helped creating wholesale companies for pharmaceuticals, mostly contrast agents, to generate additional revenue. Thus several physician-led radiology networks or chains with several hundred employees formed during the last decades.

One of these company conglomerates and its affiliates in Germany sees more than three quarters of a million patients a year pass through their facilities in more than twenty cities. In some of these chains equipment manufacturers have an interest and access to data that might be helpful in developing new applications.

Medical and increasingly non-medical investors and private equity enterprises have moved into the for-

merly protected health care market and started taking over doctors' offices in a number of disciplines: radiology, orthopedics, neurology, rheumatology, dialysis and even physiotherapy.

■ Private equity enterprises pursue a *buy-build-resell* strategy. Commonly they invest in consumer, health, and industrial companies and in business services. They acquire existing firms, for instance radiological chains, keep them going, and after period of five to six years search for suitable buyers. They generate the greater part of their returns not from current income during the time they own a company, but from the higher price they score when the company is sold. Often the investors' funds are located in offshore financial centers, primarily the Cayman Islands and the Channel Islands of Guernsey and Jersey.

There is also a health-political aspect to the new landscape: the permanent call for more efficiency in medicine; pathetic statements of politicians, insurance managers and equipment manufacturers, consultants – and investors. They have no medical, practical or health ethics background, but are part of an excessive bureaucracy that has to prove that they are all-important and indispensable. It's the old game of gaining a little personal power and making money.

■ Privately, chain-employed radiologists complain that they realize a gradual loss of quality and efficiency – just the contrary of what is being preached.

There is also a latent fear of a lack of transparency of the intentions of some owners who as lay people do not understand the possible flaws of replacing some of the radiological evaluations by AI software programs. The employed radiologists are afraid that they might be forced to use AI to save money and to take the sole responsibility for the risks involved.

The radiologist generation 50-plus looks forward to – early – retirement if it is financially acceptable; on the other hand younger radiologists appreciate the offer of a better "life balance" between working and private life. Regular working hours, free weekends, long holidays, less responsibility, little management and administrative tasks are major attractions.

The salary of an employed certified radiologist in Germany is around € 140,000 per year. After taxes and health insurance that's sufficient for a decent middle-class life. However, as one elderly radiologist told me:

> "In the long run it's not enough any more to build or buy a house for the family. For the younger generation it will be tight. They don't want to work as hard as we did, but even if they do they will feel the difference."

He retired some time ago and added:

> "I have worked and paid into the physicians' pension fund for 35 years. I get that pension and a second, smaller one. After taxes and health insurance payments less than € 1,400 are left per month. That's not enough to survive. You have to have additional means. Some school mates of mine were high school teachers. Their state pensions and fringe benefits are far better. And the young minister of health just bought a villa for 4 million euros. He is lucky, he hasn't studied medicine."

References

1. Ward P. U.K. radiology's looming crisis deepens in COVID-19 pandemic. AME (Aunt Minnie Europe) 28 April 2021.
2. VIDI: Manifeste. www.groupe-vidi.fr/pionnier-radiologie-liberale-vidi

Rinckside, ISSN 2364-3889

Citation: Rinck PA. New realities in medical imaging. Rinckside 2021; 32,2. 5-6

All quiet at the MR contrast agent front?

Peter A. Rinck

There is not much innovation in the clinical use of MR contrast agents, but numerous "market reports" have been released during recent years predicting a roaring future — although they were mostly written by people without deep insight into the field. These reports are being offered at prices of several thousand dollars each. According to them, the future of the MRI contrast agent market is bright, most of the big companies have just introduced new agents, and at least a 4% annual increase in sales can be expected. Thus, they are as accurate as today's weather forecast for February 2031. It is rumored that their publishers also sell market forecasts for bitter orange marmalade for 2022-2031, same predictions, same bitter off-taste.

The so-called "new" agents according to these reports are generics, mostly copies of Gd-DOTA, the "Dotarem" the French company Guerbet brought out more than thirty years ago. The novel trade names are different, but this is how far novelty goes.

Ongoing research in the field of MRI contrast agents at universities and other research institutions paint a different picture: there are plenty of ideas and developments — applicable for biomedical research, but not for clinical life. Among them are compounds capable of being activated by outside factors and targeted ones; they all seem to function nicely in animal models. An excellent 100-page overview was given by a research group at MGH / Harvard Medical School in 2019 [1], a shorter and more clinical basic introduction to MR contrast agents was published by TRTF/EMRF in 2021 [2].

Still, no new products have reached the market; on the contrary, a number of approved compounds were withdrawn because they didn't sell. Others — linear gadolinium based agents — had to be removed because they were considered a risk for patients after the overdosing of gadolinium compounds led to the NSF (nephrogenic systemic fibrosis) scandal [3].

Gadolinium deposits have also been found in other body tissues. Yet, there is currently no evidence that gadolinium deposition in the brain has caused any harm to patients. In 2019, a major study provided evidence from a large animal model that linear gadolinium-based contrast agents leave traces of gadolinium within the deep cerebellar nuclei, while there was no significant difference of gadolinium residue between three macrocyclic agents marketed in Europe and a saline control group [4].

The European Medicines Agency (EMA) recommended restrictions and suspensions for some intravenous linear agents in order to prevent any risks that could potentially be associated with gadolinium brain deposition. EMA stated that the intravenous linear agents gadoxetic acid and gadobenic acid can continue to be used for liver scans because they are taken up in the liver and meet an important diagnostic need. All other intravenous linear products (gadodiamide, gadopentetic acid and gadoversetamide) are suspended in the EU [5].

On the other hand, the US Food and Drug Administration did not restrict any Gd-containing agents [6]. Only the intravenous linear blood pool agent Gadofosveset trisodium (also known as Ablavar or Vasovist) was withdrawn from the US-market; the manufacturer discontinued production in 2017 due to poor sales.

Gadolinium contrast agents are still the safest contrast agents one can use in diagnostic imaging, far safer than x-ray agents.

Gadolinium contrast agents are still the safest contrast agents one can use in diagnostic imaging, far safer than x-ray agents. The dream of some of the early developers to create outstanding and safe contrast enhancers was destroyed by corruption sprees and greedy abuse of the gadolinium agents. Their reputation was severely damaged by avarice and depravity on the one hand and, on the other, by cheap sensationalism in the press [7,8].

The main question is if there is room for a new agent today or in the future — and if so, how and why — when the remaining Gd chelates are so universal in terms of their application. Gadolinium extra-cellular fluid agents are the only ones that have grown into a realistic market size. Thus, it will be extremely difficult to develop a new MR contrast agent that fulfills unsatisfied clinical needs and has a large enough range of application to justify development [9]. New agents for e.g. liver or pancreas imaging may have difficulties to gain a foothold.

The global market value of gadolinium contrast agents still is in the billions of dollars per year although it shrunk in the U.S.A. between 2019 and 2020 from more than 500 million USD to about the half — it contracted significantly during the Covid-19 lockdowns and the market has not yet returned to pre-pandemic levels.

There is, of course, the financial inducement. The American market is huge and the retail prices of contrast agents are high. Generally speaking, prescription drug prices in the United States are two and a half times the prices elsewhere, the gap between prices in the United States and other countries is even larger for brand-named drugs, with U.S. prices averaging 3.44 times those in comparison nations. A recent study by the Rand Corporation found that among G7 nations, the United Kingdom, France, and Italy generally have the lowest prescription drug prices, while Canada, Germany, and Japan tend to have higher prices, still far below those in the U.S. [10].

For connoisseurs and lovers of obscure statistics: average life expectancy in years in these countries is as follows: Japan 85.0, Italy 84.1, France 83.1 Canada 83.0, Germany 81.9, United Kingdom 81.8, and the United States 79.1. In other words, one lives longer where drugs are cheaper.

Reimbursement

Until some five years ago, reimbursement of contrast agents by health agencies and insurance companies was generally generous — a number of people took advantage of this behavior. The sums involved were horrendous. Then the evidence trickled down to the media and the public. One corruption scandal followed the next.

As a result in Germany, for instance, reimbursement by the local Statutory Health Insurances dropped substantially. Originally these insurance companies used to reimburse between 3900 and 6000 Euros per one liter of contrast agent (50 doses) to the manufacturer or wholesaler; since 2019, only 970 Euros are reimbursed. Probably only 700 Euros per liter will be paid in the future. However, the ten percent of the population who are not members of the national insurance scheme and are covered by private insurance coverage continue paying substantially more per contrast-enhanced MR examination.

In some parts of Germany, radiologists are not allowed to decide which contrast agent they can use and they are not told how much it costs. It's a secret between the local Statutory Health Insurance and the company delivering the agent. Again, venality is part of the game.

Lower reimbursement discourages the clinical development of new agents since it requires tens, perhaps hundreds of millions of euros for the pre-clinical and clinical studies in humans. More so, compared to thirty years ago, the registration authorities demand far more stringent safety studies. There is also a simple rule: The better the specificity, the smaller the market will be — and the smaller the market, the higher the price per dose has to be — and higher prices might be an insurmountable obstacle.

Thus there is the attractive idea of applying new paradigms to already approved agents that were withdrawn from the market before the gadolinium phobia, such as the use of Mn-DPDP for cardiac and brain applications and ferumoxtran for the enhancement of metastases. New patents cover these new applications. In these cases re-introduction should be less complicated — but apparently, it still is rather expensive and very time consuming.

At the same time, the equipment manufacturers are doing everything they can to come up with non-contrast agent alternatives. In addition, AI applied to imaging looks set to change the goal posts both in terms of diagnosis and also in highlighting subtle differences and abnormalities. This technology will be fully integrated with the equipment.

Another question is what will be the clinical need for imaging agents when in vitro diagnostics will begin to provide useful information. Advances in gene sequencing and in molecular biology underline the significance and impact of linking diagnostics and biotechnology, for instance in identification of cancer from blood samples. Long-term thinking is not the

business approach of many companies, but some invest in innovative lateral thinking, hoping and already seeing commercial success.

References

1. Wahsner J, Gale EM, Rodríguez-Rodríguez A, Caravan P. Chemistry of MRI contrast agents: Current challenges and new frontiers. Chem Rev. 2019; 119(2): 957-1057. doi:10.1021/acs.chemrev.8b00363.
2. Rinck PA. Contrast agents in magnetic resonance imaging. Free offprint from: Magnetic Resonance in Medicine. A Critical Introduction. The Basic Textbook of the European Magnetic Resonance Forum. Preprint of the 13th edition. 2021.
3. Rinck PA. Gadolinium — will anybody learn from the debacle? Rinckside 2015; 26,9: 23-26.
4. Radbruch A, Richter H, Fingerhut S, Martin LF, Xia A, Henze N, Paulus W, Sperling M, Karst U, Jeibmann A. Gadolinium deposition in the brain in a large animal model – Comparison of linear and macrocyclic gadolinium-based contrast agents. Invest Radiol 2019; 54: 531–536.
5. European Medicines Agency. EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans. Recommendations conclude EMA's scientific review of gadolinium deposition in brain and other tissues. 20 July 2017.
6. FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue. 19 December 2017.
7. Rinck PA. Adding fuel to the flames: Gadolinium – the German follow-up. Rinckside 2016; 27,1: 1-3.
8. Rinck PA. German newspapers and the gadolinium controversy. Rinckside 2018; 29,3: 7-8.
9. Rinck PA. MR Imaging: Quo Vadis? Rinckside 2019; 30,3: 5-8.
10. The Rand Corporation (Mulcahy AW). Prescription drug prices in the United States are 2.56 times those in other countries.

Rinckside, ISSN 2364-3889

Citation: Rinck PA. All quiet at the MR contrast agent front? Rinckside 2021; 32,3. 7-9

Magnetic Resonance Imaging • The 50th anniversary

Peter A. Rinck

On an evening in early September 1971, two men met at a fast-food restaurant for a hamburger dinner in the small town of New Kensington in Pennsylvania. One of them was Paul C. Lauterbur, a professor of chemistry in charge of the NMR laboratory at the State University of New York at Stony Brook. The other one was Don Vickers, another NMR scientist.

During the dinner Lauterbur explained to Vickers his idea to create images with an NMR equipment, an idea he further developed during the meal. The concept sounded simple in theory: superimpose on the strong magnetic field of an NMR spectrometer a second, smaller and adjustable field.

The next day, Lauterbur bought a laboratory notebook and put down in writing the background and outline of *Spatially Resolved Nuclear Magnetic Resonance Experiments*, signed the text and had it witnessed by Vickers on 3 September 1971.

Magnetic resonance, or nuclear magnetic resonance (NMR) as natural scientists 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. The two scientists, Edward M. Purcell and Felix Bloch, were awarded the Nobel Prize in Physics in 1952. 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.

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 new technique 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 though an object or in three dimensions of the entire object.

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 some "normal" tissues had different signal properties compared to pathological tissue, and he believed that his technique 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.

In earlier years, several people had described possible applications of NMR in medicine and biology. Erik Odeblad was the first of them. In 1953 he had met Felix Bloch in Standford. Odeblad asked him whether he could use his NMR spectrometer to study human samples, but Bloch's response was negative. He made it clear that NMR was a tool for physicists, not for research into physiology, medicine, or biology. Odeblad returned to Sweden and got his own machine.

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 [1] and Paul C. Lauterbur.

Lauterbur also stumbled when he tried to publish his invention. In late 1972 he received an apologetic letter from the editor of the journal *Nature* 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 his new imaging technique he had dubbed zeugmatography. For those who did not study Greek at school, zeugma - ζεγμα is the yoke, or as the author put it: "That what is used for joining." and graphein - γράφειν means to write, to depict.

Lauterbur replied:

> "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?"

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* [2].

Thirty-two years after his invention, 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.

This was the first Nobel Prize in Physiology or Medicine awarded in the field. Lauterbur commented on this in a lecture given in Lund, Sweden, some days after the Nobel Prize Ceremony in Stockholm in 2003:

> "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."

References

1. Odeblad E, Lindström G. Some preliminary observations on the proton magnetic resonance in biological samples. Acta Radiol 1955; 43: 469-476.
2. Lauterbur PC. Image formation by induced local interactions: examples of employing nuclear magnetic resonance. Nature 1973; 242: 190-191.

Parts of this column were published 30 years ago as the first Rinckside: "How it all began". Rinckside 1990; 1,1: 1-3.

Rinckside, ISSN 2364-3889

Citation: Rinck PA. Magnetic Resonance Imaging • The 50th anniversary. Rinckside 2021; 32,4. 11-12.

Epidemics and medical imaging

Peter A. Rinck

Epidemics or, worse as in our recent case: pandemics, pose a great threat to humanity. They have claimed more lives than all the wars and natural disasters in history combined. Many millions of people fell victim to the great plague outbreaks centuries ago, to cholera pandemics or, at least during the last 500 years, influenza pandemics that seem to appear in 20- to 50-year cycles. Despite great successes in medicine, infectious diseases continue to claim millions of lives today.

The outbreak of Covid-19 has shown how quickly a virus can bring life in today's world to a standstill and threaten the existence of millions of people. The dedicated Special Exhibition: Epidemics – Curse of the Past, Threat to the Future at the Roemer-and-Pelizaeus-Museum in Hildesheim in Germany traces the history of epidemics through the centuries and offers a glimpse of the future. It is the biggest ever special exhibition on the topic – and was planned long before the outbreak of Covid.

Exhibition at the Roemer- und Pelizaeus-Museum, Hildesheim (Germany): Seuchen. Fluch der Vergangenheit — Bedrohung der Zukunft (Epidemics. Curse of the past — threat to the future). 2 October 2021 until 1 May 2021.

The poster announcing the exhibition reminds of medical imaging. Radiology is the interdisciplinary crossroads for most medical specialities, from traumatology to cardiology. There is one exception: usually, not too many high-technology examinations are requested by the infection wards. In radiology, therefore, there was not much contact with the specialists in infectious diseases, and often limited knowledge about these diseases exists among radiologists.

Anyhow, if physicians dealing with infectious patients want to refer one of them to radiology there is always trouble and discussion because, in contagious cases, the imaging facilities used have to be closed and disinfected after the examination. Usually today, these wards have their own mobile imaging systems allowing plain imaging of their patients.

Rapidly after the outbreak of Covid-19 several thousand papers were published about diagnostic imaging of the disease – very often as non-reviewed preprints [1]. Getting an overview is nearly impossible. One helpful overview of nearly 5000 publications was published in the *Cochrane Database of Systematic Reviews* [2].

Imaging techniques, especially computed tomography and to a lesser extent ultrasound, play an important role in diagnosis and treatment assessment of the disease.

A rewarding description of what a major French radiology center had to face when all of a sudden they were confronted by a tidal wave of Covid-19 cases was written by Robert Lavayssière [3].

> "We had to cope with several different problems at the same time: staff absenteeism (colleagues who got sick or were confined to home due to potential contacts, closed schools, etc.), global fear of the unknown, problems of cancer patients in our cancer-focused center, lack of protective gear because the authorities gave priority to public hospitals, global unpreparedness, and the drastic reduction of overall activity, leading to potential financial problems …
>
> "Thanks to the national and international publications and information campaigns, we have become quite aware of the Covid-19 CT features, but soon we had quite a lot of nontypical cases, including patients with extrathoracic findings or severe cases in young people."

For those practicing medicine in Europe, the worldwide extent of infectious diseases was difficult to imagine before Covid-19. In the late 19th century, or even as recent as eighty years ago, the situation was different. In 1892, 21% of the German population died of infectious diseases, in 1920 13.6%. The figure dropped to 0.83% sixty years ago, and to 0.78% in 1987.

In the years before World War I, the slums of London and many other big cities all over Europe were characterized by dirt, drunkenness, terrible poverty, and

exploitation. One in three infants died before reaching its first birthday. After the introduction of medical examinations at schools, it was reported that nearly 20% of the children were unfit to be taught because they suffered from worms or other infectious diseases.

Resurgence of Tuberculosis

Tuberculosis was one of the foremost and most feared killers. In a treatise on climatic health resorts published in the mid-nineteenth century, the author underlined that at least 25% of the customers of pharmacies suffered from phthisis, i.e. tuberculosis [4, 5]. The author recommended moving to Madeira as a possible remedy.

Improved sanitary and living conditions and better medicines – in particular antibiotics -- developed after the First and Second World Wars changed this situation. In Europe and parts of North America the incidence of tuberculosis declined steadily from the 1930s until the 1980s.

Cavities in the lungs may form quite early in tuberculosis. Reading chest x-rays, looking for single cavities or diffuse spread, typically constituted a major, albeit rather boring, daily task for a radiologist still 60 years ago. Fluoroscopy and x-ray population screening became a household part of radiology between the 1930s and the late 1970s. At this time, finally, tuberculosis was considered almost eradicated in Europe. Although tuberculosis was no longer deemed a threat to mankind, the disease still remains a marker of poverty and social decline.

Today we once again see a rapid increase in tuberculosis, most dramatically in the big cities of the U.S.A. but also in France, Great Britain, Central and Northern Europe. Tuberculosis is primarily seen in immigrants but also connected to HIV infection. In one Northern European country, 5% of the immigrants proved positive for tuberculosis in the late 1970s; 25 yeards later that number has climbed to 40%.

The worldwide situation looks even worse. The tuberculosis bacterium has infected at least 1.75 billion people; of the millions of people who die every year all over the world, some 2-5% die from tuberculosis. It is the leading killer among infectious diseases. In comparison, less than “only” 2% die from malaria.

As many other contagious diseases, most cases of tuberculosis occur in developing countries, as nowadays malaria does too. Overpopulation, lack of water and hygiene in many parts of the world, as well as the general absence of or the failure to realize health programs are the cause of the increased incidence of contagious diseases.

Travelling adds to the problem, but the single most important factor behind the resurgence of tuberculosis is the worldwide spread of AIDS, a disease that often accompanies tuberculosis infection and of which tuberculosis may well be the first sign.

Tropical Diseases

It should not be forgotten, however, that there are many tropical or "exotic" diseases. Among those that are almost unknown to Europeans but are not exclusive to the tropics is amoebiasis. Many radiologists are familiar with the name of the disease, but have you ever seen an amoeboma? When performing abdominal imaging it can look like a carcinoma constricting the colon.

The World Health Organization (WHO) estimates that some 200 million people, most of whom live in tropical and subtropical countries, are infected with bilharziasis, or schistosomiasis. This infectious water-borne disease is transmitted by snails carrying the parasitic flatworm that causes it. Once bilharziasis is established in an area, it is virtually impossible to eradicate — and the disease is on the rise in many regions of Africa.

As with tuberculosis, at least one quarter of the world’s population suffers from ascariasis. The roundworm ascaris is the most common cause of jaundice in children all over South America, Africa, and Asia.

The round dance of infectious diseases continues with echinococcosis, trypanosomiasis, typhoid, leprosy, and, of course, malaria. When I attended a course on tropical diseases as a medical student, the professor pointed out that actually most of these diseases are exotic rather than tropical – because they are exotic to us and extinguished in most of Europe. But malaria was found in England, Italy, southern Switzerland, even in the Baltic States not so long ago. The last epidemic in Germany was in a region in the north-east of the country in late summer 1946 – 6,000 cases within a month. Leprosy was also wide-

spread all over Europe. Geographical names such as Rosenheim, a town close to Munich, are proof of it – the name has nothing to do with roses, as the local tourist board claims – but rather means "leprosarium".

Role of Radiology

Let's return to radiology: Although the diagnosis of infectious diseases is not a primary indication of diagnostic imaging in Europe, radiologists are increasingly performing examinations of immigrants and travellers returning from the tropics. Plain x-rays, ultrasound and other basic imaging examinations are helpful in primary diagnosis and follow-up. CT and MR imaging are useful in the diagnosis of a limited number of these diseases, such as cysticercosis, particularly if cerebral or spinal affections are being investigated.

Sometimes, when you read images with changes or lesions inexplicable to you – and without proper medical history on the referral sheet, you should think twice and ask the patient: "Have you been abroad?".

Patients might not mention recent travels to the referring physician because they may not consider it pertinent. With many parasites or infections there is a delay before symptoms of the disease occur, and I have seen a number of cases where the radiologist directed the referring physician towards the diagnosis of a tropical disease.

In spite of this, radiography or other imaging methods are rarely mentioned under the heading of diagnostics in manuals or textbooks on tropical diseases, such as that written by Bell [6]. Physical examinations and laboratory tests remain the backbone of diagnostics. The major exception is again tuberculosis.

But new epidemics are also spreading as we have seen with the "novel" corona virus. According to WHO, several dozens new pathogenic agents have been discovered in recent years, among them the Ebola virus and new types of hepatitis. They might become a prominent health issue, even in Europe, because it appears that treatment with anti-viral durgs, and vaccination will become more and more difficult. Due to the increasing drug-resistance of some strains of bacteria, use of antibiotics might not prove successful.

Will there also be a role for radiology, especially high-technology radiology, in the diagnosis of these diseases? It seems unlikely. Exceptions might be in monitoring disease with CT or MR imaging, ultrasound or CT-guided biopsies, and interventional radiology, for instance in tuberculosis. However, just the enormous number of patients will be prohibitive for high-tech or even low-tech imaging.

It is always good to know more about the diseases we do not normally see, first, to be able to recognize them in case we happen to come across patients suffering from them, and second, not to be mentally stuck with the ordinary diseases we encounter every day. Just as common European diseases may be regarded as exotic in other parts of the world, those that Europeans call "exotic" are common elsewhere.

References

1. Rinck PA. Speech is silver, but silence is golden. Rinckside 2020; 31,6: 11-12.
2. Islam N, Ebrahimzadeh S, Salameh J-P, et al. Thoracic imaging tests for the diagnosis of Covid-19. Cochrane Database Syst Rev 2021, 16;3 (3): CD013639.
3. Lavayssière R. Hard truths from Covid-19 front line in Paris. Aunt Minnie Europe, 20 April 2020.
4. Schultze R: Die Insel Madeira. Aufenthalt der Kranken und Heilung der Tuberkulose daselbst. Enke Verlag: Stuttgart 1864.
5. Rinck PA. Kleine Geschichte der heilklimatischen Kurorte im Oberitalienischen Seengebiet. in: A Small Café. 2020. (www.small-cafe.org).
6. Bell DR. Tropical medicine. 4th ed. Blackwell Scientific: Oxford 1995.

Parts of this column were published earlier in: "Radiology and epidemics, new and old". Rinckside 1996; 7,1: 1-3.

Rinckside, ISSN 2364-3889

Citation: Rinck PA. Epidemics and medical imaging. Rinckside 2021; 32,5. 13-15.

All is not what it seems in the messy world of research: Don't play it again, Sam

Peter A. Rinck

Praised a long time in advance, an American study into the reproducibility of relaxation time values in MRI was published earlier this year. It was a collaboration between the US-American National Institute of Standards and Technology (NIST) and the International Society of Magnetic Resonance in Medicine (ISMRM) [1].

The study used two methods to measure T1 relaxation constants in phantoms on different MR machines [2]. The reference standard was an inversion recovery pulse sequence and the second sequence was one of the (black box) accelerated data acquisition algorithms commonly used today on MRI machines. Comparing measured values with known T1 values in a phantom was to help unravel various possible sources of distortion.

The outcome of the study demonstrated that MRI-based calculations of T1 are subject to significant bias and variation. The fast T1-mapping estimations revealed substantially greater deviations than the calculated T1 values of the inversion recovery measurements. The authors found that there was discrepancy between different vendors but without a consistent pattern, and stated in their evaluation that clinicians are unable to translate a – what they describe as – 'diagnostic threshold T1 value' determined on one MRI system to other MRI systems. In other words, they perceived that the general validity implied by the term ‘quantitative MRI’ is just fiction and they endorsed the scientific findings of the last four decades.

The paper was written in a rather clumsy and circuitous language, beating around the bush. One gets the impression that the results had to be presented but were not really appreciated, and the knowledgeable reader feels that the references were not selected according to importance but that the authors played dice to find whatever fitted or suited them.

Relaxation time measurements were considered very important during the first years of MR imaging. All machines were programmed to create true T1 and T2 images (i.e., T1- and T2 mapping), based on SE and IR sequences. After absolute T1 and T2 values had been used unsuccessfully by researchers, combinations of T1 and T2, histogram techniques, and sophisticated three-dimensional display techniques of factor representations were applied for what is called today ‘fingerprinting’ and ‘biomarkers’.

Very early, standardized test objects and the protocols for their use to allow comparable measurements of T1 and T2 precision and accuracy were introduced in the framework of an extensive European project [3]. The findings were sobering, but scientifically predictable. In particular, the accuracy and precision with which the relaxation times T1 and T2 could be measured from the images were found to be rather disappointing and the results from different machines did not correspond with each other:

> "These limitations present a considerable obstacle to the use of *in vivo* MR imaging to identify and characterize biological tissue … The major conclusion of the trial in respect of T1 and T2 measurement was that much work remains to be done before quantitative MR imaging becomes a reality [4]."

This was known in the field for more than 30 years [5] but, strangely, the big multi-center studies heavily supported by the European Union and their follow-ups were unknown to the authors of the US-American survey since they are not cited in their papers. Still, the new results confirm and validate the outcome from the 1980s.

The helpless and embarrassing statement at the end of the American paper repeats the statement from 33 years ago:

> “We suggest establishing rigorous quality control procedures for quantitative MRI to promote confidence and stability in associated measurement techniques and to enable translation of measurement thresholds for diagnostic, disease progression, and treatment monitoring from the research center to the entire clinical community and back.”

Quality control turned out not to solve the problem — from a scientific point of view, MR imaging is a crude and not very exact technology *per se*. Repeating and regurgitating studies instead of applying and understanding the existing results does not work out and will not work out; the authors are barking up the wrong tree [6]. In many instances we need tougher supervisors and referees stopping and cutting down faux research. This also includes research in artificial intelligence, biomarkers and fingerprinting based on messy and not reproducible data. Data analytics may not be as useful in medicine as in administrative tasks and rough guesses at data in what is claimed to be precision medicine are unhealthy.

Recently, the main author of a paper met me with astonishment and incomprehension and just gaped at me when I hinted that she should also read and cite articles published before the year 2000 – in particular because those articles proved the results of her paper wrong. But wasn't it clear that the results must be like that? The numbers were there. It fitted the agenda not only of this research group, but also the commercial interests behind it.

References

1. Keenan KE, Gimbutas Z, Dienstfrey A, et al. Multi-site, multi-platform comparison of MRI T1 measurement using the system phantom. PloS ONE. 2021; 16(6): 1-19 e0252966. doi.org/ 10.1371/ journal.pone.0252966
2. Stupic KF, Ainslie M, Boss MA et al. A standard system phantom for magnetic resonance imaging. Magn Reson Med. 2021; 86(3): 1194-1211.
3. EEC Concerted Research Project. Identification and characterization of biological tissues by NMR. Concerted Research Project of the European Economic Community. IV. Protocols and test objects for the assessment of MRI equipment. Magn Reson Imaging. 1988 6(2): 195-199.
4. Lerski RA, McRobbie DW, Straughan K, Walker PM, de Certaines JD, Bernard AM. Multi-center trial with protocols and prototype test objects for the assessment of MRI equipment. EEC Concerted Research Project Magn Reson Imaging. 1988; 6(2): 201-214.
5. Rinck PA. Relaxation Times and Basic Pulse Sequences in MR Imaging. in: Magnetic Resonance in Medicine. A Critical Introduction. 65-92. Offprint from the 13th edition (2022/2023) of the textbook.
6. Rinck PA. Mapping the biological world. Rinckside 2017; 28,7: 13-15.

Rinckside, ISSN 2364-3889

Citation: Rinck PA. All is not what it seems in the messy world of research: Don't play it again, Sam. Rinckside 2021; 32,6. 17-18.