RINCKSIDE

ISSN 2364-3889

Volume 26, 2015

PRO ACADEMIA

EMRF

The Round Table
Foundation

RINCKSIDE

ISSN 2364-3889 • Volume 26, 2015

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It is listed by the German National Library.

Address the backlog issue or you will sink

Peter A. Rinck

Backlogs of unread images are one of the worst nightmares in clinical routine. Unreported x-ray or MR studies older than two days start blocking the daily routine; if they are older than one week and mounting they are the beginning of a catastrophe.

Any backlog has to be tackled urgently and with high priority – otherwise you will be watching helplessly as the ship sinks and sink with it.

The best recipe against backlogs? Finish today what should be done today

Backlogs are often homegrown problems of radiological departments, and should be dealt with there. Analyze, diagnose, and find a therapy for the problem. If the department staff is unable to handle referrals and readings, if you are relying on typists who are sick or do not exist at all, if you are depending on dictation software that does not function or the radiologists cannot handle, or if there are simply not enough trained radiologists, the head of the department has to react rapidly and smoothly.

However, in many instances the department of radiology is not at fault, but rather the hospital managers or other bureaucrats well out of harm's way who are not able to understand the work flow and sequence of operations in a department of radiology, even if you prepare and show them flow-charts – diagnostic radiology is a multi-step process not a click-and-go amateur camera system. Usually, their solution is: "Head in sand and sit it out."

Thus, the ball is back in the radiologists' court: become more efficient, only perform necessary studies, and only accept examinations for which you have the personnel. However, do not allow other medical disciplines to take over and perform imaging examinations – with the following exceptions: insertion of a device under x-ray screening. Here, a physician experienced in the procedure uses x-ray imaging, commonly fluoroscopy, to place the device accurately – and places a report of the procedure in the patient's files immediately afterwards. A similar exception from the rule holds for the treatment of bone fractures and other orthopedic problems where fluoroscopy is necessary [1].

However, it doesn't hold for chest x-rays required by the surgeons or orthopedists. I know of a German hospital whose department of radiology had to hire a *locum tenens* to read a four-years backlog of chest x-rays recovered from the department of surgery. It was difficult to find a radiologist for this task, but Europe has open borders and one day a foreign radiologist arrived with his trailer home, settled down in the parking lot of the hospital, and after some weeks the job was done.

During the last five years, backlog scandals have also shaken Ireland and Great Britain. An Irish hospital had a backlog of more than 57,000 unread studies and, in addition, thousands of unprocessed GP referral letters. Many images could not be found any more. An investigation pointed to “problems with governance, management and administrative practice, as well as a shortage of radiology staffing at the hospital”.

A recent review of the London-based Royal College of Radiologists describes a projected national picture of about 300,000 patients who are currently waiting more than a month for their x-rays to be read and about 6,000 patients waiting more than a month for the results of CT and MRI scans.

The College asks: “What are the implications?" – and answers:

- Potential to cause delays in diagnosing cancer and other serious illnesses;
- anxiety for patients waiting for test results;
- wasted journeys for patients expecting test results;
- waste of time and other resources, not just in radiology but throughout the healthcare system [3].”

A possible “scientific” solution I found in a German radiological *Dr.med.* thesis: According to the

statistics applied the median image reading time per patient study is 76 ± 77 seconds; as I understand this, the studies of some patients can be read in negative time which would be perfect to kill backlogs [4].

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. Address the backlog issue or you will sink. Rinckside 2015; 26,1: 1-2.

Relaxing times for cardiologists

Peter A. Rinck

The holy grail of diagnostic imaging is non-invasive tissue characterization and the external identification of human cell structures and organ function, if possible without even touching the body. Magnetic resonance was meant to bring this most sought-after achievement in medical diagnostics: T1 and T2 relaxation times were to be the key to it.

The use of relaxation times for medical applications was introduced in 1955/1956 by Erik Odeblad and Gunnar Lindström. Since then, this idea has occupied the minds of many researchers. Nearly 20 years after Odeblad's description, a New York physician, Raymond Damadian, patented a method for relaxation time measurements in malignant diseases.

Unfortunately for him and mankind it didn't work.

What is T1 and which factors are influencing it? T1 depends on several parameters, among them the resonance frequency (field strength), temperature, the microviscosity of observed spins, the presence of large molecules, and the presence of paramagnetic ions or molecules. The precise calculation of true T1 and T2 values is extremely complex and *in vivo* almost impossible.

When we started creating synthetic images based on the three main contrast parameters in MRI, viz. T1, T2, and proton density, in the early 1980s [1] and the image simulation software "MR Image Expert" some years later, these parameters were based on time--consuming, but precise data acquisitions and exact calculations. They allowed the creation of outstandingly good simulations of MR images – but still simulations. More details can be found in textbooks, for instance online at "Magnetic Resonance in Medicine" [2].

Researchers have left no stone unturned: *In vivo* relaxation time measurements based on MR imaging have been tried out over the years by a large number of people, who have measured relaxation time values for tissue characterization in the brain and all over the body, including 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 plotting methods of relaxation curves, inherent variability of tissue composition, partial volume effects, and interobserver variability. Researchers realized that it is futile to measure a point or a region of interest because too many different components such as tumor, fat, fibrotic or necrotic cells, small vessels, calcifications, and other structures can be found within a volume of interest.

In addition, T1 and T2 values of diseased cells overlap with those of other pathologies, edema, and sometimes normal tissue: T1 and T2 of normal tissue change with age and hormonal cycles, breast tissue being a good example.

When absolute T1 or T2 values were finally deemed not leading anywhere, 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.

Then, after more than 30 years of unsuccessful trials, the cardiologists arrived!

Then, after more than 30 years of unsuccessful trials, the cardiologists arrived. They would like to distinguish fibrotic, inflammatory, and infiltrative cardiomyopathies, myocardial edema, as well as normal myocardium from each other and quantitatively diagnose myocardial fibrosis.

Since the acquisition of quantitative tissue data from a beating heart has to be very fast, they rely on a modified pulsed NMR sequence proposed by David C. Look and Donald R. Locker in 1969. MR imaging

did not exist at that time, and Look and Locker used their time-saving one-shot method for NMR spectroscopy instead of the conventional methods to measure the T1 relaxation time. The spectroscopic "LL" method was within 10% of the conventionally calculated value [3].

In the 1980s, the method was further developed for MRI by Graumann and his colleagues [4]. Others followed. The modified sequences for cardiac MRI used today are called MOLLI [5] and ShMOLLI [6]; some different pulse sequences, e.g., SASHA and SAPPHIRE are also being tested.

The support is enthusiastic, several thousand papers were published during the last ten years and approximately 150 patents were applied for.

Most cardiac T1 papers are based on mathematical simulations and hypotheses or speculations. Although in many publications there is a lot of talk about accuracy and precision, a major problem of MOLLI and ShMOLLI is their inaccuracy and their errors. The MOLLI scheme does not calculate true T1 but apparent T1 values for which a new, non-fitting name was invented: T1* (T-one star). In review papers [7, 8] more pages are filled with explanations of errors, euphemistically dubbed "confounders", than about real measurements and comparative results. Just reading these papers clarifies the futility of the method.

Many researchers seem not to be scientifically literate, lacking understanding of basic and established principles of physics and engineering. Far away from solid magnetic resonance science, mainstream cardiac MR research seems to develop into a kind of pseudoscience aiming at rather vague T1* MOLLI numbers. If the values measured cannot be reproduced on different days or on different machines of the same model they are useless for science and medicine.

Still, there are no comparative studies of such sequences and true T1 and T2 measurements. Instead, the developers and researchers continue to discuss infinitesimal refinements and modifications of their sequences.

■ At a meeting in January, Robert N. Muller, professor emeritus of the University of Mons and former head of one of the world's most prestigious centers for NMR relaxometry and MRI contrast agent design, dismissed the studies as scientifically without foundation and stated: "If you don't measure T1, you cannot talk about T1-mapping. It measures MOLLI time and is MOLLI-mapping. If you can't be precise from the onset, don't continue."

Even measurements of true T1 and T2 relaxation times allow only global statements but no clear tissue characterization or grading.

From *dernier cri* of cardiological technology to *déjà vu* of recurrent failure of T1-mapping is a short step.

■ Where is the value or added value for research and patients? I don't see any. Churning up and out numbers is meaningless. There is a wide range of "normal" values, the range of normal myocardium at 3 T stretches from 1000 to 1300 ms; but hardly any "apparent T1 values" of pathologies were published. It is foreseeable that measurements of pathologies will overlap with each other and those of with normal tissue. One cannot trust these numbers. However, the clinicians just seem to be in awe of the pulse sequence researchers – because they don't understand anything; most of them lack the background in pulse sequence design, biochemistry or metabolism.

I found the following well fitting statement in a recent editorial of a cardiology journal: "Cardiology journal editors have adopted a laudable policy of intentionally reporting negative studies in humans, viewing these negative results as important contributions to the understanding of the field. This may very well include high-ranked journals such as the JACC or the EHJ." [9]

However, one should also try to find some research that contributes to the positive furtherance of cardiology (and radiology).

■ This article uses some text passages I published more than 20 years ago in *Radiology* and elsewhere. Not much has changed since [10].

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. Relaxing times for cardiologists. Rinckside 2015; 26,2: 3-5.

Does ECR increase patient survival rate?

Peter A. Rinck

Spring is in the air – the conference season has arrived. Meetings of all major and minor medical disciplines take place. And some of us will be there.

Congresses of and for cardiologists are not that different from those of radiologists, in particular the major ones. Of course, our brothers are richer than we radiologists, but we are holier than them. Patients with a cardiac problem are usually more afraid of death than radiological patients; therefore they pay more.

Cardiologists' congresses are a mixture of sales shows, continuing education, research news (called "science"), social affairs and company news: lunching and lounging. This year's European cardiologists congress will be in London; the global one next year in Mexico. On top of it, there are national and regional conferences by the ton, the German one in Mannheim … of the oldest and biggest cardiological society in Europe (they say).

It seems as if cardiological congresses are beneficial for heart patients. What about radiological congresses?

However, the side effects or fringe benefits may differ between cardiological and radiological conferences: Not necessarily those for the physicians, but those for their patients. It seems as if cardiological conferences are beneficial for heart patients.

Among the tens of thousands research articles published every year, there was one dealing with the influence of scientific meetings upon the survival of patients. It was published in JAMA this February [1]. The authors examined for a period of ten years the outcome of cardiac emergencies in patients admitted to a number of hospitals in the United States during the periods of two national cardiology meetings, and then compared them with identical non-meeting days in the three weeks before and after conferences. The study included major teaching hospitals and non-teaching hospitals. For this purpose, the authors performed a retrospective analysis of 30-day mortality among patients hospitalized with acute myocardial infarction, heart failure, or cardiac arrest.

Their published results: High-risk patients with heart failure and cardiac arrest hospitalized in teaching hospitals had lower 30-day mortality when admitted during dates of national cardiology meetings. High-risk patients with acute myocardial infarction admitted to teaching hospitals during meetings were less likely to receive percutaneous coronary intervention, without any mortality effect. No mortality differences existed for low-risk patients in teaching hospitals or high- or low-risk patients in non-teaching hospitals.
In other words, major conferences are a win-win situation for both patients and doctors. The doctors get some days off, and the patients survive.

There should be a study like this for radiologists and their patients during the ECR. If the results are similar, ECR might attract more radiologists to Vienna and leave happy patients at home.

■ Please note: The part on radiology is a satire, although the paper in JAMA is real.

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. Does ECR increase patient survival rate? Rinckside 2015; 26,3: 7.

Functional charlatans

Peter A. Rinck

PRO ACADEMIA EMRF THE ROUND TABLE FOUNDATION

This year, functional brain imaging celebrates its 25 anniversary. Basically, *functional imaging* or *fMRI* is a misleading term because it is mainly used for the depiction of changes of local blood supply in the brain activated by specific stimuli. In contrast to EEG and MEG, it does not provide a direct measure of neural activity [1].

In 1990, Dr. Jack Belliveau and colleagues published the first observation of the stimulation of the human visual cortex by magnetic resonance imaging [2]. They watched the first pass effect of a contrast agent after bolus injection to demonstrate changes in cortical perfusion upon activation with a photic stimulus. However, this approach required two contrast agent injections. This disadvantage was resolved by the demonstration of brain activation using the blood oxygenation level-dependent (BOLD) effect by Dr. Seiji Ogawa [3], also in 1990. Over the last few years, this very elegant technique has led to a fast proliferation of fMRI all over the world.

A real explosion of medical, paramedical, neuro--social and neuro-economic publications ensued. The outcome of commercial applications went through the media and the yellow press: of the German automobile manufacturer trying to find out which car design attracts more men, of a major US soft drink company checking the most bewitching taste … you name it. fMRI is even used as a lie detector: No science, just fiction.

Soon, research in this topic was in the hands of amateurs playing with MR imaging and functional MR, lacking the background in physics, chemistry, and medicine – and the scientific rigor necessary to work in a new field. They saw pictures with colorful enhancement of the brain and overnight became cognitive social neuroscientists, new-age phrenologists – because color pictures can be interpreted by everybody. But nobody bothered to ask: what is normal and what is pathological – or, what is an artifact?

Unfortunately, BOLD studies have a very low sensitivity and signal-to-noise ratio. The signal changes related to cerebral activation are close to the noise level and therefore numerous signal processing and, beyond this, statistical techniques are used to overcome this handicap. Many blood flow alterations described in functional brain imaging rely on signal-intensity changes of less than 5%. More so, T2* to estimate blood oxygen saturation is only one singled-out factor; oxygen supply and saturation are dependent on several additional and independent parameters, among them lung and heart function, vessel size, and hematocrit.

Even the inventor, Seiji Ogawa, added some very detailed and critical remarks about the techniques in a review article twenty-two years after the first description of BOLD [4].

As Gustav von Schulthess pointed out in the early days of fMRI:

"... a caveat for fMRI: it is a very interesting technique but signal changes are but a few percent. Hence, the method is technically demanding and 'the threshold of nonsense production is low' [5]."

An outstanding proof of his claim can be found reading one of the most famous publications in this field published in the last years: the fMRI story (at 1.5 Tesla) of a dead Atlantic Salmon (Salmo salar) [6]. Here are some excerpts.

From the *Methods Section*: "The task administered to the salmon involved completing an open-ended mentalizing task. The salmon was shown a series of photographs depicting human individuals in social situations with a specified emotional valence, either socially inclusive or socially exclusive. The salmon was asked to determine which emotion the individual in the photo must have been experiencing. The photo stimuli were presented in a block design, ..."

The beginning of the *Results Section*: "A t -contrast was used to test for regions with significant BOLD signal change during the presentation of photos as compared to rest. The parameters for this comparison were $t(131) > 3.15$, p(uncorrected) < 0.001, 3 voxel extent threshold. The relatively low extent threshold

value was chosen due to the small size of the salmon's brain relative to voxel size. Several active voxels were observed in a cluster located within the salmon's brain cavity. The size of this cluster was 81 mm³ with a cluster-level significance of $p = 0.001$."

This article presents in a really imaginative way the often overlooked main problem of fMRI. If the fMRI study of the little brain of a dead fish appears to give cognitive social scientists indications of brain functions and answers to some of their puzzles, how much confidence can we have in studies that follow the same or similar paradigms in far bigger live human brains? With their very catching experiment and a later paper, Bennett and collaborators stressed how pivotal it is in fMRI to apply statistics properly and scrupulously because random noise may yield spurious results in the acquired images [7].

■ Some years ago I pointed out that the number of good medical – among them radiological – papers is less than one percent of all papers published. Much of the rest is without rhyme or reason, more chaff than grain. It seems even worse in fMRI. For that reason, good papers are laudable – and who cares about bad papers, as long as they disappear in the sea of scientific trash? Still, the scientific reputation of fMRI research is poor, and the charlatans ruin the standing of the serious scientists in the field.

Sadly, a few papers are bad *and* ugly.

Sadly, a few papers are bad *and* ugly. During the last years I followed the publications of a group of authors that now should be marked as dubious, worrying, and malign. These people did something similar with presumed pedophiles as the others did with the dead salmon. They tried to identify pedophiles by changes of BOLD effects after showing the study subjects pictures, in this case of nude adults and children. For these experiments, the authors used small heterogeneous groups of presumed pedophiles attracted to either boys or girls, and similarly sized comparison groups of healthy heterosexual and homosexual men. They found BOLD activation when applying (uncorrected) thresholds, and claim to be able to distinguish between pedophiles and non-pedophiles; their accuracy is 95% [8].

In a study published two years later about stimulation of what appears the same study subjects, this time shown pictures of adult and children faces, whole sections are poorly written and incomprehensible, the materials and methods section is irreproducible, the statistics are unsound and not applicable, and all results are probably false positives [9]. More so, there are always the caveats of very small comparison groups and the lack of knowledge of what is normal.

The problem is not the bad research performed; this is common; it's the ugly and deeply disturbing conclusion, where the authors turn dilettantism into a weapon:

"Functional brain response patterns to sexual stimuli contain sufficient information to identify pedophiles with high accuracy. The automatic classification of these patterns is a promising objective tool to clinically diagnose pedophilia." [8]

This conclusion is, politely phrased, highly problematic. Using fMRI as a biomarker (i.e., a detector) for pedophilia is unethical – because the technique does not allow to identify pedophiles. The employment of fMRI to diagnose pedophilia may have unforeseen consequences. It is a misuse and abuse of medical imaging. None of these articles has the rock-solid foundation which would be necessary for the conclusions the authors draw at the end.

The impact of such papers might be hurtful and detrimental, even deadly for some members of our societies. Readers of the articles might draw conclusion and take actions that are not appropriate, taking for granted that "scientific" publications even in obscure journals can be taken as the last truth.

■ The authors (Ponseti et al. from Kiel, Siebner from Copenhagen, and Beier et al. from Berlin) and the ethical committees of the respective universities as well as the editors and reviewers of the journals the articles were published in are responsible for possible harm caused. The authors' claims are false and have to be actively countered as forcefully as possible. The papers should be retracted.

Note: Writing this column has taken a good year. References 6, 8, and 9 have been retrospectively peer-reviewed by four leading scientists in the field. All of them thought that paper 6 is one of the best papers ever written in fMRI; and all of them rejected papers 8 and 9. Meanwhile, some critique of the two latter papers (8 and 9) has appeared on the Web. It concurs in what is said in this column. More so,

statements that many neuroimaging papers are of inferior quality are also being underlined in numerous blogs, for instance in reference 10, together with a discussion to retract all these papers, *en masse*, because they can be harmful: "Neuroscientists working with such controversial populations need to be especially careful in analyzing their data, and aware of how their work may be used in a broader social context [11]."

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. Functional charlatans. Rinckside 2015; 26,4: 9-11.

MR fingerprinting returns to radiology – and hopefully disappears again

Peter A. Rinck

PRO ACADEMIA EMRF THE ROUND TABLE FOUNDATION

Earlier this year I wrote an article about some cardiologists' scientific shortcomings in imaging science [1]. I happened to write it after I had seen and read a number of papers dealing with rough estimations of relaxation times of the myocardium. The experiments, methods, and results described had gone out of date years ago; even dressed in new clothes they are inadequate and deficient in precision and accuracy.

I know that I laid it on a little thick to make the point, as I often do. It's part of these columns – for instance, to pinpoint scientific or ethical blunder. Some days after publication, I got a response from a good friend of mine, a well-known cardiologist, who politely pointed out:

> "Your negative attitude can be of some help. However, I guess that there are some bright spots in the darkness you describe … Isn't the fact that T1 mapping is not the real T1 of the tissue unknown also to the majority of radiologists? I guess yes.
>
> "Cardiologists and me personally are tempted to use T1 mapping with the hope to repeat the spectacular results obtained by T2* for measuring cardiac iron overload, which is, so far, one of the most useful approaches of modern cardiac medicine (several thousands of patients are probably surviving due to this quite rough measurement). In other words, to be imprecise does not preclude specific use.
>
> "By the way, I guess this would have to be applied to the vast majority of medical papers."

He made me think, and I believe that he is correct in what he says. Thus, at this point, I make a formal apology to my friend, the cardiologist, and all cardiologists. Yet, I still don't believe that their methods are scientifically solid – a charge he seems to accept.

Ignorance in matters concerning MRI was, for instance, revealed in a paper by Dan Ma published in *Nature* in 2013 [3] – including a telling mistake. The cardiologists invented a new relaxation time T1*, whereas the paper in Nature cites a newly coined radiological relaxation time T-star 2 which should read T2-star, T2*. The term was first used by Warntjes some years earlier [4]. Nobody seems to have realized this mistake and it multiplies in "scientific" copy-and-paste papers.

When you reinvent the wheel, always consider the flat tire problem.

Ma proposes a method called "magnetic resonance fingerprinting". The only true novelty was the acronym: MRF; there are hundreds, perhaps thousands of papers dealing with this issue, and the European Union supported numerous research activities on the topic. As for the methods: they have been described decades ago; and rejected. We called it "the holy grail of MR imaging", Ma describes it as a "robust, fully quantitative multiparametric acquisition [that] has long been the goal of research in MR".

The resurrection of multiparametric MR imaging and the MR fingerprint were announced with the same words in an ECR statement written by Siegfried Trattnig representing the ESR Subcommittee on Imaging Biomarkers [5]. They summarized their claims in the following key points:

- MR fingerprinting (MRF) is a new approach to data acquisition, post-processing and visualization.
- MRF provides highly accurate quantitative maps of T1, T2, proton density, diffusion.
- MRF may offer multiparametric imaging with high reproducibility, and high potential for multicenter/ multivendor studies.

A peer reviewer would have rejected this "statement" immediately: it is not a new approach, even not a new name, only a new acronym; and as for accuracy and reproducibility, the authors should come up with a proof of concept: statistics, look at the influence of

noise, reproducibility on the same patient in the same conditions. I am sure it is impossible to extract stable and robust parameters from those kind of multifunctional data because we and others have tried more than 30 years ago, with more robust methods than today and, when this didn't work, with multispectral analyses [6]. When you reinvent the wheel, always consider the flat tire problem. The cardiologists are not to blame for their limited knowledge of magnetic resonance basics. However, I expect that the leaders of specialized magnetic resonance centers would know. I also understand that one of their major worries in managing such a center is to get money to run the institute, sometimes whatever it costs – in this case scientific creditibility.

On the other hand, as so often is the case, the entire procedure and its possible consequences have not been thought out through. Quantified data will gain legal status, even if they are woolly. Lawyers will grab these numbers and start suing, as they did with data from diffusion tensor imaging [7] – because they will find out that patients were not treated according to the "robust, fully quantitative multiparametric data." Thus, a little more humility regarding such data would be fitting before propagating "fingerprinting".

Or, as Giovanni Guareschi's protagonist Don Camillo once said: "It is too much knowledge which leads to ignorance, because from a certain moment on people only see the calculable part of things. And the harmony of numbers becomes their god". [8]

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. MR fingerprinting returns to radiology – and hopefully disappears again. Rinckside 2015; 26,5: 13-14.

Max Factor – for the beauty of your curriculum vitae

Peter A. Rinck

Max "Make-up" Factor was one of the most famous developers of cosmetics in the first half of the 20th century, and had a reputation for being able to enhance and maximize the outer appearance of, in the beginning, mostly movie actors and actresses: to make them attractive and beautiful. His slogan was: "Glamor is created."

People do strange things to try to increase their attraction, sex appeal, and social position.

"Max" Impact Factor is the correlate of all this in certain academic and management circles. I have written earlier and in detail about it [1]. The IF, as it is known to "insiders," is simply the number of quotations of a journal per article published within a certain period. It is not a measure of the impact or even quality of a journal. There is no scientific relevance of accumulated citations. Still, many editors and publishers consider the IF as a "rating"; journals fight and beat each other in the ratings – like television stations with their soap operas.

More so, there is absolutely no connection of this factor with the scientific relevance of the authors of articles published in IF journals.

Already the calculation method of the IFs is iffy. There is an arithmetic problem and there is a statistical problem. The rules of rounding recommend one decimal place more than the raw data, but Thomson rounds to three (i.e., 100 divided by 30 = 3.333, but it should be 3.3). I guess its marketing department has decided this looks more precise. As for the statistics and the selection, read the article by Roediger published in 2013 [2]. Manipulations such as coercive citation [3] and cheating, retraction of publications because of scientific misconduct, scientific decline of journals with high IFs, as well as social pressure, and manipulation and string-pulling are nicely summarized by Brembs et al. [4], with an excellent list of references. There is without doubt a certain amount of marketing and sales hidden in the grooming and preening process of certain journal's impact factors, helped by the artificial and bizarre inclusion and exclusion schemes of articles and citations.

Still, many people believe in these factors zealously and dead earnest; it says a lot about them. Others, I suspect, merely drift with the IF numbers, not caring what they really mean (or don't mean) because they allow them to make judgments and decisions without having to painstakingly deal with a true evaluation of a publication or an author. The power of seduction to rely on the IFs seems inescapable.

Their decisions can be compared with looking out of the window: If one candidate drives a Mercedes and the other one rides a bicycle, of course the Mercedes driver should get the job or grant, and those people believing in Thomson Reuters' impact factors and making decisions based on them prefer Mercedes drivers. Bicycle scientists stay where they are. Reviewers and evaluators who react like this lack academic ethics and are lazy and tiresome and unsuitable for such selection processes.

Journal impact factors are promotional instruments for journal publishers and a goldmine for Thomson Reuters – nothing else.

Journal impact factors are promotional instruments for most journal publishers. Sold by the North American mass media conglomerate Thomson Reuters, they play with the fascination of humans to become powerful, rich, and famous – and to get something cheap by cutting corners. They also rely on the ignorance of people with a limited understanding of the impact factors' background, among them science managers, administrators, and politicians who like to talk about IFs and are the best salespeople for Thomson Reuters.

A warning hint for those who still do not understand; there is a reaction and a movement against Thomson's IFs. Referring to "personal" impact factors of publications of a single applicant or a group – be it for grants or for positions – might have a rather negative outcome and be counterproductive. Such applications might be excluded at the very beginning of

the selection process. It is also rumored that proposals for major prizes and awards are tacitly passed over if impact factors are mentioned or cited.

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. Max Factor – for the beauty of your curriculum vitae. Rinckside 2015; 26,6: 15-16.

An expensive dilemma: Tablets versus textbooks

Peter A. Rinck

Printed medical textbooks are dead, e-publishing is the future. That's what some people think, but the electronic format is not always best for teaching and learning. Certain kinds of publications are appropriate for e-publications, but others need to be in print.

The starting point. To use a real-life example, let me tell you about our very successful basic textbook on MRI. Since the mid-1980s, new print editions were published every four or five years. Five years ago, the sixth edition was turned into an e-learning textbook. One and a half years of demanding work resulted in a new website with about 320 pages and several hundred figures and animations. Meanwhile, two more electronic editions have followed. The print edition was translated into six languages, the electronic version is being translated into Spanish and Chinese.

The bookshop price of a copy of the last English print version was around 120 euros. The electronic version is free because we believed that a free and easily accessible textbook would be beneficial for everybody in the field [1].

In the foreword to the e-book I wrote:

"We like books – printed on paper, if possible with a beautiful hardcover binding. Thus, putting one of the standard textbooks on the Internet was a challenge for us. We hope that the looks of the real textbook have not been lost completely – and, at the same time, that the advantages of e-learning bear fruit."

The brave new world of e-publishing. The reasons for the change from print to web were the commonly heard arguments: e-books and texts are cheaper, faster, easier to make and environmentally better. If one has an existing infrastructure to create educational material, as we had, you also need neither a publisher nor distributors – both are very costly.

Digital publications of all kinds are taken for granted to be the concept of the future, printed books are considered outdated. However, after these last years I started wondering. Although layout-out and printing processes have also gone through rapid changes, the final result, the printed book, is still the same. Creating an e-textbook in Hypertext Markup Language (HTML) involves far more effort, time, and money than a printed book. Besides, hard- and software for electronic publications change every year; it's a typical unstable throwaway society technology and will remain so. Do the advantages of the final product justify a close to seven digit project budget?

An attempt to come to terms with the topic was published some time ago in the monthly *Scientific American* [2], and an in-depth review of printed versus electronic books was written by Valerie A. Moore as a master paper in library science in 2014 [3].

What we learned the hard way was partly thrilling, partly disillusioning.

The lessons. What we learned the hard way was partly thrilling, partly disillusioning. First, contents and layout of a printed textbook have to be adapted for e-learning. To facilitate reading from a computer screen, sentences have to be shortened and additional paragraphs introduced. E-publications are not necessarily for simpler minds, but they are processed in different parts of the brain. Figures have to be newly fitted, scrolling pages should be kept at a minimum. On the other hand, animations and short videos can be added, but they are costly.

Feedback rapidly made clear what others had already described in recent years: Even with high-resolution screens, reading is more tiring and contents are forgotten faster. Reading from a screen tires one's eyes; headache, muscle tension of the neck and back, and blurred vision are typical complaints of people spending a long time in front of any screen. Users seem to screen the text, but don't read it in depth. Now and then they move to other programs, reading e-mails or newspapers or playing games. Their concentration is split, not focused.

Using and owning. The personal relationships to books and e-books are different. Physically, books on computer screens are temporary and bodiless. Readers might not be able to recreate the text five years from now or even tomorrow on their machines, nor on a different machine. Even on the same computer, text and figures change according to the software used. One doesn't own a textbook on computer; usually one pays for a license to read; even if the files are downloaded they are here today, perhaps gone tomorrow. If the vehicle necessary to read the textbook breaks or runs out of electricity, the contents and notes are gone.

Books in their traditional paper style don't change, the text doesn't disappear and doesn't require a complicated carrier – and they can easily be archived. Archiving computer files for more than a few years is difficult and expensive. Therefore a whole industry has developed around data archiving.

Differences to take into account. The human brain processes and reacts differently to printed books and to text on screens. Although the text and figures of a printed book and an e-book might be the same, the reader does not extract the same information from them.

It seems as if long texts are easier navigable when published in books. As a side effect, books allow readers to find a physical satisfaction, both hapticly and tangibly, sometimes even in smells and the general craftsmanship of books. More so, books have an easier topography; their mapping is clearer for the human mind. One can go forward or backward just by flipping some pages. People easily lose the overview of the entire book when it is turned into an e-book.

Which medium is best? There is a multitude of studies from all over the world examining and highlighting people's likes, dislikes, and objections to certain aspects of reading texts from computer screens. Of course, most of the responses researchers got were subjective, for example that many people consider reading and learning from a book as more serious than reading a text on an e-reader, tablet, or regular laptop or desktop. However, can one really play one medium off against another?

Valerie A. Moore summarizes in her thesis: 'Some readers seemed more likely to trust information they read in print than in electronic form. Print's immutability and material stability helped reassure them that the information could not be altered surreptitiously and would be accessible in the future.

'Print was preferred for reference materials or "heavier" reading by some as well, primarily due to its physical structure that allowed readers to flip back and forth through the pages ... The focus inherent in print's self-contained pages, too, facilitated learning.

'For others, however, the immediate access to supplementary information enhanced their ability to learn, so they preferred digital text for serious reading.'

In this context, however, it is interesting to observe that paper use has increased nearly linearly during the last thirty years. To not lose the information, people print notes, e-mails, protocols, all kinds of text they see on their screen. The "paperless office" has turned into a fairy tale.

Similarly, sales of printed book versions of both fiction and non-fiction books are said to rise after people have read parts of e-books.

Personal conclusions. Which consequences did we draw from our observations? Certain kinds of publications seem to be appropriate for e-publications, others rather for printed publications. E-publishing is popular and fashionable. Yet, it's questionable whether it fulfills its declared objective in teaching and learning. What is and will be the best vehicle for certain reading and teaching/learning applications remains unclear at present. The professor/teacher plus textbook combination is proven over centuries, in particular if both professor and book are good.

For the very limited sector of scientific textbooks it is clear that people don't read them entirely on screen to acquire fundamentals of a certain topic. After following more than half a million page clicks over a continuous period of time, I clearly understand that, in this case a magnetic resonance e-textbook – and most likely other e-textbooks too – are not used for in depth learning.

Will we go back to a printed version of the magnetic resonance textbook? Perhaps. But only parallel with the (or an) e-version. It's also a question of price, both in production and for the reader, as well as of readers' reactions and feedback.

To give this column an electronic touch at the end: There is a beautifully Spanish-made video about books [4]. It's short. You should watch it.

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Rinckside, ISSN 2364-3889

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

The calamity of medical and radiological publications

Peter A. Rinck

PRO ACADEMIA EMRF THE ROUND TABLE FOUNDATION

The recent Volkswagen scandal reflects a general trend that, most likely, is as old as mankind. It's a typical confidence trick: Company engineers faked the exhaust results of more than 11 million of their diesel cars.

They were found out by somebody who checked their measurements and tried to reproduce them: the measurements were wrong. Instead of developing a better diesel engine, some Volkswagen engineers invested a lot of energy and enthusiasm into sophisticated software faking *clean air*.

There are numerous facets of this affair that also apply to medicine and radiology; let's once more look at a very important one: publications in journals, both original research, but also review papers. During the last 20 years I have written a number of columns on many aspects of radiological and scientific publications; I have re-read them before writing this comment to not repeat what I said before [1-7]. However, a lot of arguments should be repeated, over and over again – until there is a reaction. The law won't or can't touch the culprits; we have to try to redress the problems ourselves.

Reproducibility of results is one of the major prerequisites of good scientific papers. Articles whose methods cannot be replicated are not scientific papers and should not be accepted for publication.

Reproducibility of results is one of the major prerequisites of good scientific papers. My estimation is a majority of all medical research papers cannot be reproduced by other investigators because there is no clear description of the methods used. The cause in most cases is lack of the bare fundamentals of research – dilettantism is common at most universities, but also misconduct, manipulation of data, or even straightforward fraud. Plagiarism is still widespread, though it seems to be on the retreat.

Many people have completely lost their faith in medical research, even if the results are published in Science or Nature. Or Radiology. There are certain "excellent" institutions whose publications are known to be balderdash.

Last year, the Lancet – a well-known British medical journal – published a series of five articles on increasing value and reducing waste in biomedical research. In an abstract of one of these papers, the authors point out:

"In this report, and in the Series more generally, we point to a waste at all stages in medical research ... Studies of published trial reports showed that the poor description of interventions meant that 40-89% were nonreplicable [8]."

Papers whose methods cannot be replicated are not scientific papers. They should not be accepted for publication. This means the majority of radiological papers could be rejected before review. This would be an approach to start cleaning up the explosion of research papers and journals.

However, hardly anybody is interested in decreasing quantity and increasing quality. The problem is not particularly new, has been discussed often, and everybody is against it – in theory. However, the financial incentives are too high for everybody involved. On the one hand, there is the anxiety about the personal future of the researcher, about the survival of labs, departments, even universities. This includes journal editors who in most cases were selected by the publishers and thus show an indifference and lack of moral courage to speak up for balanced and honest scientific publications. On the other hand, there are state and EU administrations, and – most important – the publishers making money.

The publishing houses count among the main culprits of the decay and decline of scientific publications.

The Lancet, for instance, used to be a solitary outstanding journal; nowadays there are 11 different

subdiscipline editions of the Lancet, pushed into the market by one of the major publishing houses in medicine: Elsevier.

Another publisher, Wiley-Blackwell, had a 2015 fiscal year revenue of US$ 1.8 billion; research journals alone delivered 4% revenue growth for the year.

However, there is a clear loss of journal quality due to internal restructuring during the last few years. To achieve higher profit margins and increased shareholder value, Wiley-Blackwell has changed priorities from quality scientific editing to outsourcing, cutting payments to qualified staff, and turning to mass production by publishing an ever-increasing number of journals. For the publishing industry, scientific journals exist for the sole purpose of profit, not for the furtherance of knowledge or distribution of scientific information. In many instances, quality is out, quantity is in, although the explosive increase of pulp science (fiction) papers is prone to kill the entire established publishing industry.

Wherever there is easy money, there are copycats. Publishers and editors of "predatory" journals promise immediate peer-reviewed open-access publication on the Internet – if the authors pay a processing fee [9]. Although many of the "predatory" journals are the dregs of the market, they are a growing competition of the established publications.

Thomson Reuters Impact Factors, the halitosis of the publishing industry, has substantially contributed to the negative tendencies in research publications, appealing to greed and vanity – which moves some researchers to cut corners, fabricate, or fiddle with results, and inflate the list of authors.

How can one stop this trend? Do we really need all this industry around research publications? Major publishers who believe that financial or quantitative growth is the center of their business will not change, nor will those parasite enterprises that pop up all over and pretend to publish peer-reviewed journals on any discipline under the sun.

Many universities have their own publishing branches. Why can't they or other scientific institutions start publishing honest and solid journals – and guarantee the quality standards every scientist wants? Many universities have their own publishing branches. Why can't they or other scientific institutions start publishing honest and solid journals – and guarantee the quality standards every scientist wants? Or, why not create publishing cooperatives – they also could assure the ideals of scientific publishing, perhaps even better than universities.

To make an important point at the end: We should never forget that most engineers at Volkswagen are reputable, as are most researchers in medicine, radiology included.

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. The calamity of medical and radiological publications.. Rinckside 2015; 26,8: 21-22.

Gadolinium – will anybody learn from the debacle?

Peter A. Rinck

PRO ACADEMIA EMRF THE ROUND TABLE FOUNDATION

For some months I have been following with interest the uproar about the finding of gadolinium deposits in brain tissue of some patients after serial MR examinations with nonspecific gadolinium agents.

The news broke when some radiologists saw high signal intensity stemming from the pituitary gland on T1-weighted MR images – on non-enhanced images. However, the patients had undergone several enhanced studies earlier in their life [1-3].

It is not clear whether gadolinium is still bound to the chelate of a contrast agent, whether it's elemental, or in another, newly formed compound; the latter seems most likely. There is strong evidence that the deposit of gadolinium can be traced back to the linear agents gadodiamide (Omniscan) and gadopentetate dimeglumine (Magnevist). Both of these compounds have already been involved in the NSF scandal ten years ago but are still on the market [4].

As early as 1988, at one of the first big and independent meetings on contrast agents development for MR imaging, Michael F. Tweedle pointed out that Magnevist could become unstable *in vivo* and release free gadolinium whereas macrocyclic compounds such as Gd-DO3A (ProHance) and Gd-DOTA (Dotarem) remain stable [5]. At the same meeting researchers from the company producing Gd-DOTA presented similar results and stressed the importance of macrocyclic compounds "to minimize the *in vivo* dissociation process and avoid[s] potential biological disturbances produced by the presence of free species." [6]

What happens to free gadolinium in the human body?

During the early preclinical development of Magnevist, Weinmann and his co-authors [7] compared the pharmacokinetics of Gd-DTPA and of gadolinium trichloride in rats. 80% of Gd-DTPA was excreted from the organism in urine within three hours, after seven days 90% of the dose was recovered in urine, another 7% in the feces. Less than 0.3% was found in the body, with 0.08% detected in the liver and 0.1% in the kidneys.

In the case of free gadolinium (i.e., gadolinium trichloride) only 2% was excreted after seven days. The rest remained all over the body, mostly in the liver and in the spleen, one sixth elsewhere. The conclusion was that chelates such as DTPA can be extremely effective to remove the highly toxic but diagnostically very helpful gadolinium from the body.

However, if the chelate doesn't work properly, patients might be at risk.

A major review on metal ion release from paramagnetic chelates (entitled: *What is tolerable?*) published in late 1991 ended with the sentence [8]:

"Although MRI contrast agents are unlikely to be administered repeatedly in patients, which could result in accumulation of metal ion, the long-term effects of such potential deposition have yet to be demonstrated."

Only two percent of free gadolinium was excreted after seven days. The rest remained all over the body …

Two years later, the results of animal experiments were published [9]:

"Although intended for single administration in patients, gadodiamide injection has been studied extensively in a range of subchronic studies in rats and monkeys. The compound was well tolerated in monkeys even when administered at doses up to 1.25 mmol/kg daily for 28 consecutive days. In rats, significant toxicity occurred only at high doses ... the pattern of toxicity (involving the stomach, testes, and skin) suggested a disturbance of zinc metabolism."

However, only rats injected with 50-fold the recommended clinical dose three times a week for three weeks developed severe lesions.

The amount of gadolinium one needs to enhance contrast in pathologies on T1-weighted MR images is minimal – particularly compared to the amounts of iodine needed for x-ray contrast agents. Nearly everybody believed what they were told: There were hardly any acute side effects; in general, "gado" is safer that iodinated x-ray contrast agents – which is true. As always with drugs, the dose and the galenics make the distinction between poison and remedy.

My first encounter with what would become Magnevist happened more than 30 years ago. At that time independent researchers at universities were more interested in the performance of such agents than in their safety, in particular because the safety was guaranteed by the manufacturers. We trusted the characteristics of, e.g., the Gadolinium-DTPA complex that were presented to us. The challenge was how to apply the compound within the given limits – which was worked out step by step.

Soon the new compounds were used for all conceivable kinds of examinations. One outstanding example is the follow-up of treatment of multiple sclerosis patients – in some instances MS patients underwent contrast-enhanced studies once a month for two or three years. The general attitude for all medical or not-so-medical indications was: "Gado is a dye and can be used repetitively as often as possible."

I remember people in R&D, even companies' leading scientists, complaining that their hints and proposals were pushed aside by the marketing department and the management: "Off-label use is the responsibility of the doctors."

The recommended dose, best enhancement, and MR angiography

On some of the first MR images in animals and in humans parts of the body were highlighted after the injection of Gd-DTPA, but others turned black. The pituitary gland became bright like a streetlight, the bladder dark. The question was: why; the answer was the correct dose to be injected.

Here the manufacturer of Magnevist was cautious and finally agreed upon 0.1 mmol/kg body weight. All other manufacturers followed this recommendation. This dose provides excellent enhancement at low and medium magnetic fields. The reason is easily visible on an animated simulation*.

* www.magnetic-resonance.org/ch/13-03.html#13-03-02

A dose increase beyond the recommended dose may lead to loss of contrast. This is because a T2 shortening remains and can take over primary influence upon image contrast.

Parallel to the nonspecific gadolinium agents, angiographic blood pool agents were being developed because non-enhanced imaging technologies did not fulfill the requirements for high-resolution angiography. The manufacturers anticipated a substantial market because contrast-enhanced MR angiography was to cut a big slice out of the conventional and CT angiography cake. Yet, the development of the blood pool agents was slow and plagued by setbacks.

Then, suddenly a group of doctors proposed the use of the existing nonspecific agents together with special patented techniques and hardware to perform MR angiography. They all underlined that high-dose gadolinium chelates (up to 0.3 mmol/ kg) were significantly less nephrotoxic than iodinated contrast agents [10]. In a textbook of contrast enhanced MR angiography, Martin R. Prince, Thomas M. Grist and Jörg F. Debatin stated in 2003:

"From an image quality point of view, generally the more contrast the better… Gadolinium compounds have no clinically detectable nephrotoxicity. They can be used safely at the maximum dose in patients with renal failure." [11]

Already in a US patent applied for in 1993, one finds the following description:

"The dose of the gadolinium chelate may be within the range of 0.05 millimoles/kilogram body weight to 0.7 millimoles/kilogram body weight depending upon the time required to obtain the image. It should be noted that the dose of the contrast should not be too high such that there may be undesirable toxicity or T2 effects." [12]

Since the companies involved neglected the patents, multimillion dollar lawsuits by the patent holders, then license, patent and consultancy agreements with numerous pharmaceutical and hardware companies followed [13].

Disaster strikes

Then, early in 2006, there was an outbreak of a new disease in Austria: Nephrogenic fibrosing dermopathy, later called Nephrogenic Systemic Fibrosis

(NSF). Single cases had been described earlier, but not attributed to gadolinium:

“NFD was unknown before March 1997 and some authors suggest that the sudden occurrence of the disease in the last 8 years makes it likely that a new agent or technique of examination causes NFD/NSF” [14]. All cases were related to Omniscan.

Among others, Martin R. Prince did an about-face and reacted with a paper describing fifteen patients who developed NSF after high-dose gadolinium-enhanced MR imaging compared to no patient with the standard dose. The conclusion of the paper included the following sentence [15]:

“We recommend using no more than a standard dose of GBCA (0.1 mmol/ kg).”

Shortly after the publication of this article, a letter reached the editor of *Radiology* and was published. The author stated [16]:

“The finding that all patients who developed NSF had received a high dose of a gadolinum-based contrast agent (GBCA), but none of the 74,124 who had received a standard dose (0.1 mmol per kilogram of body weight) developed NSF, irrespective of renal function, is of particular interest …

“Perhaps it is linked to the development of techniques that require the use of higher doses of GBCA, such as contrast agent-enhanced magnetic resonance (MR) angiography. For better visualization, especially of distal and small vessels, double or triple doses of GBCA are often advocated …

“This temporal coincidence may only be incidental, but it is nonetheless suggestive and may help to explain the somewhat mysterious timing of the appearance of NSF.”

This seemed not to be a serious problem for the manufacturers of Magnevist or Omniscan. These contrast agents are still available on the market today. More so, the reaction of the US-American manufacturer of Omniscan against the publication of yet another NSF outbreak in a Danish trial consisted in an attempt to silence the radiologist in charge. He had presented the late side effects of the trial, i.e., death or mutilation of twenty patients. This was brought to the light by articles in *Pro Publica* and the *Sunday Times* [17].

As the English newspaper *The Guardian* reported, GE Healthcare dropped the libel action in 2010:

"Lawyers for leading Danish radiologist Henrik Thomsen said today: 'He will be obviously relieved. Now he won't have to worry about his future financial position, and won't have to keep looking over his shoulder before he says anything.' In agreed statements released today, Thomsen said: 'I stand by my publicly expressed opinion, based on my experience and research on published papers, that there is an association between the chemical formulation of gadolinium-based contrast agents and NSF.' He added: 'It was not my intention to suggest on the basis of the evidence then available to me that GE Healthcare had marketed Omniscan knowing that it might cause NSF.'" [18]

Still, more than ten years after the identification of the culprits, those responsible evade or dismiss the moral challenge they are confronted with, however plunge headfirst into new ones: gadolinium deposits in the brain.

Admittedly nowadays one finds the following warning in the package insert: “Do not exceed the recommended dose of … and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.” Yet, the positions of the US-American Food and Drug Administration and their European counterparts leave conflicting impressions, to say it politely; why don't they stop the sale of Omniscan and Magnevist to protect possible future victims?

Gadolinium deposits don't belong in the brain.

The vultures are already circling in the air and the ambulance chasers flood the Internet with their websites: the lawyers are coming in great number. The motto is: “Are you gadolinium toxic? If yes, contact us.” They are rather clever and business minded. And they will soon find the arguments with which they will milk the manufacturers, the radiologists – and, most of all, their clients. They will argue like this:

> Lack of background knowledge of the radiologists and their incredible trust in pharmaceutical companies; the almighty dollar sign; and use of an inappropriate and unsafe drug, too

high a dose, too many serial studies, too close a study after another, examinations too often without proper indication; and, finally, off-label use.

Debacle is as good a word as any to describe what has happened here; and many of the parties involved try to sweep the problem under the rug: manufacturers, radiologists, and supposedly supervising administrations.

What is the clinical significance of gadolinium deposits in the brain and elsewhere? Nobody really knows. However, it doesn't belong there although at present there is no proof that it is harmful. NSF was a new iatrogenic disease. The (unlimited?) storage of gadolinium in the human body could be but a continuation of this disease. Already the idea attracts all hypochondriacs in town.

The recent events coincide with descriptions of the sudden appearance of gadolinium as anthropogenic contamination in tap water [19]. The cause is the use of MR contrast agents; gadolinium cannot be removed by water treatment plants.

What I am afraid of are possible long-term consequences for all of us.

Important Note: Contrast-enhanced MR examinations have life-saving benefits. I fully support the intravenous application of gadolinium-based contrast agents for diagnostic purposes. This is not an article against contrast-enhanced MR imaging. However, please apply macrocyclic contrast agents and/or agents excreted by both the liver and the kidneys. Even they should only be used if a clear diagnostic advantage for the patient can be expected.

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Rinckside, ISSN 2364-3889

Citation: Rinck PA. Gadolinium – will anybody learn from the debacle? Rinckside 2015; 26,9: 23-26.