MRI Contrast Agents from Development to Distribution to in vivo Dissociation: Can GBCAs Dissociate in the body allowing toxic free Gadolinium & toxic free Chelates to produce acute & chronic poisoning?

Summary

In 1986, two years prior to the FDA approval for the first Linear MRI Contrast agent, the makers of Magnevist Gd-DTPA were warned to produce a MRI contrast agent with a much stronger macrocyclic chelate which fully surrounded the toxic gadolinium metal atom and were much more stable in the body, but these macrocyclic agents cost more to manufacture. Unfortunately based on their original patent in 1981, the makers of Magnevist had already decided to use the less expensive to produce but kinetically unstable linear chelates in their contrast agent. The makers of Magnevist were already five years into the developing and testing of their product, so could changing the contrast chelate now with a stronger more stable macrocyclic chelate be the difference of billions of dollars in profits, especially if they were not first to the MRI contrast market and they had to start over with a new initial drug development application with the FDA? This trend was followed by three other linear contrast drug companies as they entered the multi billion dollar booming MRI contrast business, as they also wanted to get rich quick with their version of a contrast agent, these were known as "Me Too" contrast drugs. Unfortunately, linear chelates only semi surround the atom and form kinetically unstable chemical bonds to the gadolinium atom, which under many conditions in the body like high hydrogen proton concentrations, acidic conditions and competition from existing metal atoms in the body, could dissociate the toxic gadolinium metal from the original contrast chelates faster than the contrast could be fully eliminated. This can result in acute and chronic poisoning from both the free gadolinium ions as well as the dissociated free chelate, which causes death to 50% of rats (LD50) with as little as .07 mmol/kg. In contrast to free gadolinium and the free chelate, when they are bonded together as Gd-Chelate or for example, Gd-DTPA, this forms a less toxic compound with an exponentially higher LD50 of 10 mmol/kg. Dissociated Free gadolinium and dissociated free chelates are roughly 14,000 percent more toxic than the original intact contrast agent based on LD50 alone, which does not include all the functional toxic effects of gadolinium. In addition, in the case of gadolinium toxicity, using the LD50 as a indicator of toxicity can be misleading, since most of the toxic effects that free gadolinium can cause are debilitating functional toxic effects blocking calcium in the body. Gadolinium is a similar size to calcium and the blocking of calcium from gadolinium could happen with only a fraction of a fraction of the LD50, making the toxic effects of gadolinium even more toxic than advertised. This stresses why it is extremely important that these two molecules due not dissociate in the body.

Were the first contrast manufactures just rushing to be the first ones to the MRI contrast marketplace? Were the drug companies more interested in quickly establishing market dominance then insuring patient safety? Did this manufacturing cost saving chemistry decision adversely affect millions of patients? Why did the manufacture of the first linear contrast agent Magnevist, go on to quickly manufacture a new contrast agent using a stronger macrocyclic chelate? And why did they choose to only sell their stronger macrocyclic MRI contrast in Canada for 10 years before bringing it to the US market in 2011, and only after their linear agent was at risk from being removed from the market as the link was made between linear contrast agents and the development of Gadolinium Induced Systemic Fibrosis NSF. NSF is a horrible often fatal side effect of gadolinium poisoning that was estimated to have affected thousands of patients? Did the drug companies quickly manufacture the stronger macrocyclic agents because they knew there was a chance their products would eventually get pulled from the market? Is it now just coincidental that only 2 years later in 2013, researchers found that the linear contrast agents were also leaving toxic gadolinium deposits in a large percentage of patients brains and bodies, even when they had normal kidney function? Then only 4 years later in 2017, the European Medical Association voted to ban all four linear agents as the evidence about the stability of these weak dangerously unstable linear contrast agents became increasingly evident? So, what did the drug companies know back in 1986, and why were you not properly informed by the drug companies, or the radiologists? And after nearly 30 years and over 300 million injections of contrast, how have these unstable linear agents slipped under the radar as they have silently poisoned an unknown number of patients with toxic free gadolinium?

A Brief History:

The first MRI contrast agent Magnevist was invented in 1981 in Berlin, Germany, then gained FDA marketing approval in 1988. MRI contrast agents quickly became a multi-billion dollar profit making add-on for MRI facilities across the world. It was marketed as a non-toxic and safe alternative to CT scans with iodine contrast. Once injected, the contrast is supposed to leave the body within 24 to 48 hours max. Adding contrast to the scans nearly doubles the cost of an MRI to the patient, and most of this additional cost is pure profits to many medical facilities. Most MRI facilities are owned by radiologists or groups of doctors. For decades there has been an ethical dilemma around physicians selling products for financial gain, and this is why generally pharmaceutical sales are kept separate from physicians directly filling prescriptions. The use of a contrast dye is an example of where the ethical line between pharmaceutical sales and doctors' responsibility to patient well being is potentially compromised, as ~60% of all MRI scans have contrast. Doctors and their patients wanted to ensure the best scan is provided without missing any pathology, therefore contrast is often conveniently recommended. But how often is a contrast truly needed?

Most MRI contrasts contain a highly toxic metal called Gadolinium (Gd^{3+} atoms) as the main ingredient. Before gadolinium can be used in MRI contrast and injected into humans, the positively charged tiny pieces of highly toxic heavy metal gadolinium must be electrostatically bonded and fully surrounded by a chelate (which is a compound with many negatively charged atoms that will attract and bond with eight of the nine gadolinium bonding sites. The ninth bonding site is taken up by a water

molecule to create the contrast effect). Gadolinium has no known biological role in the body, and its only route of entry is through an MRI contrast injection. This raises several safety questions that the medical community has not yet fully explored. What happens if the drug manufactures decide to use a cheaper and weaker protective chelate, and one that only semi surrounds the gadolinium atom and has weak flimsy bonds? What happens if that gadolinium breaks free and lodges inside the body and it stays there for a lifetime causing toxic dysfunction to cells? Once in the body, gadolinium can form insoluble complexes that for the most part, do not leave the body by themselves, depositing inside the human body like millions of tiny metal splinters. Unfortunately for many, this nightmare scenario, soon became a reality. The drug companies that created the contrast agents along with the radiology community, made billions of dollars off the injections. But possibly due to their financial conflicts of interest in keeping the linear contrast agents on the market and avoiding lawsuits to keep their shareholders happy, it appeared they were clearly reluctant to fully and honestly investigate about gadolinium poisoning from their own contrast agents. Over 300 million injections of gadolinium contrast have been performed since 1988, and free gadolinium released from these agents have been silently depositing in the body and poisoning an unknown percent of the population of patients. It does appear that Not all, but many radiologists and drug companies just wanted people to think that the toxic heavy metal gadolinium, that they left behind in millions of people and children, is just benign, inert and therefore totally acceptable. No big deal they say “it's just a little toxic metal”, unless of course there is enough free gadolinium released in the body to trigger gadolinium induced systemic fibrosis(NSF), only then will they consider it a problem. NSF is a life threatening fibrosing of the skin and vital organs caused by free gadolinium released from MRI contrast agents. This mass silent poisoning by gadolinium based contrast agents has reached epic proportions and is now a humanitarian relief effort to bring awareness to the general public. Unfortunately this subject matter currently lacks scientific understanding among most physicians, radiologists and patients, partly due to lack of long term research into the effects of gadolinium in the human body, but is well researched and documented in animals studies. Pharmaceutical companies, medical communities including research facilities and medical universities need to join forces to fund research into safer alternatives and to put patient safety at the forefront of MRI

Gadolinium is a stealth toxin because it is very difficult to detect in humans, making it very dangerous, like the poisonous snake you couldn’t see. Gadolinium atoms have about the same ionic radius as the calcium atoms in our body, which allow it to compete for the same receptor sites as calcium. Since gadolinium has a higher mass, a higher positive charge and more binding sites then calcium, when gadolinium does bind to calcium sites, it forms stronger bonds and can stay bound much longer, blocking future calcium from coming in and performing essential physiological functions and possibly causing permanent dysfunction. Many of the toxic effects caused by gadolinium come from this calcium blocking activity. Gadolinium causes profound and very difficult to detect debilitating functional acute and chronic side effects similar to low calcium levels . Gadolinium rarely causes damage to tissue structure until very high concentrations are reached and trigger gadolinium induced fibrosis NSF. Gadolinium induced NSF is a horrible and life threatening condition where the patient's skin and vital organs continue to form scar tissue and become like wood. Since gadolinium poisoning is so hard to detect due to it's mainly functional toxicities until systemic fibrosis occurs, the poisoning from unstable contrast agents has slipped under the radar for nearly thirty years. Most doctors and radiologists are not equipped to do specialized functional testing, and direct testing for gadolinium in the urine and blood did not become available until 2009, which was 20 years after the release of the first MRI contrast agent Magnevist. Doctors and patients had no way of being able to verify with certainty that the

newfound functional debilitating side effects were from gadolinium left behind by an MRI contrast agent, and therefore gadolinium poisoning has been almost 100 percent under-reported, since no connections could be made in clinics. Gadolinium does not exist in toxic form in the environment and therefore its toxicity in humans was never studied and documented. Physicians would not even know what to look for even if they did suspect gadolinium. Patients complaining of side effects were given no advice from their doctors, as their doctors were just as stumped.

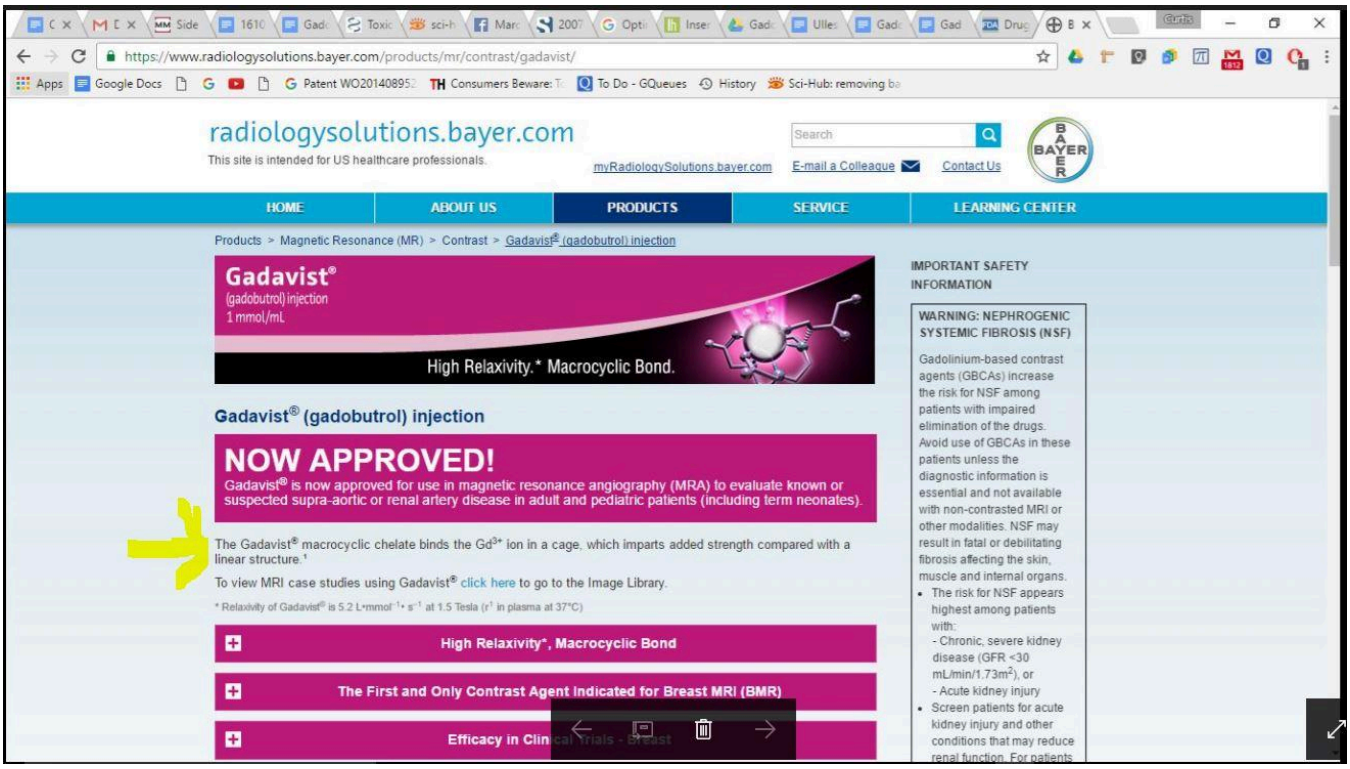
The current MRI contrast agents are made up of two different protective chelates. The linear chelates use a open chain flexible chelate that only semi surrounds the toxic gadolinium atom. In the linear chelates, each of the eight bonds can be broken off, one by one, and pulled away, allowing the gadolinium atom to be free to bind with other natural chelates in the body that also have negatively charged atoms like phosphates, citrates and chloride etc. The term "free gadolinium" refers to the gadolinium atom when it is weakly bound these other molecules, allowing the toxic gadolinium atom to easily break free and bind to calcium receptor sites in the body, causing toxic effects. The macrocyclic chelates, use a rigid ring structure that completely surrounds the gadolinium atom in a cage. With macrocyclic chelates, all four of the bonds would have to break at one time in order for the gadolinium atom to break free. This makes to macrocyclic chelates much stronger and it take the gadolinium atom significantly longer to dissociate from the chelate in the body, an amount of time that usually would exceed the contrast elimination rate by many years. Many patients with normal kidney function have reported substantial side effects from mainly the linear agents. In addition, they have strong evidence to backup their claims. These patients have very high levels of gadolinium found in their urine and blood samples weeks to years after their last contrast injection. Most of their testing was performed by either Mayo Clinic labs or Doctor's Data. These high gadolinium levels in urine and blood are consistent with the very long 254 day elimination half life of "free gadolinium" found in rat studies. This long elimination rate of "free gadolinium" is in contrast to the short 1.5 elimination half life of the original contrast bound Gadolinium. Many of these patients gadolinium poisoned patients have chosen to do IV chelation with a weaker chelate called EDTA, which is also FDA approved for lead poisoning. In addition, an emergency IND for the use of DTPA to treat gadolinium deposition disease was approved by the FDA in 2016. DTPA is the same chelate used in the original formula for Magnevist Gd-DTPA, so it made sense to try and use this chelate to try and recapture the dissociated free toxic gadolinium atoms, unfortunately, it is also the same kinetically unstable chelate that allowed for dissociation in vivo in the first place. But regardless, after chelation, these patients had a significantly elevated amount of gadolinium come out in their urine compared with their baseline pre chelation treatment urine amounts 20ug vs 1ug respectively. This high elevation chemically proves 100% that the form of gadolinium that was stored in their body after being released from the original contrast, was the free weakly bound toxic form. Chemically, neither EDTA or DTPA, would not increase the urine output of any existing intact contrast that could have possibly remained in the body. And even if there was still some intact contrast in the body, EDTA would not be able to chelate the gadolinium atom away from existing contrast agents. For the most part, this chemistry fact also apply to DTPA as well. It has also been shown that gadolinium is not absorbed in any significant amount in the body from the environment . In patients that have never had a contrast agent before, they do not show any evidence of gadolinium within the detection limits after chelation therapy with EDTA, nor do they have evidence of gadolinium retention in their bones as verified by prompt gamma neutron activation analysis* . This is a very significant observation, since the form of gadolinium, whether free form or intact contrast, was so highly debated for so long by the drug companies and radiology, and since the toxic effects of free gadolinium in

micromolar concentrations in animals is already well established to cause toxic effects. Therefore the toxic effects of free gadolinium in the body does not have to be re litigated. In some in extreme cases, the macrocyclic contrast agents are capable of dissociation as well, however, chemically speaking, the cause of concern is mainly from the linear contrast agents, which go by the most common brand names Magnevist, Multihance, OptiMark and Omniscan due to the weaker chemical bonds and open chain structure used in its protective chelate. General Electric Healthcare's brand Omniscan, marketed in 1993, was almost a carbon copy of Bayers' Magnevist contrast, and was quickly made in order to quickly get rich quick too, in the multi billion dollar MRI contrast gold rush during the early 90's. But since General Electric could not just copy Magnevist, they designed Omniscan contrast with two weaker non ionic bonds than the Magnevist chelate. Their product released significantly higher amounts of free gadolinium in the body which is why they had to use the largest amount of extra chelate to mop up dissociated free gadolinium atoms. So even though Omniscan had a fraction of the market share, their less stable copycat contrast resulted in 75% of all gadolinium induced NSF cases. This profit making rush to the marketplace using unsafe chelates initially caused an estimated thousands of patients to develop the deadly Gadolinium induced systemic Fibrosis NSF. NSF which was first identified in 1997, but took eight more years until 2006 before the link was officially made with the gadolinium contrast and admitted as such by the radiology community. And two more years of profitable sales went by before the black box warnings were even put on the contrast labels. Ten years later to make the official link to a deadly disease from a drug after the first observation was made? That is a lot of stalling...and a lot of money made with continue sales of contrast agents during that time.

And now in 2015, the FDA has issued new warnings: This warning came after US FDA found clear evidence of toxic gadolinium deposits in the brains of patients with healthy kidneys, years after the last injection of contrast. Deposits were the again result of using linear MRI contrast agents. And of course, research has shown much higher levels of gadolinium deposits throughout the rest of the body. The bones contained on average 23 times the concentration in the brain, but unfortunately, the radiology community does not fully look at the rest of the body deposits. The drug companies claimed their products would not dissociate or break apart in the body. And since this now has been shown to happen, even in patients with healthy kidneys, the manufactures and radiology community want to tell public that this toxic waste they left behind in the body, is not toxic at all, and it is somehow acceptable t leave toxic metal in your child's brain. And they have certainly not gone out of their way to investigate all the potential toxic effects of this retained gadolinium. In fact, the small amount of investigation they have done, they claim they have found no histopathological changes seen from these brain deposits. Which is very misleading to the average consumer and even most physicians, since, gadolinium by nature generally only causes non histological changes gadolinium is well known to cause major functional toxicities and functional changes to the brain and body, the type of changes that cause disabilities. Gadolinium generally does not cause histopathological damage until concentrations become very high, and induce systemic fibrosis of the skin and vital organs. In addition, damage to the cells may take many years to finally develop after long term cellular dysfunction. In addition, they have not even begun to fully investigate the gadolinium deposits in the rest of the body. The manufactures and radiology community know the average person does not know the difference between histology or structural damage and functional toxicities, and therefore the average person might just assume it's safe, just because beside the presence of toxic gadolinium metal atoms that should not be there, their is no apparent histology or structural damage seen. And of course they won't bother to study or report on the functional toxicities, since this would be self incriminating. How many more years will it be this

time, before the link to other crippling and life altering functional pathologies from these deposits are made, especially in our kids who have not fully developed yet? And the patients who have presented proof of retained toxic free gadolinium that have been complaining of functional toxic effects for the last 30 years, why are they being ignored and not studied despite numerous attempts and well documented correspondence between these patients and the FDA as well as key Radiologist in the community? These patients were told the contrast would leave the body in 48 hours max. Why aren't these patients with proof being studied? Yes, something is very wrong here, and we need to make sure the scientific truth is uncovered and published, and not take another 10 years to do it while the pharmaceutical companies and the radiology community profit.

Is Gadolinium poisoning a result of drug manufactures who decided to cut costs and use much weaker chelates or protective coatings to secure the toxic gadolinium atom? These linear agents have very low kinetic inertness, which means they have fast dissociation rates. The toxic gadolinium atom can break apart from the chelate quickly in the right conditions in the body, long before the contrast can be fully eliminated. They could have used the much stronger more expensive macrocyclic chelates, and were even warned in 1986 by many scientists to do so, even before their products were released to the market. But was their decision influenced by money and the need to insure they made it to the market quick enough before their competition? Was it about establishing market share first? If they could get the MRI facilities to sign long term contracts to purchase their product before another company could, was this the goal? Did Bayer Ag, makers of the first linear agent Magnevist, know their product was weak and unstable? Bayer quickly made a much safer and stronger macrocyclic agent called Gadovist within only a few short years after the release of Magnevist. Why would any drug company spend 500 million on producing a new contrast agent, if their existing linear agent was strong safe and already did the job? Their website even advertised the new contrast agent Gadovist as being produced with having stronger bonds than linear contrast agents, see below. Why would they say that? And since the market share was so good with their linear product Magnevist in the US , they sold the new Gadovist macrocyclic agent in other countries but not the US for ten years before gaining FDA approval in the US. They probably had no plans to bring it to the US market except that an estimated thousands of patients who developed NSF Gadolinium induced Fibrosis from the linear agents by 2007. They then brought it to the US market in 2011 in fear that their flagship linear agent Magnevist would be pulled from the market. Did Bayer the makers of Magnevist know what was coming? Coincidentally, in 2013 researchers found deposits of toxic free gadolinium in the brain of patients with normal renal function years after the injection of these same linear contrast agents. And in 2017, finally, the European Medical Agency voted to ban all four unstable linear agents, costing the contrast manufactures billions in future sales and profits.



Did the contrast manufacturers know their agents were unstable?

1. In 1984, Dr. Weinmann, the inventor of Magnevist stated in his publication “However, care should obviously be taken in patients with impaired renal and/ or hepatic function where high in vivo concentrations of GdDTPA may occur for prolonged periods.” Quoted from: Gadolinium-DTPA as a contrast agent in MRI: initial clinical experience in 20 patients. http://www.ajronline.org/doi/pdf/10.2214/ajr.143.2.215
2.

Why did contrast manufactures decide to use less stable linear chelates instead of stronger macrocyclic chelates?

On May 10, 2017 the EMA (the FDA equivalent in Europe) requested to ban all four unstable linear MRI contrast agents. However, EMA will also tell you, that in their limited investigation, they did not find any harmful side effects from the deposits “yet”. Of course, they too have only looked at physical cell damage and not functional toxicities. But why would they pull products and ruin a multi billion dollar drug market, when there is no real cause of concern? What they are really saying is, they did not find in obvious physical damage that stands out like a sore thumb yet, knowing that all the functional disabling functional toxicities have not been studied yet, and since they anticipate to find them, it is best to bow out now. In addition, they have not looked thoroughly in the rest of the body either. They know that the functional toxicities would represent the bulk of the side effects reported by patients. Regulatory agencies don't pull drugs off the market for no reason. A very safe precautions move to avoid being

sued for failure to warn all of Europe when the investigation finalizes. Unfortunately, the FDA does not worry about this since, they can not be sued by the public for Drug company mistakes. The EMA took the advice of their toxicologists and lawyers, and got out when they could, and not when they had too.

Who is a risk for getting Gadolinium Poisoning?

Like any toxin, the severity of gadolinium poisoning is dose dependent and depends on a number of factors. It does not depend on the dose of contrast received, but the amount of toxic free gadolinium that dissociates or breaks free from the original contrast and stays in the body. This is primarily an issue with the linear contrast agents, since under certain conditions, linear agents can dissociate or break apart inside the body releasing the toxic gadolinium atoms at a much faster rate than the contrast can be eliminated from the body. It is possible that this can also happen with the macrocyclic agents as well under the right conditions in the body, however due to the chemical structure of the macrocyclic chelates, this is less likely to occur. Recent evidence from many interviewed patients indicates that there is some dissociation with the macrocyclic agents as well, so this needs to be further investigated. The more free gadolinium released, the more severe the acute and chronic side effects will be. Three levels of gadolinium poisoning have been identified in patients.

Level 1: Gadolinium Storage Condition:

In this condition, patients have a small retained amounts of Gadolinium in either free gadolinium form or intact GBCA or both. These patients may not notice any acute or severe side effects. However, the long term toxic effects of these small deposits are not fully understood yet but are currently being investigated. The free gadolinium will cause dysfunction as the gadolinium ion either lodges somewhere in the body as it forms insoluble complexes with endogenous chelates or it may bounce around constantly changing form as various endogenous chelates compete for the ion in various dynamic conditions in the body, especially in different pH levels in extracellular and intracellular fluids may fluctuate. The effects of these small deposits may be so subtle that the patient does not notice or complain until enough injections have been performed and enough free gadolinium has been stored. As with most heavy metals in the brain, they may cause immediate dysfunction to cells be may take many years for any histology to take place as a result of constant dysfunction. These patients will often clear most of the contrast from their body within the normal pharmacokinetic 1.6 hour half life of the contrast agent, usually within 48 hours, but retain a small amount of free gadolinium and or intact GBCA. At 96 hours post GBCA injection, these patients should have a normal levels of gadolinium in both blood > .5 ng/ml and urine >.7 mcg /24 hour specimen .These small deposits may eventually cause increased T1 signals on non contrast MRI brain scans if enough injections are performed, consistent with Gadolinium deposits. However, it is important to note that in order for gadolinium deposits to show hyperintense signals on MRI scan, the gadolinium must be chelated in a way that allows water molecules to bind to its inner orbit, which quickly relaxes the protons in near by water molecules and creates the contrast effect or T1 shortening. Since it is unknown how much free gadolinium form complexes in the body that show up as hyperintense on T1 MRI scans, signals that do occur with free gadolinium, may severely underestimate the amount of stored free gadolinium in the brain and patients with high levels of Free gadolinium in the brain may have no evidence of hyperintense signals as well. As small amounts of free gadolinium are stored in the bones, free gadolinium may be mobilized daily into the system as osteoclasts break down bone through resorption, as it attempts to maintain free ionic calcium levels in

the body. Bone breakdown may also occur from medications or pathology that incease bone turnover, releasing a constant stream of free gadolinium to bind to and interfere with calcium homeostasis in the body and cause functional disturbances.

Level 2: Gadolinium Deposition Disease:

In contrast to patients with GSC or small gadolinium deposits from multiple injections of linear based gadolinium contrast agents, Gadolinium Deposition Disease GDD is the result of a patient's who has a large percent of free gadolinium dissociate inside the body after just one injections before the contrast can be safely eliminated, regardless of kidney health. Chemically, the number one cause of very fast dissociation rates is proton assisted acidic conditions and transmetallation with endogenous metals, followed by conditions that cause increase GBCA retention times. It is believe that these patients either met one or both or all of these conditions that resulted in a much higher percentage of dissociate free gadolinium, than normal. The severity of the side effects are directly proportional to the amount of gadolinium that dissociates from the original injection of contrast. The patient becomes acutely ill within minutes to hours, since this is when most of the contrast is still in the body to dissociate, and mainly in the extracellular fluids where increased protons and low pH levels can exist in the absence of albumin. The extracellular and intracellular fluids can become severely dehydrated long before any changes in labs or pH will be seen in the patient's blood. This is even more so in patients with kidney disease that have difficulty in maintaining pH regulation. The patients progressively gets worse over several days and weeks with symptoms that often mimic hypocalcemia, as gadolinium ions compete for calcium binding sites and bind with a much stronger bond, they may or may not let go, and may permanently alter the function of the cell. Except for high gadolinium blood and urine levels, these patients seem to have normal labs, and imaging reports, making the diagnosis or link to gadolinium, nearly impossible. Free gadolinium has a plasma half life in rats of 37+ hours before the ions deposits in organs. In patients with normal renal function, they will have elevated urine and blood gadolinium levels at least 96 hours after the contrast injection, indicating the presence of free gadolinium consistent with its long plasma half life. As the free gadolinium works it’s way out of the blood and extracellular spaces and makes it’s way into the cells and vital organs over the next few months, the patient will move from the acute phase of side effects to the chronic phase. The symptoms may change or worsen as the gadolinium leaves the blood, and extracellular fluids and deposits into vital organs and nervous system . In rats, the systemic half life of free gadolinium is 254 days and is eliminated primarily through the liver. It is unknown how long it takes to eliminate free gadolinium in humans. The percent of patients that develop GDD after injections GBCA is unknown. But in the case of the linear agents that have rapid dissociation half life < 5 seconds at pH 1, which can be significantly faster than the contrast elimination half life rate of 1.6 hours, the percent of patients with GDD can be rather high. This is a significant chemistry issue.

Level 3: Gadolinium Induced Fibrosis NSF:

Nephrogenic Fibrosis or NSF. A suggested name change to from NSF to GIF, gadolinium induced fibrosis, was proposed by Dr. Todd and Dr Kay in 2016. Along with several other scientific publications, they show convincing proof that NSF is not related to the kidneys, but is a result large amounts of free

gadolinium dissociated and released inside the body. These patients have the highest amount of free gadolinium released inside them at one time after an injection of usually linear based GBCAs. Generally three conditions must be met for GIF to occur. 1.) The patient must have severely delayed elimination of the contrast primarily caused by reduced kidney filtration rates. Chemically speaking, the longer the contrast stays in the body, the more free gadolinium is dissociated. 2.) The patient must have acidosis in some form. Most patients with kidney disease have some form of acidosis as the kidneys are responsible for maintaining acid/base balance in the body. Acidosis will occur in intracellular and extracellular fluids long before any signs of acidosis will show up on labs, primarily via bicarbonate levels and anion gap readings. Even patients with severe kidney disease can eliminate most of the contrast before it can dissociate, as long as proton assisted acidosis in blood or extracellular fluids is not present. Transmetallation may also occur from excess endogenous metals such as zinc or copper. Since the kidneys are not filtering the contrast as fast, the half life of the contrast can be severely delayed up to 30 hours. The longer the contrast stays in the body, the more gadolinium can break away from it's protective chelate, relevant mainly to linear agents. Many patients with renal failure also have some form of acidosis. And even when bicarbonate levels are normal, acidosis can exist in the extracellular or intracellular fluids, especially if there is fluid retention. Low pH or acidosis, can dramatically lower the strength of the bonds between the gadolinium and the chelate and rapidly increas how fast these gadolinium complexes come apart, leading to very high amounts of free gadolinium released in the body. This extremely high concentration of free gadolinium reaches a tipping point in the body and triggers a cascade of immune responses leading to systemic fibrosis. Along with fibrosis, calcium tends to deposit where gadolinium deposits*. A 15 year retrospective study published in 2017 shows that the only patients that get better from this condition, are ones who improve their ability to eliminate gadolinium as their kidney function improves*.

In Patients with normal kidney function who develop GDD or serious side effects from dissociated gadolinium, most gadolinium dissociation from the original chelate will happen within the first few hours post contrast injection while a much larger percent of the contrast is still in the body. And most of dissociation will take place in the extracellular fluids, since this is where most of the the contrast goes in the body after injection of most GBCAs. In contrast to the blood, the extracellular fluids are also environments that can be subject to rapid fluid loss, retention, and very rich in competing hydrogen protons, acids, competing chelates, metals, and overall represents a much more fluctuating dynamic environment that can provide the ideal factors for rapid dissociation of linear contrast agents. In addition, the kidneys tubules are responsible for removing excess hydrogen protons from the blood, making the tubules a very rich environment for proton assisted dissociation of the contrast producing free gadolinium. But making matters even worse, the kidney tubules are also responsible for reabsorbing filtered calcium back into the blood, the now free gadolinium with a similar ionic radius and binding affinity for calcium binding molecules, can be mistaken for calcium and absorbed back into the bloodstream as well, especially if parathyroid hormone is increased which increases the rate of calcium reabsorption in the tubules. Parathyroid hormone is often elevated in kidney diseased patients who in addition can often have tubule acidosis, which may impart, explain why these patients can have significantly more free gadolinium stored in the body than patients with normal kidney function, which may be the tipping point to trigger systemic fibrosis.

In patients with reduced renal function or retention of contrast from other normal or pathological conditions, gadolinium dissociation can happen over days and even weeks, and as a result, have more of a delayed onset of side effects.

Risk Factors to Gadolinium Dissociation in vivo

What are the main risk factors that can cause the gadolinium to dissociate from the contrast agent while in the body?

1. Acidic conditions in the body accelerates the dissociation half life of the gadolinium chelate complex, allowing the contrast to break apart faster in the body. This is also known as kinetic inertness, and is the main factor related to contrast toxicity. At a pH 1, all the linear agents can begin to dissociate in less than 5 seconds, which is much less than the 1.5 hour elimination half life of the contrast. This results in free gadolinium and free chelates released in the body and the severity of toxic side effects in a dose dependent manner. The contrast with the longest dissociation half life at a pH of 1 is Dotarem, taking 26.4 hours. Since with most MRI contrast agents approximately 91% +- 12% will be eliminated in the first 24 hours, it is easy to see why Dotarem would have the least chance of dissociating before being eliminated from the body.

TABLE 3. Overview of Dissociation Half-Lives ($T_{1/2}$), Determined at Different Conditions, Illustrating the Kinetic Inertias of GBCAs at pH 1 and at Higher pH in the Absence of a Biological Matrix

Class	Trade Name	Short Name	$T_{1/2}$, pH 1	Reference	$T_{1/2}$, pH >5	Reference
Linear	Not specified	Not specified	<5 s (25°C)	14	5–7 d (pH 7.4, 25°C)	21
Macrocyclic	Gadobutrol	Gd-BT-DO3A	7.9 h (37°C)	14	65 yr (pH 5.3, 25°C)	39
	Prohance	Gd-HP-DO3A	2.0 h (37°C)	14	36 yr (pH 5.3, 25°C)	39
	Dotarem	Gd-DOTA	26.4 h (37°C)	14	37 yr (pH 5.3, 37°C)	40

The values were taken from the cited references or were calculated from the given rate constants. Because of the differing conditions, the values are not directly comparable, but they give an impression of the marked differences between the dissociation rates of macrocyclic and linear GBCAs.

2. Retention of the contrast. The longer the contrast stays in the body, the more gadolinium dissociates from its protective chelate. The body is a dynamic constantly changing environment with many complex factors, and does not reflect to any degree the static in vitro environment in a dish that most experiments were performed in, while originally determining the safety of these contrast agents.

3. Competition from other metals and chelates in the body.

1. **Acidic conditions:** Acidic conditions mainly found in kidney tubules and the extracellular fluids, were most of the contrast resides after injection. Any acidic conditions in the body at the time of or after the injection of the contrast while the contrast is still abundant in the body.
    a. Any conditions that leads to dehydrations and lower pH levels in certain areas of the body including inside the kidney tubules, and extracellular fluids or pockets of inflammation, capsules from implants etc...
    b. Acidity from Not drinking enough water
    c. Hormonal imbalances
    d. Certain medications and diuretics
    e. Metformin can cause lactic acidosis
    f. Exercise
    g. Inflammation
    h. Chronic illness
    i. Drinking alcohol decreases antidiuretic hormone and can lead to dehydration.
2. **Conditions Resulting delayed elimination of the GBCA:** Conditions that cause retention of the contrast and delayed elimination. The longer the contrast stays in the body, the more gadolinium dissociates from the original protective chelate. These conditions may include but not limited too:
    a. Renal disease
    b. Hormonal imbalances
    c. Areas of Trauma or pockets of inflammation
    d. Cardiovascular disease
    e. Chronic lung diseases
    f. Pulmonary hypertension
    g. Thrombosis
    h. Venous insufficiency
    i. Extravasation of the injection into the arm. Which forms a bolus and pocket of inflammation with an acidic environment. Gadolinium slowly dissociates and poisons the patient
    j. Patients with breast implants, knee or hip implants etc. Where the contrast is held in the capsules for years in an acidic environment that slowly releases the free toxic gadolinium into the patient.

3. **Competition from Endogenous Molecules:** The chelates in the Contrast agents can also be broken down by competition from endogenous positively charged metals or negatively chelates in the body such as:
    a. Certain vitamins and minerals supplements or medications such as Zinc Citrate, copper etc…
    b. Certain supplements with strong chelating abilities like polyphenols with catechol and gallate groups.
    c. Foods: Amino acids, citric acid, lemon or orange juice and other medications that have strong chelating effects like certain antibiotics Etc…

Gadolinium Poisoning Symptoms

1. Symptoms may mimic those of hypocalcemia (low calcium levels).
2. Muscles weakness,spasms, twitching
3. Joint pain
4. Burning and or itching of the skin, muscles etc
5. Discoloration of the skin
6. Hardening and fibrosis of the skin, joints etc.
7. Neurological dysfunction
8. Neurocognitive dysfunction: ie: Brain fog, loss of memory, focus and concentration. Behavioral and psychological changes. Personality changes. Depression, anxiety, post traumatic stress syndrome etc..
9. Changes in vision
10. Shortness of breath
11. Cardiovascular changes
12. Reduced energy levels and rapid aging for mitochondrial dysfunction
13. Migraines, altered vascular reactivity
14. Bradycardia
15. Hormonal imbalances.
16. etc.

Diagnosing Gadolinium Poisoning

Gadolinium poisoning is real, and can now be easily verified by urine and or blood testing for gadolinium. Unfortunately current gadolinium testing does not differentiate between gadolinium bound to the original chelate or the presence of free gadolinium. Tests for free gadolinium similar to free ionic calcium, will make diagnosis much easier in the near future. However, diagnoses can still be made since the plasma half life of most gadolinium contrast agents is 1.6 hours. Usually patients with normal kidney function gfr >60 will eliminate all the contrast within 48 hours. There should be no significant level of contrast left in the body by 96, according to the pharmacokinetic data and Mayo Clinic

Laboratories gadolinium testing interpretation guide. Since we know the plasma half life of free gadolinium chloride in rats is 37+ hours, patients with normal renal function who have elevated gadolinium levels in urine and or blood tested at least 96 hours post gadolinium contrast injection, indicates the presence of dissociated free gadolinium or the presence of pockets of fluid retention in the body where contrast could have been stored for extended periods of time. To verify the patient has free gadolinium, intravenous chelation with Calcium EDTA can be used as a diagnostic tool to verify the presence of free gadolinium. Since the chelator EDTA will not increase the rate intact GBCAs elimination from the body and will not chelate gadolinium ions away from any existing GBCAs, then if the amount of gadolinium found in a 24 hour urine collection after infusion with calcium EDTA is significantly increased over pre EDTA chelation baseline, then the patient test is positive for dissociated free gadolinium from the original contrast agent and a diagnosis of gadolinium poisoning can be made. Chemically EDTA is a significantly weaker chelator than any of the current approved GBCA chelate, and would not be able to remove the gadolinium ion from these contrast agents. The only gadolinium that EDTA would be able to remove, is free gadolinium ions.

Removing Toxic Free Gadolinium from the body.

The amount of gadolinium that is released can be rather high, and could be in the hundreds of milligrams or even grams. Even worse, the gadolinium gets inside the cells and the vital organs like tiny metal splinters where most chelators can not reach to remove the gadolinium. EDTA is not a safe chelator for gadolinium since it has been shown to release almost 50 percent of the gadolinium it grabs, the gadolinium may be pulled from the bone and end up in the brain. This is why EDTA was not used as a chelator in contrast agents. In rat studies, gadolinium bound to EDTA also showed almost equal incidence of NSF like skin lesions then the Free gadolinium alone. The Gd-EDTA complex also was reported has having it's own toxic effects not seen by free gadolinium, suggesting that the Gd-EDTA complex was toxic in it's own right. DTPA is too weak to remove the large amounts of gadolinium stored in the body within a lifetime and is the same linear chelate with very fast dissociation rates that led to the release of free gadolinium in the body in the first place. Both EDTA and DTPA are extracellular chelators and will not directly remove Gadolinium from inside the cells or deep in vital organs like the brain when many of the main toxic effects may be manifesting. However, CaDTPA or ZnDTPA can be used in acute conditions when gadolinium has not settled into the cells or vital organs yet, generally within the first 2 weeks of gadolinium poisoning. The longer one waits to chelate with these agents, the less effective at relieving symptoms. DTPA is primarily excreted through the kidneys 90%, it cannot be used to treat patients who have severely reduced renal function like in patients with Gadolinium induced fibrosis NSF, as this could just cause the newly formed Gd-DTPA complex to dissociate again due to increased retention times. EDTA and DTPA or also nephrotoxic and may be contraindicated in patients who are concerned about their kidneys or have existing nephrology. An ideal chelator will be safe and selective for gadolinium without disrupting essential endogenous metals, remove Gd from inside the cells, vital organs and brain, be taken orally with a longer residence time in the body, remove significantly more Gd than other known chelators (higher stability constant), be kinetically inert and not dissociate in the body after grabbing gadolinium, be eliminated primary through

the liver bile vs the kidneys, making it also effective for patients with poor renal function. Bile elimination is also ideal since the cells in the intestine can regenerate, however, the nephrons in the kidneys cannot if they are damaged. Therefore potentially nephrotoxic chelators, are not recommended for most patients, since kidney function allowing the body to remove traces of gadolinium seems to be a dominating factor in symptom relief for patients with NSF.

What Should Drug Regulatory Agencies Do?

1. The most unstable and volatile linear contrast agents should be immediately removed from all markets worldwide, all four linear agents. They do not offer any additional advantage for imaging then the stronger Macrocyclic agents and the linear agents are very unstable in the body under too many known and unknown circumstances.
2. Fully investigate and put out warnings about the use of Macrocyclic agents in people with additional risk factors that may lead to reduced systemic clearance and increased dissociation rates.
3. Severely restrict the use of the Agents to be only medically necessary.
4. Provide a strong, safe and effective oral antidote to prevent or treat gadolinium poisoning.

Preventing Gadolinium Poisoning.

1. Avoid gadolinium based contrast agents unless they are medically necessary. Only utilizing contrast if the additional data will alter the treatment for the patient's benefit?
2. To error on the side of caution, only use the strongest macrocyclic agents with the longest dissociation half life at the lowest pH, that also provides the best image for your particular condition
3. Ensure the patient is well hydrated for several days prior to the contrast injection to minimize acidic conditions that may lead to acid assisted dissociation of the toxic free gadolinium and toxic free chelates. Dehydration is also the number one cause of contrast induced nephrology, or injury to the kidneys, which could will further result in delayed elimination of contrast or acid base balance and which may result in the release of more toxic free gadolinium in the body through hydrogen proton assisted dissociation. Physicians, radiologists and MRI technicians should be aware of additional risk factors leading to dissociated gadolinium and to properly screen for these conditions to make necessary corrections prior to contrast injections. In addition, since it may be difficult to screen for all the additional risk factors, the patients could be hydrated with IV fluids prior to the injection of contrast. Unfortunately, many techs are unwilling to do this because they are concerned the patient would have to void prior to the completion of the MRI scan. This can interfere with the scan and the line of patients waiting. But the this would help insure the patient's safety which should be paramount.
4. If extravasation occurs where the contrast misses the vein and is injected directly into surrounding tissues in the arm. This can form a bolus or pocket of stored contrast in a very acidic environment as inflammation sets in. The contrast can then dissociate rapidly and over time, as it slowly leaks toxic free gadolinium into the patient. Damage done done to the local

tissues as well as calcification and fibrosis can also occur. Procedures should be put into place to proper and urgently treat this condition by attempting to drain the bolus formed before the contrast is further absorbed deeper into tissues. A prescription for an oral chelator with a long elimination half life, should be prescribed to mop up any dissociated Gadolinium and remove it from the body.

Discussion:

Gadolinium poisoning is a real phenomenon and the severity of the side effects from free gadolinium is dose dependent. In order to understand how patients develop it and how many are potentially affected, we must understand some basic chemistry of the linear and macrocyclic chelates and the gadolinium atom. Their in vivo toxicity is dependent on their dissociation rates, how fast they can release the toxic gadolinium atom in the body. And their dissociation rates depends on their structure and the bonds they used in their protective chelates, whether the bonds are ionic or non ionic bonds. Gadolinium prefers ionic electrostatic bonds. The weakest chelates use an open chain linear structure, and have less ionic bonds. Omniscan uses the weakest protective chelate, and this is why Omniscan is responsible for approximately 75% of all gadolinium induced NSF cases, despite having only a small market share at the time. Contrast manufactures use an extra amount of free chelate in their linear contrast agents to attempt to collect any free gadolinium that may dissociate from the contrast, with the linear contrast with the weakest non ionic bonds needing the most extra chelate, ie Omniscan. This can be seen as an admittance that they knew their products would dissociate in the body. In contrast to linear agents, macrocyclic agents do not have to use any extra chelate in their products.

There are three main factors that can trigger rapid dissociation of free gadolinium from the original contrast protective chelate in the body, regardless of renal function. 1.) Any acidic environment in the body that the contrast might come in contact with. 2.) Competition from excessive endogenous positively charged metal atoms, or natural chelates with strong negatively charged atoms in the body. 3.) Any condition in the body that causes fluids to be retained for longer than normal including capsules from Implants. There are many normal and pathological conditions that can lead to all of these risk factors, and all three can happen at one time. If these risk conditions are met, linear agents, especially the ones with weaker non ionic bonds, can rapidly dissociate faster than the contrast can be eliminated from the body resulting in significant toxic free gadolinium released, and toxic side effects can be experienced by the patients. This can also happen with the macrocyclic agents as well, but the environment would have to be extremely acidic and the dissociation would take exponentially longer, so the contrast would have to be held hostage in the body for significant longer periods of time. The likelihood of macrocyclics dissociating is very low, but the linear agents is like putting paper in a fire. The contrast agents were not thoroughly tested under these conditions in clinical trials. Before the marketing approval of Omniscan, one scientist for General Electric admitted that he had produced a study regarding the release of free toxic gadolinium from their product showing it was unstable, but the report was either destroyed or lost by General Electric, but the testimony was still used in court as proof of the report's existence. The weak unstable chemical bonds makes linear agents extremely dangerous. The use of linear agents has resulted in estimated thousands of patients who developed gadolinium induced NSF, and potentially millions of patients with toxic gadolinium poisoning in adults

and developing children. Since there is no imaging benefit over the macrocyclic agents that outweighs the risk of gadolinium poisoning, there is no need to keep the linear agents on the market.

We also need to understand the nature of gadolinium and how it causes toxic effects. most of its toxic effects do not show up as structural damage. Instead, gadolinium causes significant functional disturbances by blocking proper calcium metabolism in the body. Gadolinium cannot easily be detected until patients retain enough free gadolinium to reach a threshold and begin to develop full blown gadolinium induced fibrosis NSF. This makes diagnosing gadolinium poisoning extremely difficult and highly under-reported, since there is still very little information about how to identify its functional toxic effects. And most of the radiology community is still in denial about it functional toxic effects, because they just don't know the facts. Additionally, attempting to imply false and misleading claims that these products are safe because they have not identified any histopathological findings from brain deposits yet (meaning no physical cell damage seen), is like saying you are perfectly healthy because your outer skin looks fine. In fact, radiologists have not even began looking throughout the rest of the body where the majority of the deposits are, and just looking for cell damage instead of functional toxic effects is like looking for apples when they should be looking for oranges. Histology screening does not rule out functional toxicities. And the mere presence of toxic gadolinium deposits anywhere in the body, is a pathological finding in itself. This is toxic metal foreign to the body, and it should not be there in the first place, in any amount. Even a tiny amount left behind by the manufacture contrast agents is completely unacceptable, and patients were not warned, nor did they consent to these gadolinium deposits. In light of the new FDA warnings and the onslaught of damning research being published, the contrast manufactures and radiology community continue to attempt to try and thwart the gadolinium phobia that is raging out of control as people are beginning to refuse contrast. Drug companies and radiology are making misleading statements like "no histopathology has been identified", purposely leaving out the "yet", and, "the contrast agents have an excellent safety profile". But how can they say that the contrast agents have enjoyed an excellent safety profile when an estimated thousands of patients developed gadolinium induced NSF and potentially millions of patients now have toxic gadolinium deposits in their body that produce non visible functional disturbances? Due to the non visible and difficult to test for or verify functional toxic effects of free gadolinium, gadolinium poisoning without systemic fibrosis is almost 100% under-reported. Until researchers begin quantitative testing of free gadolinium in their patients and begin testing for all the functional toxic effects that gadolinium is mainly well known to cause, symptomatic patients without signs of obvious skin or organ fibrosis will continue to be ignored and the real risks associated with these unstable contrast agents will continued to be downplayed.

Patients must continue to educate themselves on this matter to protect themselves and their children. The drug companies and many affiliated pharmaceutical funded radiologists like Dr. Prince would certainly financially benefit if it took another ten years before the truth about the linear agents were fully exposed and before being pulled from the market. The burden to expose the truth once again on these contrast agents, gets placed on the poisoned patients to ensure that there are no more delays and the FDA takes immediate action to ban the less chemically stable agents. The linear agents are way to volatile, like throwing paper in a fire, and should be pulled immediately from the market. In addition, the Macrocyclic agents should receive stern warnings about certain risk factors that may lead to their dissociation in the body as well. Until we have safer contrast or non contrast imaging options, we must understand that certain medical conditions still require the use of MRI contrast to make life saving diagnoses. We must work with the stronger macrocyclic agents we have right now and ensure they are

safely administered by managing the risk factors and using only when medically necessary, and not for profits. Due to the very high market share and use of linear contrast agents, there is potentially millions of patients that have gadolinium toxicity today. Doctors and radiologists are very busy and have very little if any chemistry background to properly understand how this matter has happened and slipped under the radar for nearly thirty years. And unfortunately, in the busy world of caring for patients, most physicians and radiologist will not take action until stern warnings come across their radar from the FDA about the safety of a product. They will just continue to claim they did not know. But the information is out there, and it has been there if they dig for it. It is their job to know what is safe for you and your children despite what the manufactures tell them. Is it too much to ask doctors to research drugs thoroughly before allowing potentially toxic drugs to be injected into our children, especially when over 200 scientific articles have been published on this subject? But who has time for that? So for now, the patients must continue to take matters into their own hands and keep pushing the issue until enough concerned radiologists begin to take their jobs as lifeguards serious. And pray that they begin to dig a little deeper into research instead of waiting for published articles to just land on their laps. In addition, concerned radiologists, being the ones that ultimately injected all this contrast into patients, should immediately begin to study and listen to these symptomatic patients who have clear proof of free gadolinium deposits. In the meantime, chemists, and toxicologists that understand this as a chemistry issue, should further weigh in on this subject to publish the scientific facts in a form that everyone can understand and take action with.

Gadolinium poisoning is real, and can now be easily verified by urine and or blood testing for gadolinium. Unfortunately current gadolinium testing does not differentiate between gadolinium bound to the original chelate or the presence of free gadolinium. Tests for free gadolinium similar to free ionic calcium, will make diagnosis much easier in the near future. However, diagnoses can still be made since the plasma half life of most gadolinium contrast agents is 1.5 hours, so normally patients with normal kidney function gfr >60 will eliminate all the contrast within 48 hours. There should be no significant level of contrast left in the body by 96 hours as reported by Mayo Clinic Laboratories. Since we know the plasma half life of free gadolinium chloride in rats is 37+ hours, patients with normal renal function who have elevated gadolinium levels in urine and or blood tested at least 96 hours post gadolinium contrast injection, indicates the presence of dissociated free gadolinium or the presence of pockets of fluid retention in the body where contrast could have been stored for extended periods of time. To verify the patient has free gadolinium, intravenous chelation with Calcium EDTA can be used as a diagnostic tool to verify the presence of free gadolinium. Since the chelator EDTA will not increase of rate of existing contrast to be eliminated from the body and will not chelate gadolinium ions away from any existing contrast, then if the amount of gadolinium found in a 24 hour urine collection after infusion with calcium EDTA is significantly increased over baseline, then the patient test is positive for dissociated free gadolinium from the original contrast and a diagnosis of gadolinium poisoning can be made.

Since 1986, two years prior to the release of the first gadolinium based contrast linear agent, there has been over 200 scientific studies and papers published on this issue of gadolinium contrast stability, in vivo dissociation and the toxicity of gadolinium released from contrast agents including NSF and gadolinium poisoning. This has been one of the most studied subjects in the history of any drug and millions of dollars in gadolinium toxicity research, with very little attention by the radiology community or action by the major regulatory agencies in charge of ensuring the public's safety.

Some of the most recent publications and findings include:

2015 July Mayo Clinic fins Gadolinium deposition in the brain: another concern regarding gadolinium-based contrast agents.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4498420/

2015 July FDA Drug Safety Communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI)
https://www.fda.gov/Drugs/DrugSafety/ucm455386.htm

2016 August Evidence of Brain Neuro Toxicity of Gadolinium. “Effects of gadolinium-Based contrast agents on Thyroid hormone receptor action and Thyroid hormone-induced cerebellar Purkinje cell Morphogenesis: Gd-based contrast agents are deposited in the skin, liver, kidney, lung, heart, spleen, diaphragm, and femoral muscle of rats (5, 6). Skin accumulation of GBCAs may cause NSF, particularly in patients with renal insufficiency (9, 44). This is relevant to this study because Gd deposition is also observed in the brain (11), and severe behavioral changes resulted from the administration of GBCA to rat brains (15). Administration of other lanthanides has also been associated with impaired learning and memory (16). Here, we also observed suppression of TH-induced dendritogenesis in the Purkinje cells. Together, these results indicate that the abnormal behavioral alteration following Gd administration may result, at least in part, from the disruption of TH activity in the brain; however, further study is needed to confirm the mechanism.”

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4999949/

2016 August Gadolinium in Humans: A Family of Disorders. We propose naming the histopathologically proven presence of gadolinium in brain tissue “gadolinium storage condition,” and we describe a new entity that represents symptomatic deposition of gadolinium in individuals with normal renal function, for
which we propose the designation “gadolinium deposition disease.
https://www.ncbi.nlm.nih.gov/pubmed/27224028

2016 October Gadolinium induced effects on mammalian cell motility, adherence and chromatin structure. In the recent work we have extended our previous genotoxicity studies to another heavy

metal ion, namely to the cellular toxicity of Gd(III). Irreversible chromatin changes of Gd3+ toxicity manifested mainly as premature local chromatin condensation. Gd(III) is highly cytotoxic (from 0.75 μM and up)

https://www.ncbi.nlm.nih.gov/pubmed/27770270

2016 November High Levels of Gadolinium Deposition in the Skin of a Patient With Normal Renal Function: CONCLUSIONS: Our results, in contradiction to published literature, suggest that in patients with normal renal function, exposure to GBCAs in extremely high cumulative doses can lead to significant gadolinium deposition in the skin. This finding is in line with more recent reports of gadolinium deposition in the brain of patients with normal renal function.

https://www.ncbi.nlm.nih.gov/pubmed/26953564

2016 November Do gadolinium-based contrast agents affect the 18F-FDG PET/CT uptake in the dentate nucleus and the globus pallidus? A pilot study. Conclusion: The median SUVmax in the DN and GP was 16% and 27% lower, respectively, in patients who received GBCAs than in those who had not received GBCAs, possibly related to gadolinium deposition in these areas. Proof of functional toxic effects in the brain of patients with gadolinium deposits.

https://www.ncbi.nlm.nih.gov/pubmed/27834725

2016 Dr Todd and Dr. Kay proposes name change from NSF to Gadolinium Induced Fibrosis. “We encourage the medical community to embrace the term GIF as a more accurate description of this chronic fibrosing disorder that is triggered by Gd. The term GIF also permits greater scientific plasticity when considering the larger universe of fibrosing disorders and what has yet to be learned about Gd toxicity. There even may be unrecognized adverse effects of tissue Gd deposition in patients with normal renal function. For example, after exposure to GBCAs during MRI studies, Gd deposits in areas of the brain in individuals who have relatively normal renal function (93). Thus, the term GIF makes known the causative role of GBCAs in this disease, which should help to eliminate the inadvertent administration of high-risk agents to at-risk patients, lest future generations forget past experience with yet another toxin-induced fibrotic disorder"

https://www.ncbi.nlm.nih.gov/pubmed/26768242

2016 Gadolinium Containing Contrast Agent Promotes Multiple Myeloma Cell Growth: Implication for Clinical Use of MRI in Myeloma
http://www.bloodjournal.org/content/114/22/1809?sso-checked=true

2017 January Gadolinium magnetic resonance imaging during pregnancy associated with adverse neonatal and post-neonatal outcomes. Conclusions Gadolinium MRI was associated with any rheumatologic, inflammatory, and infiltrative skin condition, stillbirth, and neonatal death. Watch the Jama Report video

ttps://www.youtube.com/watch?v=T8uJ10_i9us&index=4&list=PLPcLZsSc2-Vkob3JL8TK2CLLnIbflzCQx

2017 March 10 In a stunning development, a European Union regulatory body recommended that four linear gadolinium-based contrast agents (GBCAs) for MRI scans be pulled off the market due to concerns about gadolinium remaining in the body years after scans occur http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=116837

2017 Marc 15 Nephrogenic systemic fibrosis: A 15-year retrospective study at a single tertiary care center: Improvement of renal function through either transplantation or resolution of acute kidney injury with medical management is significantly associated with improvement of NSF. As the body is able to filter out more gadolinium, the symptoms improve.

https://www.ncbi.nlm.nih.gov/pubmed/28318680

2017 May Gadolinium released by the linear gadolinium-based contrast-agent Gd-DTPA decreases the activity of human epithelial Na+ channels: CONCLUSION: These results confirm Gd3+-release from linear Gd-DTPA and indicate that the released Gd3+ amount is sufficient to interfere with ENaC's activity to provide putative explanations for GBCA-related adverse effects. https://www.ncbi.nlm.nih.gov/pubmed/28257815

2017 April Retention of Gadolinium-Based Contrast Agents in Multiple Sclerosis: Retrospective Analysis of an 18-Year Longitudinal Study: Our data corroborate previous reports of lasting gadolinium retention in brain tissues. An increased Signal Intensity Index in the dentate nucleus and globus pallidus was associated with lower verbal fluency, which does not prove causality but encourages further studies on cognition and gadolinium-based contrast agent administration. Functional disturbances. https://www.ncbi.nlm.nih.gov/pubmed/28495943

2017 May 30 Mayo Clinic researchers have confirmed the presence of gadolinium deposits in the postmortem brain tissue of pediatric patients with normal renal function who had previously received MRI contrast.

http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=117472

2017 June 10 Quantification and Assessment of the Chemical Form of Residual Gadolinium in the Brain After Repeated Administration of Gadolinium-Based Contrast Agents: Researchers confirm that the gadolinium found in the brain deposits is in the toxic free form bound to endogenous weak chelates. Prof of Gd dissociation in the body form gadolinium contrast agents. https://www.ncbi.nlm.nih.gov/pubmed/28125438

If you have side effects after receiving a MRI contrast agent, you should speak to your doctor and order a urine and blood sample be sent to the Mayo Clinic for direct testing of Gadolinium.

You can find more information about gadolinium poisoning from MRI contrast and connect with others affected by it by visiting:

On Facebook at, MRI Gadolinium Contrast Awareness , where you can learn more about the toxic effects and have an open discussion on the subject.

On Facebook at , MRI Contrast Side Effects & Research Group . Where you can share more personal experiences about your gadolinium encounter with other patients who have gadolinium poisoning and get advice from people and caring researchers.

On the web at , www.GadoliniumToxicity.com

Or at Yahoo Gadolinium Toxicity support group in Yahoo groups

Doctors, scientists, radiologist, researchers or journalist please Email the author of this article for more information at ToxicContrast@gmail.com

The MRI Gadolinium Contrast Safety Side Effects & Research Group

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