2012 Letter to FDA regarding Gadolinium Toxicity from GBCAs

On October 23, 2012, our efforts to bring attention to the issue of gadolinium retention in patients with normal renal function began with a letter I wrote to the FDA. Because of the significance of that letter and its relevance to our ongoing work in patient advocacy, education, and research, I have decided to make it available to the public by posting a PDF of it on www.GadoliniumToxicity.com.

The purpose of my letter was twofold. First, I wanted to bring attention to the health problems that patients with normal renal function were experiencing after administration of a Gadolinium-based Contrast Agent. Second, I hoped to bring about a realization of the serious health threat that GBCAs might pose to potentially all patient populations including patients with normal renal function. (Note: The individual Patient Accounts mentioned in the letter are not included in the PDF.)

When I wrote the letter, the only gadolinium-related problem recognized by the FDA and medical community was Nephrogenic Systemic Fibrosis (NSF), and it was widely published that it only occurred in people with severely impaired renal function. Patients with an estimated glomerular filtration rate greater than 60 (eGFR >60) were routinely told they would not retain gadolinium. Despite urine test results which showed elevated levels of gadolinium months and even years after their contrast procedures, people with normal renal function continued to be told that their unexplained symptoms could not be caused by the gadolinium-based contrast agent they had received for their MRI.

My research of the literature published prior to 2012 seemed to indicate otherwise, and I believe that more recently published studies have confirmed my concerns and those expressed by other affected patients. Published evidence of gadolinium retention in patients and animals with normal renal function has existed for quite some time. The toxic effects of gadolinium are also well-documented.

I have been in periodic contact with someone at the FDA since early 2013. Though I believe that the FDA seriously considered my letter, it took until July 27, 2015 to issue its first Safety Announcement regarding gadolinium retention in patients with normal renal function. Research is ongoing; however, in my opinion, it is moving much too slowly all while patients continue to be adversely affected. As I stated in my letter, “I believe the already published scientific data related to Gadolinium-Based Contrast Agents and the toxic effects of free Gadolinium call into serious question the long-term safety of using these contrast agents in all patient populations. Based on the totality of the facts, I believe immediate action by the FDA is warranted.” I said that in 2012, and I believe that even more strongly now in 2016.

My letter to FDA Commissioner Margaret A. Hamburg, M.D., dated 10/23/2012, is copyrighted material and my intellectual property. Proper credit should be given when reposting or sharing all or any part of my letter on any print or electronic media.

Due to privacy and security concerns, my phone number and address have been removed. Anyone wishing to speak to me should contact me via email at Sharon@GadoliniumToxicity.com.

Sharon Williams
10/28/2016


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Re: Gadolinium Toxicity from GBCAs

October 23, 2012
Commissioner Margaret A. Hamburg, M.D.
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Bldg. 1, Room 2217
Silver Springs, MD 20993

Dear Dr. Hamburg:

My name is Sharon Williams. I am writing to you about Gadolinium-Based Contrast Agents, which I believe may be placing millions of people at serious risk of irreparable harm. I have come to this conclusion after researching Gadolinium-related articles in order to try to make some sense of my own medical situation. My research has led me to believe that I am a victim of Gadolinium Toxicity caused by the Gadolinium-Based Contrast Agent I received for MRIs. I had 5 MRIs with Magnevist (Gd-DTPA) with a cumulative dose of 90 cc. Since April 6, 2010, 18 days after my 5th MRI with Magnevist, I have suffered from several unresolved and as yet still unexplained health issues. However, this letter is by no means meant to be just another adverse event report about a single patient. This is about a far more complicated and serious situation that has the potential to adversely impact countless others both here in the U.S. and around the world.

Because this situation is so important, I hope you will take the time to consider everything that I have to say before reaching any conclusions. I believe you will find my comments well-reasoned and fact-based.

I have spent more than two years doing extensive research into the problems associated with Gadolinium-Based Contrast Agents (GBCAs). All of my research has been taken from published research studies and articles; nothing I say is based on biased reporting from blogs, message boards or attorney web sites. Despite all my research, I do not for one moment think that I know more than trained researchers and medical professionals; I definitely know that I don’t. However, after reviewing several hundred articles related to Gadolinium-Based Contrast Agents and Gadolinium Toxicity, I believe I can offer intelligent comments that are based on both published scientific facts and logic.

While Gadolinium Toxicity does directly affect me, my overriding motivation is to provide a voice for those who it seems are currently left to fend for themselves in their search for both answers and appropriate medical care. Those with confirmed NSF and the families of deceased NSF patients have an existing community of support; however, those of us with “normal” renal function are still being told that our problems could not possibly be related to our contrast-enhanced MRIs. I believe the published facts indicate otherwise; references are enclosed.

Everything that I’m going to say is based on the fact that Gadolinium (Gd$^{3+}$) is a toxic Rare Earth Element (REE) and it has no known biological use in the human body.$^{1,2}$ Research using Gadolinium Chloride (free Gd) provides proof of its toxic effects.$^{3,4,5,6,7,8,9,10,11,12,13}$ But because of its paramagnetic properties, it was determined that the Gadolinium ion could be chelated or bound to a ligand so that it could be used as a contrast agent for MRI.$^{14,15,16}$ It was thought this complex would permit the GBCA to move rapidly through the body and then be excreted primarily via the kidneys before the toxic ion and ligand could separate.$^{15}$ However, even the report from the initial clinical experience in patients using Gd-DTPA (the first GBCA), warned that “care should obviously be taken in patients with impaired renal and/or hepatic function where high in vivo concentrations of Gd-DTPA may occur for prolonged periods”.$^{17}$ Since at least 1992, dechelation or separation of the ion and ligand due to transmetallation and acid dissociation was confirmed in animal studies.$^{18,19,20,21,22}$ Human in vivo comparative studies confirmed transmetallation occurs in healthy humans.$^{23,24}$ In addition, the release of Gadolinium from all linear Gd$^{3+}$ complexes in human serum from healthy volunteers, was several orders of magnitude greater than predicted by conditional stability constants.$^{25}$ As you read the rest of my letter, please keep the findings in healthy volunteers in mind as I believe these findings provide strong evidence that patients with normal renal function can be adversely affected by the toxic effects of Gadolinium.
Some Background Information: Although it wasn’t known at the time, evidence of a problem related to Gadolinium-Based Contrast Agents first appeared in 1997. Because the problem first presented clinically in a group of dialysis patients with severe skin changes and joint contractures, the disease was named Nephrogenic Fibrosing Dermopathy (NFD).26,27 Further evaluation including autopsies on deceased NFD patients, found that the damage went far beyond the skin.28,29,30 The name was then changed to Nephrogenic Systemic Fibrosis (NSF) to reflect the systemic nature of the disease.31 In 2006 the connection was first made between Gadolinium-Based Contrast Agents administered for MRI and the disease currently known as NSF.32, 33

Since 1997, when problems first appeared, much of the focus has been in trying to determine how and why NFD/NSF happened only in renally-impaired patients and although NSF is known to be a systemic disease, the diagnosis seems to still be driven by the skin changes and “visible” evidence of the disease.34,35 However, residual Gadolinium from GBCAs has been found in bone and other tissue of study animals that did not have NSF-like skin lesions36,37,38,39 and since the free Gadolinium ion is toxic,40 it would seem that any amount of Gadolinium that remained in the body would be of concern due to the damage that it is known to cause.

Here is the problem. It appears to me that the FDA and others are proceedings as though NSF and the problems related to Gadolinium-Based Contrast Agents have all but been eradicated41,42,43 since the FDA instituted new screening and use guidelines in renally-impaired patients.44,45,46 The FDA’s own funding opportunity (RFA-FD-12-029)47 will employ an existing Quality Assurance (QA) registry of patients with renal failure who received GBCAs as a means to evaluate the effect of Cumulative Dosing. While more will be learned about the effects of Cumulative Dosing of GBCAs, the problems associated with GBCAs go well beyond the narrow community of renally-impaired patients and beyond just the skin manifestations of NSF.

There is a growing body of research that provides evidence of Gadolinium or its toxic effects also being found in bone and tissue of both study animals and humans with normal renal function.48,49,50,51,52,53,54,55,56 Based on that research, it seems logical to believe that patients with “normal” renal function (meaning eGFR>60) might also be at risk from injected Gadolinium-Based Contrast Agents.

However, now that there are far fewer cases of biopsy-confirmed NSF, it seems that some NSF experts are moving on to other research interests, which is unfortunate since the toxic effects of Gadolinium still exist. Please keep in mind that NSF is not just a skin disease and it is not caused by the kidneys. Dr. Jonathan Kay, Director of Clinical Trials at Massachusetts General Hospital, has suggested that the disease be called Gadolinium-Associated Systemic Fibrosis or GASF, since as he said, “NSF neither originates in the kidney nor is caused by factors originating in the kidney”.57 It’s the Gadolinium in tissue that seems to drive the fibrosis.58 This is supported in part by several 2010 studies that found that GBCAs and Gadolinium Chloride stimulate fibroblast proliferation in tissue taken from healthy subjects.59,60,61 It should be noted that all GBCAs, including macrocyclic GBCAs, were found to stimulate fibroblast proliferation.62 Macrocyclic agents are thought to be more stable and thereby safer to use; however, even they have been found to deposit in tissue,36,63,64 and there are now confirmed cases of NSF caused by macrocyclic agents as well.65

Despite growing evidence that Gadolinium also affects the blood and tissue of those with normal renal function,59,60,61,62,66,67,68,69 it appears that no one is looking for more widespread evidence of Gadolinium Toxicity or Gadolinium-Associated Systemic Fibrosis (GASF) in all patients. Or if they are, that information has not yet made its way to the local physicians who are treating patients like me. I have conferred with other patients who despite having “normal” renal function also continue to suffer from unexplained health issues after their exposure to Gadolinium. I have enclosed information provided by 6 such patients; I know others that I feel certain would come forward with their medical records, and I suspect it would take little effort to identify many more. However, since we don’t have severe renal impairment (meaning eGFRs <30), most doctors won’t even consider that we could be adversely affected by GBCAs, which in turn means that no one is being told about this potential evidence of a more widespread problem related to the use of Gadolinium-Based Contrast Agents in all patients.

I decided that I could wait no longer for someone else to do something, so I made the decision to contact the FDA myself. I have three requests of the FDA related to Gadolinium Toxicity that I consider equally important; I will provide facts to support each of them. First, the FDA should take a much broader look at the risks
associated with Gadolinium-Based Contrast Agents beyond just the “visible” skin changes and joint contractures described in NSF-related documents, and it should place more focus on what might be happening on the inside of all patients, including those with normal renal function. Second, the FDA should issue new warnings stating that GBCAs can be harmful to patients with normal renal function, and the FDA should issue warnings about Long-term Cumulative Dose Risk from Multiple Exposures. From what has been learned about NSF and Gadolinium-Based Contrast Agents since 2006, it appears obvious to me that although impaired-renal function is the current marker for NSF, it is not the direct cause of NSF or Gadolinium Toxicity. That being said, it makes sense to me (logically and scientifically) that Gadolinium Toxicity can have an adverse effect on those with normal renal function as well and potentially a long-term negative impact on all (or at least many) that are exposed to Gadolinium. Third, the FDA should ensure that all groups of patients are included in future research and data gathering, as well as in retrospective studies in order to obtain a true picture of the scope of the problems caused by Gadolinium-Based Contrast Agents. If you only look at one specific patient population such as the renally-impaired, for predominantly one specific disease symptom like skin changes, how would you ever expect to know with any certainty whether or not other population are also being harmed by GBCAs?

What follows will explain the analysis that got me to this point. I have compiled much more additional information, but I have limited this account to what follows because I believe it is so compelling on its own.

After reading several FDA Advisory Committees’ Briefing Documents, I realized that no one was looking beyond the “visible” damage currently associated with NSF in the renally-impaired for more widespread evidence of the toxic effects of Gadolinium in all patients that have been exposed to Gadolinium-Based Contrast Agents. Important study findings of Gadolinium being deposited in bone of patients with normal renal function and the instability of linear GBCAs in human serum from healthy volunteers appeared to be dismissed simply because they did “not correlate with the relative number of NSF cases reported for the different GBCAs”. Post-Marketing Requirements were only requested to be done in those patients with moderate to severe renal insufficiency. To my knowledge, no one is evaluating patients with eGFRs >60. And even within that limited population of renally-impaired patients, NSF is still being diagnosed as though it only affects the skin as was first thought in 1997.

Should we only be worried if we can “see” the damage being done by a GBCA, or is it also prudent to be even more concerned about the damage that is out of sight and has the greatest potential to do serious or even fatal harm? Reviews of autopsies performed on deceased NSF patients have identified extensive multiorgan fibrosis and calcification, as well as vascular and extracellular deposits of Gadolinium, including in dura mater and cerebellum. The damage done goes far beyond what is visible on the skin; the entire body is involved to varying degrees. Autopsies have also shown that Gadolinium can have adverse effects on: liver, lungs, intestinal wall (ileum), kidney, lymph node, skeletal muscle, diaphragm, mitral valve, pleura, subcutaneous tissue, striated muscles, pericardium, aortic arch, great vessels of the heart, cardiac conduction system, left ventricle and septum, blood vessels, atrial myocardium, lesser pelvis, testes, adrenal glands, pancreas, colon, thyroid, gastrointestinal tract including esophagus and stomach, eyes (including blood vessels of chorionicapillaris), brain parenchyma, subarachnoid space, dura mater including that surrounding the spinal cord. None of these findings are visible with the naked eye, but they are there nonetheless.

Gadolinium is neurotoxic. Brain bio-electric changes have been detected after IV administration of contrast. GBCA Product Labeling indicates that Gadolinium-Based Contrast Agents “do not cross an intact Blood-Brain Barrier”; however, “disruption of the Blood-Brain Barrier” (BBB) or “abnormal vascularity” allows accumulation in lesions such as neoplasms, abscesses, and subacute infarcts. There appear to be multiple ways that BBB permeability might be increased or temporarily altered including by MRI itself. Other ways the BBB might be crossed or altered include: the lack of a BBB on the Optic Nerve Head and circumventricular organs (CVOs) and Choroid Plexuses; having Type II Diabetes or a white matter hypersensitivity like hypertension; diffusion into the vitreous and aqueous humors of the ocular globes, perivascular spaces, and ventricles of the brain; diffusion into the subarachnoid and subdural spaces; effects of Electromagnetic Pulse (EMP), Electromagnetic Fields (EMF), and RadioFrequency (RF) fields. Findings of delayed and hyperintense enhancement of Cerebrospinal Fluid (CSF) have been reported in patients with normal renal
function. What long-term neurological effects might Gadolinium have on all patients when it crosses the Blood-Brain Barrier and/or deposits in brain tissue?

Is there really a logical reason to believe that all these things would happen only to those with severe renal problems? Or is it more likely that even those with normal renal function may have an ongoing fibrotic process that manifests in a chronic rather than an acute manner? It’s estimated that approximately 1% or 15 mg of injected Gadolinium remains in the body from each standard dose – even in those with normal renal function. So what happens when patients have 5, 10, 15, 25 or even more MRIs with contrast such as might routinely happen to MS patients? Might that deposited Gadolinium explain reports of chronic worsening of MS symptoms after contrast MRIs? Could the brain atrophy associated with hyperintense MS plaques also be the result of deposited Gadolinium? And what happens to patients who receive more than the standard dose, especially the triple dose which is often administered for Off-Label use for an MRA? Does anyone really know?

I must say that I’m left wondering why the FDA has allowed GBCAs to still be administered now that it’s known that 1% and perhaps even more of free Gadolinium, a toxic heavy metal, will remain in the patient’s body.

A 1991 article entitled: “Metal Ion Release from Paramagnetic Chelates: What is Tolerable?” found that “minute amounts of chelated or unchelated metals are likely to remain in the body for an extended period and could possibly result in a toxic effect.” The authors acknowledged that this could “result in accumulation of metal ion” and that the “long-term effects of such potential deposition have yet to be determined”. They also said it was “unlikely that MRI contrast agents would be administered repeatedly in patients”. Unfortunately, their assumption was incorrect and many patients do have multiple scans with contrast which results in even more remaining in the body. How much “accumulating metal ion” in the form of free Gadolinium can we tolerate? Have clinical studies been performed to make that determination?

A 2007 study by Abraham et al found that “dermal inorganic Gadolinium concentrations increased over time in patients with multiple sequential biopsies” which was considered to suggest that “Gadolinium may be mobilized over time from bone stores” – “regardless of renal function at present”. Based on what I’ve read this isn’t surprising; since at least the early 1950s, Lanthanide Elements such as Gadolinium have been called “Bone Seekers” and more recent research confirms that free Gadolinium does deposit in bone. Gadolinium was found in hip bones taken from a patient with normal renal function as long as 8 years after the patient’s last dose of contrast. Dr. Henrik Thomsen of Denmark suggested that “long-term observations (e.g., 20 years) will be necessary before we can conclude anything about the safety of Gadolinium-Based Contrast Agents, in particular those with the lowest stability”. The long-term effects of deposited Gadolinium are still unknown and Cumulative Dose is considered by some researchers to pose a long-term risk for potentially everyone at some point in the future, including patients with normal renal function.

While doing my research I came across a 2007 article written by J.F.M. Wetzels, Department of Nephrology, Radboud University Nijmegen Medical Centre, the Netherlands that really caused me to pause and think about the problems associated with Gadolinium-Based Contrast Agents. The title was “Thorotrast toxicity: the safety of Gadolinium compounds”. Thorotrast was a radiocontrast agent used from 1930 to 1960. It wasn’t until the late 1940’s that the first “Thorotrast-related malignancies” were described. Thorotrast particles had been deposited in cells in the liver, spleen, bone marrow, and lymph nodes where they stayed and continually exposed the surrounding tissue to radiation. The problems created by Thorotrast had such a long-latency period that malignancies might not show up for 45 years or more later. Wetzels described what was happening with Gadolinium and NSF through 2006. He said that “Gadolinium is a heavy metal, is very toxic, and free Gadolinium causes severe hepatic necrosis. Therefore, the currently used Gadolinium-Based Contrast Agents are all chelates, which must ensure that no free Gadolinium is present in the circulation”. Wetzels closed by saying, “we must keep in mind that toxic effects may occur less frequently, later, and only after repeated exposure in patients with less severe renal dysfunction”. Like Wetzels, I also wonder if Gadolinium-Based Contrast Agents might be the next Thorotrast. Might they?
These are very sobering thoughts to say the least. So what happens to the estimated “1%” of Gadolinium that was left behind after each MRI? And that “1%” assumes you had good kidney function, with no transient Acute Kidney Injury (AKI),160,161,162 you were not acidic,163 and you had none of the other risk factors known to cause more to remain in your body such as might happen during transmetallation.164,165,166,167,168,169 Other than impaired renal function, researchers have found that transmetallation presents the greatest potential risk for the release of the toxic metal ion from the chelate40,148 this can and has happened in those with normal renal function.23,24,170 Of note is the fact that GBCAs themselves have been found to be Nephrotoxic.171,172,173,174,175,176,177 On autopsies of NSF patients, Gadolinium and/or the fibrosis it caused have been found in many of the same areas where Thorotrast deposited, plus more.178,179,180 At what point will the Gadolinium someone received make its presence known - a month, a year, or 10 years from now? Or will patients spend their lives suffering from nagging, chronic health issues that no one can explain? And how much shorter might their lives be because of Gadolinium Toxicity or Gadolinium-Associated Systemic Fibrosis?

While some may be convinced that the potential benefits outweigh the risks, it doesn’t appear to me that patients even know these risks exist. And yes, a tumor or lesion might be seen that may have otherwise been missed, but while it’s being enhanced it’s also being deposited with a toxic substance in the form of Gadolinium which is known to accumulate in abnormal tissue.15 A 2009 presentation made by Fulciniti et al, found that Gadolinium Containing Contrast Agent Promotes Multiple Myeloma Cell Growth and autopsies on 8 multiple myeloma patients also found “massive quantities of Gadolinium accumulation in tissues regardless of their renal function.” 35 A 2010 study by Xia et al found Gd-containing deposits in brain tumors following contrast-enhanced MRIs in patients without severe renal disease.56 Since at least 1984 it has been known that Gadolinium (Gd-DTPA) “does accumulate at sites of blood-brain barrier disruption with obvious enhancement of central nervous system lesions including tumors and abscesses.15 Since Gadolinium is known to be neurotoxic, what adverse effects might this accumulating Gadolinium have on all patients at some point in the future?

Up until now, it appears that a determination as to whether or not a patient has been adversely affected by Gadolinium is being determined primarily by two things – renal impairment and presentation of skin changes in the patient consistent with the current diagnostic criteria for NSF. Is it possible that when varying amounts of Gadolinium remain in the patient’s body for whatever reason, that it might result in different skin findings or possibly few if any visible skin changes at all? NSF has presented as a progressive myopathy with minimal skin findings and with osseous metaplasia.181,182,183,184 It’s been reported that the skin manifestations in the late stages of NSF are different from those seen early in the disease and have a varied presentation.185,186 And a 2011 Japanese study suggested the occurrence of a non-plaque, late-onset type of NSF.187 If less Gadolinium remains in the body, might there also be differences seen between renally-impaired and non-renally-impaired patients? Based on autopsy findings of NSF patients, isn’t it also possible that the damage is being done on the inside of the patient and not readily seen with the naked eye regardless of the patient’s level of renal function? While there appear to be many unanswered questions related to Gadolinium-Based Contrast Agents, what is known from the literature is that Gadolinium is toxic to humans and varying amounts of it have been detected in bone and tissue of patients - including in patients without severe renal disease.

In addition to the facts presented in my letter which are supported by numerous references from the published literature, I hope you will also consider the Personal Accounts of Suspected Gadolinium Toxicity that are enclosed. I believe they present a strong case that Gadolinium Toxicity does occur in patients with normal renal function in varying degrees and in a variety of ways that are consistent with what has been learned about the toxic effects of free Gadolinium from both animal testing and case studies and autopsy reviews of NSF patients. The patients whose Personal Accounts are enclosed, and the doctors treating them and others like them, need diagnostic criteria that will allow for further evaluation of the possible involvement of Gadolinium Toxicity or Gadolinium-Associated Systemic Fibrosis.

When you put all these pieces of information together, I believe it should be evident that Gadolinium-Based Contrast Agents pose a potentially serious health risk to everyone regardless of their level of renal function. Based on that fact, I believe the FDA should issue a “Safety Alert” regarding Cumulative Dose Risk from GBCAs in all patients. I also believe the FDA should initiate a Retrospective Study on Gadolinium Retention and its short and long-term effects on patients with normally functioning kidneys; to accurately determine the amount of

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systemic involvement in the non-renally-impaired I believe this should also include autopsy reviews of patients having confirmed exposures to GBCAs and normal renal function.

*Until such time as those studies can be completed, patients with normal renal function who are suffering from the toxic effects of Gadolinium need to be evaluated and properly diagnosed.* While responsibility for these tasks might not fall directly under the FDA, I would hope that all government agencies and medical organizations would quickly come together to determine diagnostic criteria for Gadolinium Toxicity and/or Gadolinium-Associated Systemic Fibrosis (GASF). I know there is no cure for GASF at this time, but I firmly believe these patients (patients like me) deserve to know what it is they are facing so that they and their doctors can make more appropriate medical decisions related to their long-term care. Knowing the facts will allow these patients to avoid more unnecessary testing and the related medical expenses. But more importantly, it will allow them to go about living their lives as best they can rather than spending their days desperately seeking answers to their unexplained and unrelenting health issues.

While I understand that the FDA has guidelines to follow, I believe the already published scientific data related to Gadolinium-Based Contrast Agents and the toxic effects of free Gadolinium call into serious question the long-term safety of using these contrast agents in all patient populations. Based on the totality of the facts, I believe immediate action by the FDA is warranted.

I hope you will give this serious problem the consideration that a problem of this potential magnitude deserves. At the beginning I said this is “complicated”, but really it shouldn’t be. No amount of Gadolinium is truly safe to inject into humans, at least not without extensive further evaluation in all patients including those with normal renal function.

Thank you for taking the time to read my letter and supporting materials. I look forward to hearing from someone at the FDA about this matter. Please feel free to contact me by phone at home at [redacted]. My mailing address is: [redacted].

Thank you.

Sincerely,

Sharon Williams

Enclosures: Personal Accounts; Reference List

cc: Secretary Kathleen Sebelius, U.S. Department of Health & Human Services
    Stephen P. Spielberg, MD, Deputy Commissioner for Medical Products and Tobacco (FDA)
    Janet Woodstock, MD, Director, Center for Drug Evaluation and Research (FDA)
    Gayatri R. Rao, MD, Director, Office of Orphan Products Development (FDA)
    John Jenkins, MD, Director, Office of New Drugs (FDA)
    Ira Krefting, MD, Deputy Director for Safety (CDER - FDA)
    Regina M. Benjamin, MD, Surgeon General
    Thomas R. Frieden, MD, MPH, Director, CDC
    Francis S. Collins, MD, Director, NIH
    Sen. Tom Harkin, Chairman, Senate Committee on Health, Education, Labor & Pensions
    Rep. Fred Upton, Chairman, House Committee on Energy & Commerce
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Subtraction Angiography in Patients with Azotemia?

176 chronic renal insufficiency.


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