In 2000 Dr. Sean Cowper described what was then even felt to represent a new disease not previously experienced. Initially named nephrogenic fibrosing dermopathy (NFD) because of its predilection for the skin, it was subsequently recognized to be essentially a systemic disease. Its name was therefore modified to nephrogenic systemic fibrosis (NSF), which it maintains to this day. Unique in that it seems to be present only in patients with significant renal disease, pain, skin induration, thickening, scarring, and decreased extremity range of motion and decreased mobility are all signs and symptoms associated with this disease. It is presumed that increased collagen deposition by fibroblasts may be the cause of these symptoms and their distribution. Roughly 250 patients with biopsy proven NSF are registered at Dr. Cowper's NSF registry database maintained by him at Yale University Medical Center.

In January of 2006 Dr. Grobner first noted that all patients he studied with this disease had received gadolinium-based MR contrast agents (GBMCAs) prior to being diagnosed with NSF. He suggested that the relationship may be more than merely coincidental, and may be a true associative or even causative one. Since then there have been literally dozens of articles that have reported additional cases of NSF in which for the vast majority there was a clearly identified prior GBMCA administration. In the vast majority (more than 85%) of cases reported to date, the single GBMCA that had been administered prior to the subsequent development of NSF was Omniscan (gadodiamide), with the majority of the remaining cases apparently having been administered Magnevist or Optimark.

Although it has been known from the early stages that most cases of NSF were dialysis patients and had received higher than standard doses of a GBMCA, more recent studies have strongly suggested that total cumulative or even lifetime cumulative doses seemed to scale with both the incidence of subsequently developing NSF as well as its severity. Further, it seems that the majority of cases develop in patients with end stage renal disease/renal failure, although there do seem to be some in whom the disease has been diagnosed with they were in severe but not end stage renal disease. One nephrologist has reported seeing the disease in a patient with stage 3 chronic kidney disease (CKD) with a reported glomerular filtration rate (GFR) of 40 ml/min/1.73 m2. Finally, the disease has also now been shown to be able to develop in patients with no chronic renal disease history but who had experienced GBMCA administration during a bout of acute renal injury. In one such instance the patient was documented to have rapidly (within a few
days) recovered the full renal function that been previously present (80 GFR), but not before having received 30 ml of Omniscan. Subsequent to this the patient was biopsy confirmed to have developed GBMCA.

At this stage, although the association between (especially but not only high dose) GBMCA administration and the development of NSF is quite strong in patients with significant renal disease. However, it is important to recognize that with apparent incidence numbers of roughly 3% to 7% of severe renal disease patients who receive a GBMCA, it is not absolute. It seems as though the existence of the GBMCA is a necessary but not sufficient ingredient towards the subsequent development of NSF in these significant renal disease patients.

Present theory suggests that the above can all be explained by transmetallation, or the release of (now unbound) gadolinium into the milieu, perhaps potentiated by the in vivo presence of some molecular competitors for the attention of the gadolinium molecule or its associated ligand molecule. Significant variations in the binding and kinetic constants among the various agents are known to exist, with Omniscan and Optimark reported to have far weaker conditional stability and possibly kinetic stability constants than do the other GBMCAs approved for use in humans today. This may account at least in part for the significant preponderance of the NSF reports being in patients who specifically had received Omniscan prior to being diagnosed with NSF. Some studies have also found that the in vivo presence of high concentrations/amounts of certain potential atomic "competitors" for the molecular bonds between the GBMCA and its ligand molecule may be associated with an increased incidence of NSF development. Further, gadolinium that is almost certainly in an insoluble form (and therefore almost certainly transmetallated from its initial soluble form in which it had been initially administered to the patient) has been reported numerous times now to be confirmed to be present within the tissue biopsies of NSF patients.

There are several bodies and individuals who have issued guidelines or recommendations as to how to approach this issue in general and how to try to prevent the development of future cases of NSF in particular. The FDA had initially published a Public Health Advisory on June 8, 2006, then updated it on December 22, 2006, and again on May 23, 2007. The Europeans and the Commission on Human Medicine issued their own initial guidelines and recommendations on February 7, 2007, only to update them on June 26, 2007. The American College of Radiology published NSF-related guidelines in its "ACR MR Safe Practice Guidelines: 2007" document in June of 2007, only to update the renal disease pre-screening recommendations in the summer of 2007. These all serve to illustrate both the limitations of our own knowledge at this point regarding the disease, its pathophysiology, and avoidance strategies, as well as the rapid rate at which new information is being disseminated throughout the medical community at large regarding this disease and its associations with GBMCAs in renal disease patients.

Present ACR recommendations by the ACR MR Safety Committee include, among others:
Treating all FDA-approved GBMCAs with caution in patients with significant renal disease, but simultaneously recognizing the possibility that there may significant differences in relative rates of NSF development in patients with significant renal disease who get different brands of GBMCAs, and that the number of reported cases with Omniscan far exceeds that which can be explained away confidently by market share data alone.

As a result of the rampant nature of clinically silent significant chronic renal disease, the ACR Contrast Committee and the Subcommittee for MR Safety members now recommends, as of July 2007, pre-screening patients prior to the administration of GBMCAs. It is recommended that prior to elective GBMCA administration a recent (e.g., last 6 weeks) GFR assessment be reviewed for patients with a history of:

1. Renal disease (including solitary kidney, renal transplant, renal tumor)
2. Age >60
3. History of Hypertension
4. History of Diabetes
5. History of severe hepatic disease/liver transplant/pending liver transplant. For patients in this category only, it is recommended that the patient's GFR assessment be nearly contemporaneous with the MR examination for which the GBMCA is to be administered.

For patients with stages 3 or greater CKD (i.e., GFRs at or less than 59 ml/min/m2) or known acute kidney injury, we should consider not administering a GBMCA unless specific case review for that patient suggests that it is still advisable to do so. When administered to these patients it should only be after having first obtained informed consent, when practical, and then only after being ordered by a duly licensed physician for that particular patient at a specified dose and route. Further, as a dose response relationship seems to exist between administration of GBMCA to significant renal disease patients and the development of NSF, serious consideration should be given to administering the lowest dose diagnostically required for the specific pathology and anatomy being examined. It might also be advisable to be more wary of patients with elevated serum iron, calcium, phosphorous, Fosrenol levels, etc. as these might be among the prime competitors for the gadolinium-chelate bond.

Patients already on hemodialysis should be sent to at the very least an initial dialysis session directly from the MR scanner upon the completion of the MR imaging part of the examination.

Finally, for patients who already carry a diagnosis of NSF, it would seem prudent that they not be administered any further GBMCAs.

We are clearly dealing with a rapidly changing and developing issue, and it behooves us all to actively follow the recent developments in this regard for the sake of the safety of the MR imaging process for all involved therein.