Since the initial description in early 2006 (1), a firm epidemiologic link has been established between gadolinium-based contrast (GBC) exposure and development of nephrogenic systemic fibrosis (NSF). When looking back in time, it is interesting to recall that GBC-magnetic resonance imaging (MRI) garnered increased use in patients with kidney disease in the early to mid-1990s based on a perceived safe renal profile (2). Also, higher than approved doses were being used to study renal and other arterial beds with MR angiography. Recognition of NSF in 1997 as a new disease of patients with kidney disease fits nicely as an entity that developed due to a “new exposure,” in this case from GBC. Notably, use of GBC MR studies in patients with end-stage renal disease (ESRD) increased significantly over a 6-yr period (January 2000 to June 2006), which also parallels the increased recognition of NSF (3).

When one surveys the literature, multiple publications (40 case series; 8 case-control studies) strongly argue for an important role of GBC in increasing NSF risk in patients with advanced kidney disease. Greater than 80% had ESRD on dialysis, whereas no clear-cut cases have been described in chronic kidney disease (CKD) stages I to III. All of these studies show a temporal association of GBC exposure and occurrence of NSF, most within weeks to months of exposure. The odds ratio for development of NSF in exposed ESRD patients compared with those not exposed ranges from 20 to 46 (3–6). The prevalence of biopsy-proven NSF in exposed ESRD patients ranges between 1.5% and 5% (3–6), which increases to 13% when primarily clinical criteria are used (7).

The epidemiologic link is further supported by both qualitative and quantitative evidence of gadolinium within tissues of NSF patients (8,9). Gadolinium amounts were 35 to 150 times higher in NSF tissues versus control tissues from healthy patients administered GBC (9). In a recent study, rats were exposed to 4 different gadolinium preparations (gadolinium-EDTA, gadodiamide with/without excess chelate, and gadopentetate), as well as chelate alone, and saline control (10). Based on pharmacokinetic data, the doses administered were similar to twice a triple-dose of GBC in a patient with advanced kidney disease. Skin lesions and histopathology nearly identical to those seen in NSF patients developed with 3 of the gadolinium preparations but not with gadopentetate, chelate, or saline. Interestingly, gadolinium was present in tissues of all exposed animals and was highest in those that received gadolinium-EDTA, gadodiamide (without excess chelate), and gadodiamide with excess chelate, and lowest with gadopentetate. This study strengthens the role of GBC as a causative agent and suggests differences in GBC in causing NSF-like skin lesions.

Although GBC exposure in patients with advanced kidney disease is important in the development of NSF, other risk factors (inflammation, vascular injury, metabolic disturbances, high-dose erythropoietin) are likely involved, but they are far from confirmed (11). Focusing on GBC characteristics is critical to tease out the risk of these agents. In NSF cases where type of GBC was noted, gadodiamide was overwhelmingly the most common agent (>80%), followed by gadopentetate. MedWatch data, with the acknowledged weaknesses confirm this (12). The Yale NSF Registry notes a similar pattern with approximately 85% associated with gadodiamide and the rest with gadopentetate (13). Importantly, market share does not explain these differences as gadopentetate has the highest in the United States. Thus, are differences in GBC characteristics the explanation?

In the United States, 5 GBC agents are available for use; their differences are due primarily to chelate structure (macro cyclic versus linear) and charge (ionic versus nonionic). Briefly stated, macro cyclic structure and ionic charge are associated with better chelate-Gd\(^{3+}\) stability based on both in vitro and in vivo measurements, with structure more important than charge (14). Thus, a nonionic-linear chelate will be least stable and more likely to release Gd\(^{3+}\) and participate in transmetallation (Figure 1), whereas an ionic-macro cyclic chelate will be most stable and not readily release Gd\(^{3+}\). Transmetallation is more likely to occur the longer the GBC agent sits in a test tube or within the bloodstream. Advanced kidney disease, particularly that requiring dialysis, portends the highest risk for transmetallation due to the long elimination half-life for GBC, and thus longer exposure time (11). This may explain why gadodiamide, which uses a nonionic-linear chelate is most commonly associated with NSF, whereas there is a paucity of reports with the macro cyclic chelate-Gd\(^{3+}\) preparations.

In this issue of CJASN, Reilly reports the experience of the North Dallas VA with gadoteridol and sheds light on its asso-


