What can we learn from NSF about broader potential toxicity?

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Conflicts of Interest

Contracted Research: Bracco and Navitas Life Sciences GmbH.
What did we learn from NSF about GCCA toxicity?
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• We proved what Carr, et al. warned against in 1984 (1)
  – “…care should obviously be taken in patients with impaired renal function where high in vivo concentrations of Gd-DTPA may occur for prolonged periods.”

• We probably explained why Wedeking, et al. (2) found the best correlation of long term deposition of Gd in mice with GCCA dissociation rates at pH 1 (acidic) rather than pH 7.4 (physiologic)
  – Lysosomal pH = 4.5-5 (Mindell (3))
  – Gd detected in lysosomes of macrophages (Mizgerd (4))

• An experimental model of fibrosis triggered by lysosome-processed Gd nanoparticles acting through NLRP3 inflammasome release has been developed by Li, et al. (5)

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What do we still need to know?

- **How does one define gadolinium toxicity?**
  - What is a normal gadolinium level? (inputs: dose, EGFR, agent, etc.)
  - Are there other objective measures? (labs, clinical exam, imaging)
  - Is depression a component of the syndrome?
  - Do some patients with NSF have superimposed gadolinium toxicity?
    - What is different about those with NSF who do not have gadolinium toxicity?

- **Are symptoms of gadolinium toxicity reproducible?**
  - Can they be measured quantitatively and objectively?
  - Are they self-limited or progressive?
  - Are deposited foci predictive of symptoms/signs?

- **Is dechelation required to produce symptoms?**
  - If so, in the absence of increased dwell time, is this a dose effect?
  - Is incidence equal among available agents?

- **What are the stabilities of GCCA at lysosomal pH?**
  - Can they be made more stable?