centers need to have more actionable algorithms to monitor and decrease exposure to low dialysate potassium and calcium levels, and more diligence is needed on the part of clinicians regarding monitoring and adjustment of the dialysate prescription. Finally, more in-depth and mechanistic research is needed to evaluate potential SCA etiologies whereby effective interventions can be developed to prevent SCA in hemodialysis patients. Mortality rates remain unconscionably high for dialysis patients, and we, the nephrology community, must do all that is possible to prevent this deadly outcome.

DISCLOSURE
The author declared no competing interests.

ACKNOWLEDGMENTS
This work was supported by grant R01 DK079745 from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, to Bessie Ann Young. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health. This material is the result of work supported by resources from the VA Puget Sound Healthcare System, Seattle, Washington, USA.

REFERENCES

1. United States Renal Data System. *Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health: Bethesda, Maryland, USA, 2009.
2. Bleyer AJ, Russell GB, Satko SG. Sudden and cardiac death rates in hemodialysis patients. *Kidney Int* 1999; **55**: 1553–1559.
3. Davis TR, Young BA, Eisenberg MS *et al.* Outcome of cardiac arrests attended by emergency medical services staff at community outpatient dialysis centers. *Kidney Int* 2008; **73**: 933–939.
4. Bleyer AJ, Hartman J, Brannon PC *et al.* Characteristics of sudden death in hemodialysis patients. *Kidney Int* 2006; **69**: 2268–2273.
5. Lafrance JP, Nolin L, Senecal L, Leblanc M. Predictors and outcome of cardiopulmonary resuscitation (CPR) calls in a large haemodialysis unit over a seven-year period. *Nephrol Dial Transplant* 2006; **21**: 1006–1012.
6. Karnik JA, Young BS, Lew NL *et al.* Cardiac arrest and sudden death in dialysis units. *Kidney Int* 2001; **60**: 350–357.
7. Drechsler C, Krane V, Ritz E *et al.* Glycemic control and cardiovascular events in diabetic hemodialysis patients. *Circulation* 2009; **120**: 2421–2428.
8. Parekh RS, Plantinga LC, Kao WH *et al.* The association of sudden cardiac death with inflammation and other traditional risk factors. *Kidney Int* 2008; **74**: 1335–1342.
9. Krane V, Heinrich F, Meesmann M *et al.* Electrocardiography and outcome in patients with diabetes mellitus on maintenance hemodialysis. *Clin J Am Soc Nephrol* 2009; **4**: 394–400.
10. Winkler K, Wanner C, Drechsler C *et al.* Change in N-terminal-pro-B-type-natriuretic-peptide and the risk of sudden death, stroke, myocardial infarction, and all-cause mortality in diabetic dialysis patients. *Eur Heart J* 2008; **29**: 2092–2099.
11. Herzog CA, Mangrum JM, Passman R. Sudden cardiac death and dialysis patients. *Semin Dial* 2008; **21**: 300–307.
12. Ritz E, Wanner C. The challenge of sudden death in dialysis patients. *Clin J Am Soc Nephrol* 2008; **3**: 920–929.
13. Selby NM, McIntyre CW. The acute cardiac effects of dialysis. *Semin Dial* 2007; **20**: 220–228.
14. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009; **4**: 914–920.
15. Pun PH, Lehrich RW, Smith SR, Middleton JP. Predictors of survival after cardiac arrest in outpatient hemodialysis clinics. *Clin J Am Soc Nephrol* 2007; **2**: 491–500.
16. Lehrich RW, Pun PH, Tanenbaum ND *et al.* Automated external defibrillators and survival from cardiac arrest in the outpatient hemodialysis clinic. *J Am Soc Nephrol* 2007; **18**: 312–320.
17. Herzog CA, Li S, Weinhandl ED *et al.* Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. *Kidney Int* 2005; **68**: 818–825.
18. de Bie MK, van Dam B, Gaasbeek A *et al.* The current status of interventions aiming at reducing sudden cardiac death in dialysis patients. *Eur Heart J* 2009; **30**: 1559–1564.
19. de Bie MK, Lekkerkerker JC, van Dam B *et al.* Prevention of sudden cardiac death: rationale and design of the Implantable Cardioverter Defibrillators in Dialysis patients (ICD2) Trial: a prospective pilot study. *Curr Med Res Opin* 2008; **24**: 2151–2157.
20. Pun PH, Lehrich RW, Honeycutt EF *et al.* Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. *Kidney Int* 2011; **79**: 218–227.
21. Suri RS, Garg AX, Chertow GM *et al.* Frequent Hemodialysis Network (FHN) randomized trials: study design. *Kidney Int* 2007; **71**: 349–359.
22. Ostermann M. Cardiac arrests in hemodialysis patients: an ongoing challenge. *Kidney Int* 2008; **73**: 907–908.

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Am I my brother's keeper?: fratricide in the kidney

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Experimental acute kidney injury (AKI) is accompanied by the death of renal tubule epithelial cells, necrosis and apoptosis of the terminal portion of the proximal tubule, and apoptosis in the distal nephron. While immune competent cells invading the kidney play a role in such cell death, intervention in these processes only partially ameliorates the extent of cell death. Given the results of Linkermann *et al.* in this issue of *KI*, an epithelium-derived component of immune mediated cell death must now be strongly considered.

Kidney International (2011) **79,** 149–150. doi:10.1038/ki.2010.441

Experimental acute kidney injury (AKI) is accompanied by the death of renal tubule epithelial cells, and the degree of renal dysfunction correlates with the extent of injury. In ischemic and cisplatin-induced AKI, cells of the terminal portion of the proximal tubule, which are most prominently involved, undergo necrosis while scattered cells throughout the nephron undergo apoptosis. How these cells die is the topic of active research, but recent focus has placed a major emphasis on the cells that mediate innate and adoptive immunity in the

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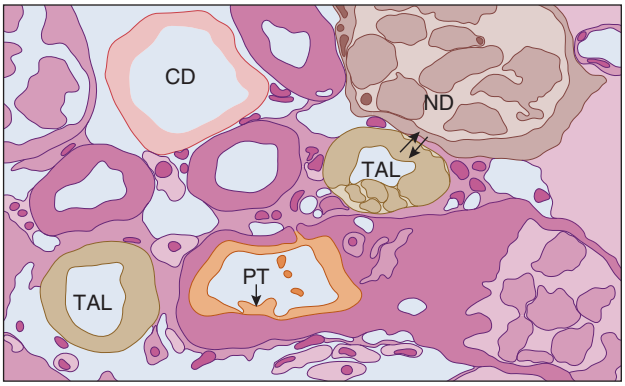

Figure 1 | Section of outer strip of inner medulla from a rat injected with cisplatin 3 days before. Note necrotic remnants of proximal straight tubule in close apposition with surviving thick ascending limb cells. CD, collecting duct; ND, necrotic debris; PT, proximal tubule; TAL, thick ascending limb.

induction of epithelial-cell death.[1] The major evidence for this focus derives from several observations. The first of these stems from the inflammatory nature of the response to injury, including that induced by cisplatin.[2] Intervention in these processes, by either genetic manipulations or inhibition of activated immune participants, has had a salutary, albeit partial, effect on the resultant AKI. An epithelial-derived component of immune-mediated cell death has been neglected.

It has long been known that morphologically intact epithelial cells express chemokines and cytokines more usually associated with leukocytes, suggesting that such cells might act as the source of inflammatory signals.[2] More recently, chimeras of Toll-like receptor 4 (TLR4)-deficient mice show that the epithelial-cell expression of TLR4, and not that associated with myeloid cells that invade the kidney, plays a dominant role in the increased cell death, reduced function, and inflammatory state that characterize cisplatin AKI.[3] These observations, coupled with the close juxtaposition of the relevant cells (Figure 1), make it highly likely that cell-death signals can emerge from neighboring cells. Until now,[4] the possibility of an epithelial-derived form of fratricide, or the killing of brother or sister cells that is much more typical of T cells,[5] has been a source of speculation only.

Linkermann *et al.*[4] (this issue) now provide unequivocal proof that epithelial-derived fratricide occurs in the kidney. It was known that the Fas ligand (FasL) and its receptor Fas, members of the tumor necrosis factor family of death receptors that execute fratricide in lymphocytes, were upregulated in kidney epithelial cells during cisplatin-induced AKI and that inhibition of this system led to protection.[6] What remained unanswered was the precise role of this epithelial-derived system in induction of cell death. Using animals without T cells and natural killer cells, Linkermann *et al.*[4] found that cisplatin induced as severe AKI in such immune-deficient animals as it did in animals with a normal complement of these cells. Only after the addition of an antibody against FasL to such immune-incompetent animals was protection both functionally and histologically achieved. The final proof of fratricide was demonstrated elegantly *in vitro*, where freshly isolated proximal tubules previously exposed to cisplatin *in vitro* execute apoptosis in coculture with similarly isolated thick ascending limbs. Here again induction of apoptosis was inhibited by a neutralizing antibody against FasL.

These experiments resolve some of the long-standing debates about the executioners of cell death in AKI but raise new questions. It would appear that the partial inhibition of AKI using strategies directed at myeloid cells now has an adequate explanation. But beyond that demonstration is the tantalizing prospect that the epithelial cells may communicate with one another on other issues of cell fate. Administration of the anti-FasL antibody *in vivo* reduced necrosis, an event restricted to the proximal tubule *in vivo*, as well as apoptosis, a result more typical of the response in the distal nephron in cisplatin-induced AKI. This suggests that information transfer in these cell types may proceed in both directions. The epithelial compartment of the kidneys of animals exposed to cisplatin is an active participant in a full range of molecular events, most prominently in cells that are not destined to die, including the thick ascending limb.[7] The possibility that such surviving cells communicate with their neighbors (Figure 1), or at a distance through the luminal fluid or via the peritubular blood, to serve other functions besides fratricide must now be considered. By demonstrating this ability of the proximal tubule under stress to affect the cell fate of a neighboring cell should bring renewed focus on the abilities of the epithelial compartment to initiate signals that are determinant of the syndrome of AKI, including regeneration and recovery. The demonstration of the cross-talk capabilities of the stressed proximal tubule by Linkermann and his colleagues[4] should foster a search for the proper spatiotemporal changes in gene expression that more fully explain the syndrome of AKI. These studies should usher in a more tubulocentric approach to issues of cell fate during AKI.

DISCLOSURE
The author declared no competing interests.

REFERENCES

1. Kinsey GR, Li L, Okusa MD. Inflammation in acute kidney injury. *Nephron Exp Nephrol* 2008; **109**: e102–e107.
2. Safirstein R, Megyesi J, Saggi SJ *et al.* Expression of cytokine-like genes JE and KC is increased during renal ischemia. *Am J Physiol* 1991; **261**: F1095–F1101.
3. Zhang B, Ramesh G, Uematsu S *et al.* TLR4 signaling mediates inflammation and tissue injury in nephrotoxicity. *J Am Soc Nephrol* 2008; **19**: 923–932.
4. Linkermann A, Himmerkus N, Rölver L *et al.* Regular tubular Fas ligand mediates fratricide in cisplatin-induced acute kidney failure. *Kidney Int* 2011; **79**: 169–178.
5. Callard RE, Stark J, Yates AJ. Fratricide: a mechanism for T memory-cell homeostasis. *Trends Immunol* 2003; **24**: 370–375.
6. Tsuruya K, Ninomiya T, Tokumoto M *et al.* Direct involvement of the receptor-mediated apoptotic pathways in cisplatin-induced renal tubular cell death. *Kidney Int* 2003; **63**: 72–82.
7. Arany I, Safirstein RL. Cisplatin nephrotoxicity. *Semin Nephrol* 2003; **23**: 460–464.