Reinnovating nephrology—a call to action

Kidney International (2021) **99,** 5–8; https://doi.org/10.1016/j.kint.2020.08.032

KEYWORDS: COVID-19 pandemic; executive order; futurism; innovation; risk-taking; single-cell-transcriptomics

Nephrologists examine cellular and crystalline components of urine as primary data in clinical diagnosis of renal disease. The first demonstration that renal tubular cells in the urine could be successfully cultured came from the urine of neonates in 1972.[1] The concept that urine might be a source of living cells for use in tissue engineering came much later. Since 2012, there has been intense interest in normal human urine as a source of pluripotent stem cells.[2] There has been little exploration of the factors that would increase the cell yield from urine, although one would expect both exercise and dehydration to have effects. The appearance of podocytes in urine presages worsening renal function.[S1]

Twenty-nine years ago, Racusen *et al.*[3] studied cell shedding into the urine in human patients with acute tubular injury and in various animal models. Dr. Racusen (Figure 1) noted that up to 100% viability of the cells shed in human patients and found that in native kidney and transplant acute tubular injury cell shedding reached a peak at 5 to 8 days after insult (Figure 2).

This surprising observation more widely applied as a noninvasive way of sampling renal tissue single cell by single cell could lead to enhanced innovation. Nephrology has been slow to innovate. Genetic discoveries have not influenced clinic practice.[S2,S3] Dialysis is unchanged in 30 years. Diagnosis is still based on the visual appearance of percutaneous biopsy samples. The lack of innovation in nephrology has led to pessimism and disinterest in the discipline. New tools, concepts, and approaches are desperately needed.

Podocyte shedding in the urine has been noted in normal individuals and increases in various disease states. The use of urine as the source of cells for kidney single cell transcriptomics,[4] as opposed to renal biopsies, would enlarge the scope of such studies several-thousand-fold. This has the potential to rapidly transform nephrology in very positive ways. The expansion of single-cell RNA sequencing (scRNA-seq) efforts such as the Human Cell Atlas (HCA) project has the potential to use Dr. Racusen's observations from 1991 as a steppingstone to a deeper understanding of the kidney at a cellular and molecular level.[S4]

The paradigm shift in classification models arising from single-cell transcriptomics will sharpen our understanding of disease etiology, which is currently hypothesized from imperfect phenotypes. Analysis of HCA data redefined blood dendritic cells beyond the traditional combination of cell function, surface markers, and morphology, doubling the number of known cell types. Although the functions and relationships of these newly discovered cells need to be examined in greater detail, the updated classification will undoubtedly improve the accuracy and impact of research in this field. A similar taxonomic revision in kidney medicine through single-cell analysis might increase the number of cell types in the kidney and allow classification of lesion- and disease-state definitions based on definitive cell populations.[4] The discovery of new dendritic cell subtypes helped to explain the ambiguity in traditional blood cell definitions; it is high time that a similar transition from consensus to biology occurred in kidney medicine. Using culturable renal cells naturally shed into the urine provides an avenue for a noninvasive single-cell study.

The U.S. president's executive order of July 10, 2019[S5] had a dramatic effect on the average person's awareness of kidney disease in the United States, and to a lesser extent, in all other parts of the world. It is the first time that the health of a single organ has been the focus of presidential attention. It is interesting that although Google Trends that week showed the short-term effect of the announcement (a doubling of interest that then rapidly came back to baseline over a week), the more impressive graph is the slow and steady 67% rise in interest over the past 5 years (Figure 3). Clearly this is the effect of long-standing American Society of Nephrology (ASN), Renal Pathology Society, International Society of Nephrology, and National Kidney Foundation policies and initiatives that laid the groundwork for the 10 July announcement, such as the

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Figure 1 | Dr. Lorraine Racusen.

Kidney Health Initiative, KidneyX, the rebrandings of these organizations, and the International Society of Nephrology Academy.

The potentially improving profile of nephrology was much in evidence at the ASN Kidney Week 2019 in Washington, DC. Mark Rosenberg emphasized in his Presidential Address that the time is now for unleashing innovation and that the partnership among the American Society of Nephrology, International

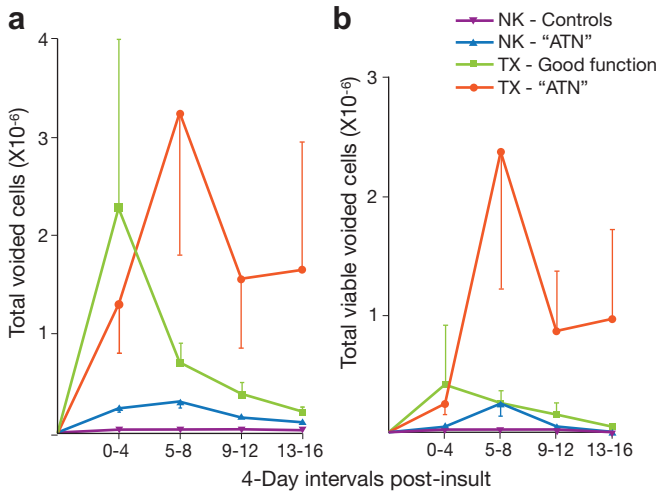

Figure 2 | Excretion of viable tubular cells in the urine over time from original 1991 Laboratory Investigation article.

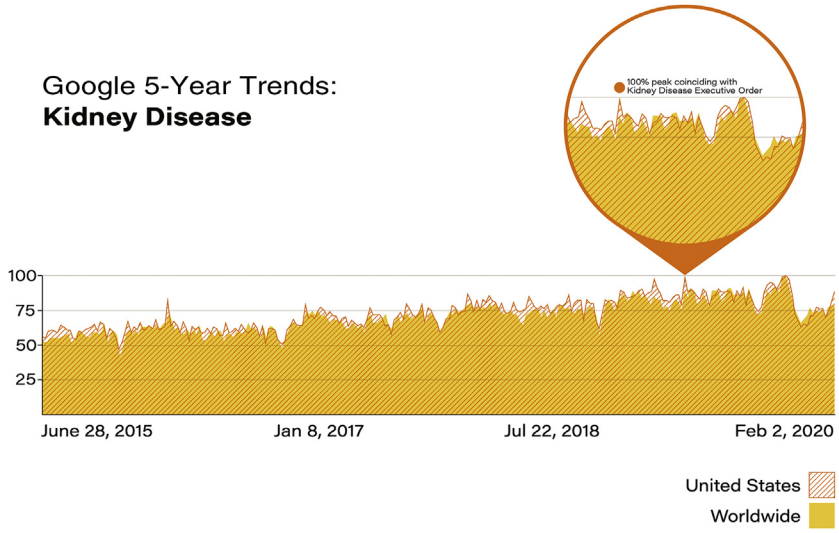

Figure 3 | Google Trends kidney disease over the past 5 years. A slow, steady increase with roller-coaster pandemic alterations in 2020.

Society of Nephrology, and European Renal Association–European Dialysis and Transplant Association allows those organizations to speak with one voice to advocate for patients with kidney disease.[S6] Two days later, the State-of-the-Art lecture, "Perspectives on Innovation and Transformation in Kidney Care," by Dean Kamen, Bruce Culleton, and ASN Executive Vice President Tod Ibrahim outlined the broad possibilities for what should, and must, happen to deliver a brighter future for people with kidney diseases, framing this as a unique moment in nephrology for innovators to begin developing new technologies for diagnosis and treatment.[S6]

This possible new era could mean that quirky things about the kidney, such as the fact that viable culturable renal tubular cells and stem cells so commonly decide to detach from the basement membrane and go out into the urine to see the world, can now be used the capture the imagination of the general public that perhaps previously did not think about the kidney at all. Before 10 July 2019, this fact would have interested few people, but now it can stimulate interest among other areas of medicine regarding how urine stem cells can be the starting material for regenerative medicine initiatives in many organs. So as important as the executive order announcement was for nephrology, it was more important for medicine as a whole, which will greatly benefit from the attention.

The authors teach a course titled Technology and the Future of Medicine LABMP 590 at the University of Alberta.[S7,S8] A 2013 article about the course[S7] is the first publication in the medical literature with the phrase "technological singularity" in the title. The course includes such futuristic subjects as quantum biology and quantum supremacy, digital avatars, and mind uploading. The resistance to these new ideas, and even simple and obvious ones like digital pathology,[S9] was considerable, so much so that it could easily be argued in the past that the course was promoting "ideas ahead of their time" (https://www.youtube.com/watch?v=xXb06CAsPKU).[S10]

All that was changed by the coronavirus disease 2019 (COVID-19) pandemic, which caused a rejigging of mindsets and sudden interest in doing things differently. Resistance to digital pathology melted away, and suddenly everyone was doing it. Society reconfigured itself as we prepared to fight the common enemy—the virus. Kidney disease rapidly emerged as an important component of COVID-19,[S11,S14] and this caused a resurgence of interest in kidney disease in February 2020 (Figure 3). This abated again as everyone fought for basic survival and went into total lockdown in March. Then recently, at least in the United States, there has been a rebound, probably in part due to recognition that COVID-19 causes disease in all four histologic compartments,[S10–S14] including a rejection-like endothelialitis in medium-sized arteries.[S15] The roller-coaster nature of the Google Trends curve at the upper right in Figure 3 is a good metaphor for the way the COVID-19 pandemic has had an impact on all of humanity.

The pandemic, although representing one of the most devastating misfortunes to befall humanity in recent times, has caused renewed openness not only to innovation in nephrology but also in related disciplines of regenerative medicine and tissue engineering. The notion of tissue engineering pathology as the successor to transplant pathology, which was also an "idea ahead of its time" when proposed in 2018,[S16] finds greater acceptance in this new culture of openness.

The fate of new ideas is very much tied to the intellectual climate in which they are born. Originally Dr. Racusen's observations about shedding of living culturable tubular cells into the urine was overshadowed by the Banff Classification founded in the same year, 1991. Now, 3 decades later, the same ideas can be reexamined in light of the spirit of adventure within the intellectual climate that has been brought about by the reopening of the pandemic lockdown.

Nephrology innovation and risk taking is not just an abstract concept. It is also the spirit behind the bioartificial kidney project[S17] and KidneyX, the public-private partnership between the ASN and the U.S. Department of Health and Human Services, which is the conduit through which the secretary of Health and Human Services will promote innovation under the executive order. The mission of KidneyX is to "accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases."[S18] Matching words with deeds, the ASN contributed US$25 million to KidneyX, with a pledge to raise an additional $100 million over 5 years.

Robert Montgomery, a transplant surgeon who worked with Dr. Racusen for many years, recently wrote a perspective promoting risk taking in medicine.[5] With its newfound higher profile, this is the time for nephrology to come into the light and aim high, with innovation and risk-taking. We can take that bold step.

As Goethe said,

> Whatever you can do, or dream you can, begin it.
>
> Boldness has genius, power, and magic in it.

DISCLOSURE

WHF has 4 patents issued in the area of technologies for renal failure (patents 9802158, 9737653, 7332330, and 7048856) and 1 pending in that area (7540963). He is founder of Silicon Kidney LLC, a small business incubating technologies for renal failure. All the other authors declared no competing interests.

ACKNOWLEDGMENT

Dedicated to Dr. Lorraine Racusen on the occasion of her stepping down from membership on the Banff Foundation for Allograft Pathology Board of Directors on 31 December 2019 after 40 years of working in collaboration with Dr. Solez.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)
Supplementary References.

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