

## A future for nephrology?

### Um futuro para a nefrologia?

#### Authors

Richard Glassock<sup>1</sup>

<sup>1</sup> University of California, School of Medicine, Los Angeles - CA, USA.

#### ABSTRACT

It is interesting that some of my predictions came true and some did not, but I think the jury is still out on many of them. I start to remind everyone on the glorious past of Nephrology, from the physiology, translational and methodological discoveries that have contributed to the development of our discipline. I predict that the Academic branch of Nephrology will continue to excel in three domains: *Creative Research, Teaching (Training) and Innovative Clinical Care*. I foresee dramatic changes in Nephrology practice in the short term (10 years) and I discuss which areas will have a most dramatic impact. Many developments will likely curtail the growth of CKD and decrease the burden of ESRD on society. The greatest challenge will be to ensure that *what can be done* to alleviate suffering and premature death from kidney disease *will be done*, in a cost-effective manner, and that all patients with kidney disease have reasonable and timely access to care for their illnesses. Nephrologists practicing in the second quarter of the 21<sup>st</sup> Century and beyond will be justifiably proud of their discipline, just as their predecessors have.

**Keywords:** nephrology; nephrons; physiology.

#### RESUMO

É interessante que algumas de minhas previsões tenham se tornado realidade e outras não, mas acredito que algumas das que não se realizaram ainda têm chance de se concretizarem. Início relembrando a todos sobre o glorioso passado da Nefrologia, da fisiologia às descobertas translacionais e metodológicas que contribuíram para o desenvolvimento de nossa disciplina. Prevejo que o ramo acadêmico da Nefrologia continuará a se destacar em três domínios: *Pesquisa Criativa, Ensino (Treinamento) e Cuidados Clínicos Inovadores*. Vejo mudanças dramáticas na prática de Nefrologia no curto prazo (10 anos) e discuto quais áreas terão o maior impacto. Muitos acontecimentos provavelmente restringirão o crescimento da DRC e diminuirão o peso da ESRD na sociedade. O maior desafio será garantir que “o que pode ser feito” para aliviar o sofrimento e a morte prematura por doença renal “será feito”, de forma economicamente viável. Outro desafio é ver que todos os nefropatas tenham acesso razoável e a tempo ao tratamento de suas doenças. Os nefrologistas praticando essa disciplina, no primeiro trimestre do século XXI e além, terão justificável orgulho de sua disciplina, da mesma forma como tiveram seus predecessores.

**Palavras-chave:** nefrologia; néfrons; fisiologia.

#### INTRODUCTION

About two decades ago I pondered on the provocative topic of “The Future of Nephrology for the 21st Century”<sup>1,2</sup> and then again almost decade ago at a meeting in Brazil. This latter meeting led to a Chapter in the prior Edition of this book<sup>3</sup> which I now have the opportunity of a

revision by way of another look ahead. By now some of my predictions can be assessed for accuracy due to the passage of time. Not surprisingly, some came true and some did not, but also the jury is still out on many of them.

The predictions in this version of my “Nostradamian” views are nuanced by

Submitted on: 07/24/2017.

Approved on: 07/24/2017.

#### Correspondence to:

Richard J. Glassock.

E-mail: glassock@cox.net

DOI: 10.5935/0101-2800.20170087

the considerable uncertainty which grips the globe in the waning years of the first one-quarter of the 21<sup>st</sup> Century—thus explaining the enigmatic question mark (?) at the end of the Title for this Chapter. This question is not intended to be unduly pessimistic about the future of our noble discipline, but rather to highlight the many challenges that lie ahead.

At times of high anxiety about the future, it is always best to heed the words of the great Spanish essayist, poet, novelist and philosopher George Satayana who told us that “those who cannot remember the past are condemned to repeat it”. In this context, I wish to remind everyone of the glorious past of Nephrology, so its grandeur can be repeated over and over. Such epoch making events as basic as the unravelling of the wondrous physiology of the nephron, the dissection of the immunopathology of glomerular disease, the great leaps in understanding the biology of the podocyte and the uncovering molecular anatomy of the transport properties of the tubule easily come to mind.

But one cannot ignore the enormous impact of translational discoveries, such as renal biopsy, dialysis and transplantation, on the development of our discipline and the patients we care for. In many ways, Nephrology emerged and was nurtured by discovery and boldness of thinking and action. Also, methods played a prominent part of its origin and evolution.

Think of electron microscopy, immunofluorescence microscopy, tubule micro-puncture and micro-perfusion, tissue culture, the renal biopsy needle, metabolic balance studies, imaging, surgical innovation, dialysis technology, genetic analysis and modification, randomized controlled trials and *in-silico* research using large data bases, to name just a few.

These methodological discoveries, and many not mentioned, have shaped our profession in crucial ways. We need to remember these achievements and how they influenced Nephrology and its initial attractiveness to the newly minted scientists and clinicians of each succeeding generation, as we deliberate on its future. In this effort to describe a possible future for Nephrology the sub-division of speculations employed in the prior Chapter will be used; namely, Academia and Clinical Practice.

In addition, in preparation for this effort several distinguished leaders in the field of Nephrology were interviewed (in confidence) in order to obtain their views and opinions on the topic. Their views

were often less than optimistic about the future of Nephrology, but they agreed that change is needed to address the current sense of stagnation and angst facing the specialty.<sup>4</sup>

## ACADEMIA

The Academic branch of Nephrology has a long history of achievements in the three domains that characterize their contributions: Creative Research, Teaching (Training) and Innovative Clinical Care. It is likely that Academia will continue to excel in these activities going forward. The prospects in research look bright as powerful new tools, like the CRISPR/Cas9 technology for editing the genome, sophisticated imaging, expansion of computational capacities, structural biology, nanotechnology, precise animal or *in-vitro* modeling of human disease and regenerative medicine, are applied to crucial questions in the biology of the kidney and its diseases.

However, the pace of these developments depend heavily on investments from governments and Industry—and such investments seem to be in jeopardy at this moment in time. Cutting edge research will become increasingly very expensive. It seems probable that there will be a shortfall of funds available for research, leading to a requirement for prioritization and continued stiff competition for support based on a rigorous peer-review system. It does seem clear that multi-institutional collaboration will be the guiding mantra is research and small research groups or individuals will be hard pressed to sustain an independent creative effort.

Clinical trials research, an area where Nephrology has fallen greatly behind other disciplines,<sup>5</sup> may see a renaissance. But this will require a level of National and International co-operation that has not yet been broadly achieved. There is clearly a need for a better organized (and supported) global effort for clinical trials execution in Nephrology. Academic leaders hopefully will catalyse such an effort in the future, in close collaboration with the pharmaceutical industry, philanthropy and public entities (such as the National Institutes of Health, in the USA and its counterparts in other countries).

The renewal of Academic expertise through training of future leaders is a very problematic area, at present, particularly in the USA. Interest in Nephrology careers, both Academic and Clinical, has been waning in the USA for several years,<sup>6</sup> and similar

trends exist in some, but not all, other countries of the world. Hopefully, efforts to reverse this trend being undertaken by National Societies will be rewarded by a return of popularity of Nephrology as a career destination.

I am somewhat sceptical that this will happen, as many of the factors contributing to a declining interest in Nephrology are largely out of the control of National societies (e.g. re-imburement for clinical care, investment in research by government or industry, challenges in obtaining secure employment, student indebtedness). One of the major short-falls in contemporary training is the relative lack of inspirational role models, in my opinion. To remedy this deficiency, a concerted effort to identify, nurture and reward such individuals will be required.

Thus, it seems likely that a period, hopefully short in duration, of a stable or declining number of Nephrology trainees, with degrees and certificates as physicians, is inevitable. Programs to encourage talented individuals to pursue MD-PhD training as Physician-Scientists may blunt this pessimistic viewpoint, but only if ways are found to make such careers stable and productive with adequate sources of research funds, secure compensation and opportunities for academic advancement. If conditions are favourable (sufficient funding and a steady flow of enthusiastic talent) the future seems very bright for research and training in Academic Nephrology.

Future research may well find pathways that: eliminate many monogenetic kidney diseases by embryonic gene editing; create immunologically privileged (humanized) xenogeneic organs for transplantation; construct replacement organs from programmed progenitor cells grafted onto an acellular scaffold; manufacture synthetic, totally implantable, kidney units by nanotechnology; regenerate damaged nephrons; specifically modulate auto- and allo-immune reactions by antigen loaded nano-particles.

These are but a few of the exciting avenues of high-impact research of the future. In order to take full advantage of the enormous progress of research methodology, individuals pursuing academic careers in laboratory and clinical research will need to be familiar with gene analysis and editing, cell biology imaging, structural biochemistry and nanotechnology methods and be prepared to function co-operatively and synergistically within a multi-institutional, geographically-disperse environment.

Clinical trialists will focus on more “deeply” phenotyped disorders identifying potentially responsive patients to the agent or strategy under study. Disease classifications will be dramatically altered due to findings in genomics, transcriptomics, proteomics and metabolomics-new name for old disease and new diseases identified.

Tissue biopsy will evolve to a mechanistic rather than a morphologic interpretation. Epidemiological research will broaden in scope and help to identify new causative pathways for disease. Advances in computational science and bio-informatics will allow for experiments to be conducted entirely in-silico. All of these anticipated changes in Nephrology will provide a rich milieu for the development of the next generations of Academicians and will help to alleviate the burden of kidney disease on society.

#### CLINICAL PRACTICE

In my prior speculations about the future, it was posited that the clinical practice of Nephrology would change slowly and incrementally. This position is no longer tenable. I foresee dramatic changes in Nephrology practice in the short-term (10 years) future, occurring first in the developed nations and later in the less developed nations.

These changes will likely be brought about by the following forces: i) a gradual decline in the societal burden of obesity and diabetes due to better prevention and management of these disorders; ii) a gradual further decline in the progression of glomerular and vascular diseases of the kidneys, due to better diagnosis and treatment; iii) a shift to non-physician based care for outpatient care many chronic diseases, including ESRD; iv) greater use of hospitalist care for inpatients; v) increased application of conservative (non-dialysis) care for ESRD in the frail elderly; vi) greater use of telemedicine, including internet-based consultations; vii) better access to transplantation and improved long-term outcomes for patients receiving kidney transplants.

A dispassionate examination of the potential impact of these changes on Nephrology practice leads to a conclusion that the incidence of newly treated ESRD patients will likely decline, at least in well-developed nations. If the mortality rate among dialysis-treated ESRD stabilizes, then the overall prevalence rate must also decline.

Fewer patients on dialysis means over-capacity of treatment facilities. Increased use of home-based therapies, such as home hemodialysis and peritoneal dialysis, the potential for application of a wearable artificial kidney and a lower rate of return to dialysis due to failed renal transplants will place further pressure to address an over-capacity situation in out-patient hemodialysis facilities.

Unless successful prevention or treatment approaches to severe acute kidney injury (AKI) evolve, it is not likely that the burden of on hospital based dialysis units will change much. Despite these anticipated changes, the care of patients with advanced forms of CKD (Stages 4 and 5) and dialysis-dependent ESRD/renal transplant recipients will continue to dominate Nephrology practice, occupying 70-75% of total patient contact time. Forces countering these trends need to be acknowledged. Better management of hypertension and atherosclerotic cardiovascular disease during earlier Stages of progressive CKD would likely reduce the number of elderly patients who die with (not of) CKD before reaching ESRD. This might paradoxically increase the need for ESRD treatment dialysis or transplantation.

For less developed countries the burden of CKD may actually increase over the short-term, in part due to environmental factors (toxic agents, climate), infectious disease outbreaks, or a continued high prevalence of AKI. Hopefully, better ways will be found to assess the incidence and prevalence of forms of CKD that are destined to progress. Current approaches to this epidemiological challenge have many flaws and pitfalls.<sup>7</sup>

Widespread population-based screening of apparently healthy individuals will not likely diminish the burden of advanced CKD, but such screening among subjects at higher risk for CKD (diabetics, obese persons, hypertensives, those with a family history of kidney disease and indigenous populations) may eventually be proven to be cost-effective and not harmful. Such screening might also contribute to a reduction in ESRD incidence, but at this moment such a benefit is more conjecture than fact. One of the risks of over-enthusiastic adoption of screening for CKD is “medicalization” of the healthy, which would largely affect the elderly population. Other aspects of Nephrology practice are likely to change. Renal biopsy performance is well on its way to being a lost art among Nephrology practitioners, at least in the USA. The emergence Interventional Nephrology Centers, CKD

Management Clinics and Glomerular and/or Genetic Kidney Disease Centers are changing the landscape of practice and joining Dialysis and Transplant Centers in the panorama of places where care is delivered. Fluid, electrolyte and acid-base consultations continues to be shared with Hospitalists and Critical Care physicians. The diagnostic and therapeutic tool-box for a Nephrologist will almost certainly grow exponentially, demanding a systematic approach to learning and use of on-line educational programs to stay current. Genomic analysis, advanced serological testing, sophisticated imaging will become a routine part of practice. Urinary and serum biomarkers, unveiled by proteomics, metabolomics, and microRNA technology will be commonplace as diagnostic and prognostic aids.

Renal biopsy will remain as a vital component of Nephrology diagnosis, but will be interpreted in a more mechanistic fashion that as a pure morphological “snap-shot” of a dynamic process. Glomerular filtration rate will be measured accurately, inexpensively in real-time making estimating equations obsolete. Novel agents acting on well-defined targets will be become available for specific disease states.

Many “incurable” diseases of the kidney will become curable or at least controllable. It may even be possible to develop treatments that are efficacious in reversing acute kidney injury when it is detected in its early stages. The field of renal transplantation will be invigorated by the development of humanized animals as new donor sources and lasting immunological tolerance, without the necessity of continuing immunosuppression will likely be achieved.

Internet-based consultations, including live/real-time interactive sessions will become more prevalent. Computer based and cell-phone access to literature will replace text-books and hard-copy Journals. It is even possible that diagnostic or therapeutic dilemmas will be resolved by electronic interactions with voice-activated, smart cell-phone algorithms mass-produced by the informatics industry- “Alexa help me with this case, please!”.

The Nephrology “team” will broaden to consist of one or more “general-purpose” Nephrologists, CKD/ERSD Nephrology specialists, Transplant Nephrologists, Interventional specialists, a Genetic counsellors, ESRD Physician-Assistant/Nurse Practitioners, Nutritionists, Social Workers, and Informatics specialists.

All of these developments collectively will likely curtail the growth of CKD and decrease the burden of ESRD on society, but they will not affect all of the populations of the world equally. The focus will shift to primary prevention, eliminating ineffective therapies and moving beyond clinical practice guidelines to “personalized” care.

To accomplish this large multi-specialty groups will emerge providing the full spectrum of care, mostly on a pre-paid, per-capita, contracted basis rather than fee-for-service re-imburement after the fact. The greatest challenge will be to ensure that what can be done to alleviate suffering and premature death from kidney disease will be done, in a cost-effective manner, and that all patients with kidney disease have reasonable and timely access to care for their illnesses.

Meeting these challenges will not be easy but the reward will be great. Nephrologists practicing in the second quarter of the 21<sup>st</sup> Century and beyond will be justifiably proud of their discipline, just as their predecessors have.

## KNOWLEDGMENT

This article is based on a lecture presented in May 2017 at the Southern Brazilian Congress of Nephrology in Curitiba, Brazil.

## REFERENCES

1. Glassock RJ. Nephrology in the 21st century: revolutionary changes. *Am J Kidney Dis* 2000;35:S90-2. DOI: [http://dx.doi.org/10.1016/S0272-6386\(00\)70235-6](http://dx.doi.org/10.1016/S0272-6386(00)70235-6)
2. Glassock RJ. American nephrology in 2010: perspectives for its 50th anniversary. *Am J Kidney Dis* 1997;29:633-40. PMID: 9100058 DOI: [http://dx.doi.org/10.1016/S0272-6386\(97\)90351-6](http://dx.doi.org/10.1016/S0272-6386(97)90351-6)
3. Glassock RJ. A Future for Nephrology. In: Riella MC, ed. *Princípios de Nefrologia e distúrbios hidroeletrólíticos*. 5a ed. Rio de Janeiro: Guanabara Koogan; 2010.
4. Rosner MH, Berns JS. Transforming Nephrology. *Clin J Am Soc Nephrol* 2017 May 4. pii: CJN.02310317. DOI: 10.2215/CJN.02310317. [Epub ahead of print] DOI: <http://dx.doi.org/10.2215/CJN.02310317>
5. Inrig JK, Califf RM, Tasneem A, Vegunta RK, Molina C, Stanifer JW, et al. The landscape of clinical trials in nephrology: a systematic review of Clinicaltrials.gov. *Am J Kidney Dis* 2014;63:771-80. PMID: 24315119 DOI: <http://dx.doi.org/10.1053/j.ajkd.2013.10.043>
6. Kalloo SD, Mathew RO, Asif A. Is nephrology specialty at risk? *Kidney Int* 2016;90:31-3.
7. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. *Nat Rev Nephrol* 2017;13:104-14. DOI: <http://dx.doi.org/10.1038/nrneph.2016.163>