The title of this communication has been carefully chosen to indicate that it describes only one of many possible futures for the discipline of Nephrology. If the “past is prologue” then we can expect to observe many dramatic developments in a future of Nephrology. The author began his career in Nephrology more than 40 years ago, when the field was in its infancy. Who could have imagined the enormous scope and impact of developments that have transpired since the early 1960’s? The certain death sentence of end-stage renal disease (ESRD) has been lifted by dual therapies of chronic dialysis and transplantation. Untreatable diseases, such as glomerulonephritis and diabetic glomerulosclerosis, have yielded, at least in part, to innovative therapies. The armamentarium of diagnostic and prognostic tools has expanded greatly. New disease entities, hitherto unrecognized, have been delineated and extensively explored.

Predicting a future for such a dynamic and ever-evolving field is challenging. As has been wisely stated, “one should attempt to predict the future while old (or sick) lest one survives to see the predictions come true”. In order to avoid this predicament, I have chosen as my horizon for the future the year 2044, forty years from now. This is fitting because, as stated previously, 2004 represents the fourth decade of my involvement in the field of Nephrology. For purposes of clarity and organization I will divide my predictions for “A Future of Nephrology” into two broad areas; namely, the clinical practice of Nephrology and basic and clinical research in Nephrology.

Clinical Practice of Nephrology: 2004-2044

From the broadest perspective, the practice of Nephrology in 2044 compared to 2004 will be less dominated by problems of ESRD, including dialysis, and more pre-occupied by issues surrounding the prevention and management of acute and chronic kidney disease (CKD). Prevention of acute renal failure will have greatly reduced the incidence of this complication. Tools to detect and safely and effectively intervene early in the course of CKD will dramatically change, particularly in diabetes and hypertension. The effective application of these tools by physicians and their acceptance will require an enormous readjustment of attitudes and beliefs in society as a whole. Obesity, a common antecedent of Type 2 diabetes, will be the most difficult to control and will be one of the largest stumbling blocks to reducing the disease burden of diabetes and hypertension in the developing nations as well as in the developed nations of the world. Management of the co-morbid factors that frequently attend CKD (such as cardiovascular disease) will become a focus of attention. Pre-emptive renal transplantation will become the preferred modality of treatment for the great majority of patients reaching ESRD (providing that the donor pool expands) and Nephrologists will be the principal caregivers for the long-term management of the successful transplant recipient.

The workload characteristics of Nephrology practice will gradually evolve. The absolute numbers of patients maintained on dialysis (hemodialysis and peritoneal dialysis), the period prevalent population, will slowly expand between 2004
and 2020 and then will stabilize and begin to gradually decrease before 2040. The achievement of an “equilibrium” status (where newly treated patients and those returning to dialysis after unsuccessful renal transplantation equal those dying on dialysis from co-morbid factors, discontinuing dialysis or enjoying long-term success from renal transplantation) will mark a turning point in the history of renal replacement therapy. Better prevention and management strategies for CKD (most notably in diabetes and hypertension, improvements in donor availability and the prevention of late renal allograft failure from the cumulative effects of acute and chronic “rejection” will be responsible for the achievement of this “equilibrium” point. The annual growth in incidence rate of patients newly entering into ESRD therapy will be declining long before 2020 but the period prevalence will not decline until later due to better management of co-morbidity of dialysis patients leading to improved survival. Thus, the average age of the prevalent dialysis population will continue to increase. Better management of cardiovascular co-morbidity in patients with CKD may also allow more patients (mostly elderly) to survive long enough to require dialysis therapy, thus offsetting some of the effects of better management of renal progression of CKD, in terms of the incidence rate of newly treated ESRD. Paradoxically, programs to identify and modify the progression of CKD (and to better manage co-morbidity) may result in a rise in total health care expenditures (for both CKD and ESRD) at least over the short-term. Greater application of pre-emptive renal transplantation will also have a dampening effect on the incidence rate of newly treated dialysis patients, but not treated ESRD as a whole. Early signs of an attenuation of the annual increase in the period prevalence (also called “velocity”) of treated dialysis patients are already evident from inspection of databases in the USA and in Japan. The year-to-year change in period prevalence of ESRD treated by dialysis in the USA has declined from about +15% per year in 1991-1992 to about +7% per year in 2001-2002. Similar changes in the “velocity” have been noted in Japan. Even more dramatic is the deceleration of the year-over-year change in incidence rate of newly treated dialysis patients, which has occurred recently. For example, in Japan the year-over-year change in dialysis incidence rate has been declining since the early 1990’s from +30% between 1984 and 1988 to only +4% between 1996 and 2000. Negative annual growth in age specific incidence rates has been observed in Japan for patients between the ages of 25 and 49 years while the annual growth in age-specific incidence rates in patients ages 65 to 89 has slowed from +77% between 1984 and 1988 to about +19% between 1996 and 2000. It would be anticipated that the predicted changes in incidence and prevalence rates of treated dialysis patients would occur much later in developing countries of the world compared to the developed nations, such as the US and Japan. The potential for rising accessibility to chronic dialysis therapy would overwhelm any effects of better prevention and management of CKD in the developing countries. My “guess” is that the absolute period prevalence of dialysis patients in the USA will rise from about 300,000 in 2004 to an “equilibrium” level of about 750,000 in 2020 of shortly thereafter and then fall to about 600,000 in 2040. Similar projections for the total world dialysis population would be a rise from 1,000,000 in 2004 to 1,800,000 in 2020 and 2,200,000 in 2040. Other, including Collins and co-workers at the United States Renal Data System (USRDS) have projected a more rapid and greater rise in the absolute period prevalence of both ESRD and Dialysis, at least through 2030. They project an absolute period prevalence of treated ESRD (dialysis and transplantation) of 660,000 in 2010 and 2,200,000 by 2030. My much more conservative estimates are predicated on the belief (however optimistic they may be) that advances in early detection and effective intervention in diabetes and hypertension will stem the “rising tide” of ESRD, at least in developed countries. The decelerating annual growth rates in both incidence and period prevalence of treated ESRD observed in developed countries provides some further support to the more conservative projections. About 10-20% of the 2020 growth would be due to the general increase in the population as a whole. Stated in terms of dialysis patient period prevalence relative to the total population my projections for the “equilibrium” point for treated dialysis patient period prevalence will be about 1900-2000 patients per million population, in the developed nations, including the US. Restricted access policies and economic realities in the developing nations will probably place this “equilibrium” point at a lower level, perhaps as low as 800 patients per million population. Some caveats regarding these projections need to be mentioned here relating to total population growth and anticipated changes in population demographics which will likely have a significant effect on future changes in the magnitude and the characteristics of the ESRD population. In the United States the total population is expected to increase from 282,000,000 in 2000, to 332 million by 2020 (18%) and to 390 million by 2040 (38%). My projection for treated dialysis growth between 2000 and 2020 is 168% or about 8.8 times the general population growth. However, the growth will not be uniform among various age groups and ethnicities. Of the 108,000,000 added to the population between 2000 and 2040, 57 million will be between ages of 0 and 65 years, 37 million between ages of 65 and 84 years and 14 million will be age 85 or older. While the overall population growth will be 39% over this period, the growth in
those ages 0-65 years will be 24%, while the growth in those ages 65-84 will be 106% and will be 280% for those 85 years and older. The fraction of the total population 65 years and older will rise from 14% in 2000 to 23% in 2040. These changes in age demographics of the population as a whole are the consequence of the Post-World War II “Baby Boom” projected to begin in 2010 and last until about 2040. Furthermore, the fraction of the total population that are white and non-hispanic will actually fall by 20% (from 69.7 to 56.3%), while the asian, non-hispanic will increase by 85% (from 4.2% to 7.8%), the hispanic population will increase by 60% (from 13% to 21.9%) and the black, non-hispanic population will increase by 6.5% (from 12.3% to 13.1%)3. Thus, by 2040 the general population will be composed of a much higher proportion of elderly, hispanic, asian and black population than today. Since these are populations that are more “vulnerable” to CKD and ESRD (e.g. diabetes and hypertension) than younger, non-hispanic whites, the pool of individuals “at risk” will be increasing while efforts to reduce the occurrence and progression of CKD are being implemented. The success of these ventures in chronic disease control and the degree that they are actively supported by physicians, patients and governments will largely determine the outcome in terms of the future incidence, prevalence, age and ethnic composition of treated ESRD in the United States and elsewhere in the world.

Hemodialysis (HD) will very likely remain as the dominant modality for dialysis related renal replacement therapy. Peritoneal dialysis (PD) will primarily utilize an automated approach, and will be most often used as a “bridge” to transplantation and to home hemodialysis, rather than as a sole modality for long-term renal replacement therapy. My guess is that around 15% or less of the prevalent dialysis population in the world will utilize PD as the predominant modality of long-term renal replacement therapy by 2040. It is conceivable that a bio-artificial kidney or a wearable hemofiltration device could be developed, tested and become commercially available by 2040 or sooner. Conventional HD will increasingly be performed in the home or in small-sized, geographically dispersed outpatient centers utilizing a “more frequent” (e.g. 4-5 times per week) schedule. Of those receiving “more frequent” HD, about 25% will use a home-based overnight (nocturnal) unattended method, and 75% will receive daytime attended sessions in smaller (<10 beds), more geographically disperse units or in the home. Technical advances will make home-based HD easier, safer, cheaper and more accepted by physicians and patients alike. Hemofiltration or hemodiafiltration, using on-line preparation of “ultra-pure” water, will become a common method of treatment. Dialysis devices will be smaller, portable and less complex than those currently in use. Re-use of dialyzer cartridges will disappear as costs of production decline. The use of ultra-pure water (endotoxin free) and individualized electrolyte composition of dialysate will become the standard of care. Most patients (>75%) will utilize an AV fistula for vascular access. Attempts to preserve residual renal function while on dialysis will be a principal focus of management. Kt will replace Kt/V as the preferred method on monitoring individual dialysis dosage. I believe that mortality on dialysis will gradually decline in the USA to about 15% per year overall due to better management of co-morbidity, including hypertension, anemia, coronary artery disease and congestive heart failure; however. This could be offset by the gradual aging of the treated dialysis population and the attendant increase in the extend to co-morbidity in the dialysis population.

The organization of healthcare for patients with CKD and ESRD will gradually evolve. In the US most patients will be enrolled in a federally mandated program of disease management. Practice guidelines will be widespread and utilized to monitor the quality of care. Data bases on age, modality and co-morbidity adjusted outcomes will be universal and accessible to the public. Reimbursement will be based on a global “bundling” of services, including dialysis treatments, physician and physician assistant fees, primary and specialty care, hospitalizations and emergency room visits, medications (parenteral and oral), diagnostic tests, transportation and interventions for vascular access maintenance adjusted by age, diagnosis and co-morbidity score (e.g. Charlson Co-Morbidity Index). The “panel size” (e.g. number of patients under active management by a single Nephrologist lead team) will be determined in the US by Federal reimbursement policy. The median “panel size” in the US will be about 75 patients.

Assuming that the prevalent dialysis population will be about 750,000 patients in the US in 2020, we will need about 10,000 Nephrologists by 2020, or about twice as many as are available in 2004. Since training programs currently deliver only about 250 new practioners per year (<5000 by 2020) and retirement of currently practicing Nephrologists may accelerate between 2004 and 2020, it is possible that a shortage of Nephrologists to lead treatment teams will develop between now and 2020. Enlarging the size of existing training programs or expanding the number of training programs could represent a response to this possible shortage in manpower but this would require the infusion of a large amount of funds for training stipends. This is not likely to occur. Alternatively, Nephrologists could delegate more of their ESRD-related clinical activities to a cadre of specially trained assistants (nurse practioners or physician assistants) allowing for a smaller number of Nephrologists to care
more effectively for a greater number of ESRD patients. I believe that the latter is more likely to occur than the former. In any case, when the dialysis population begins to decline (in absolute terms) after the “equilibrium” period is reached, the possibility of a surplus of Nephrologists looms. The global response to the manpower issues involved with a gradually rising prevalence of treated dialysis patients is far from certain. It is likely that each country will evolve its own way of dealing with the issue consistent with the availability of specialized training and the systems of healthcare delivery. General or Family Practitioners may be called upon to deliver a significant portion of care for ESRD and dialysis, supported by a small cadre of Nephrology consultants. This has already occurred in some developing countries, as a response to a deficit in trained Nephrologists, without any apparent detrimental effect on outcome (mortality and morbidity).

In the developed countries, the Nephrologist-led team of future ESRD care-givers will consist of one or more Nephrologists, one or more physician assistants/nurse practitioners, a renal nutritionist, a renal social worker/psychologist (with expertise in compliance assurance), a technologist, a nurse educator, a clerical/data base manager and an administrator. Formal consulting agreements will be in place with Pharmacists, Podiatrists, Cardiologists, Diabetologists, Ophthalmologists, Geriatricians and other Specialists, Clinical Laboratories, Vascular Access Centers (Radiologists and Vascular Surgeons/Access Interventional Nephrologists), and Transportation Specialists. The growth in the absolute period prevalent dialysis population between now and 2020 will exacerbate the widespread shortage of nursing and technical personnel for the management of patients undergoing center-based treatments. To some extent at least, this manpower shortage will be offset by movement to greater use of home dialysis and by the development of dialysis hardware requiring less monitoring. Self-care in smaller, more geographically disperse centers using more frequent dialysis treatment schedules will also alleviate this personnel shortage.

The day-to-day practice of a Nephrologist will increasingly be segregated into Ambulatory-dominant practice (Home and Center based dialysis, outpatient Access Centers, Outpatient consultation, procedures and follow-up) and Hospital-dominated practice (Intensive care, transplantation, in-patient co-morbidity management, hospital based consultation and procedures). Selected outpatient centers will be identified as Access Centers capable of delivering a full range of diagnostic and interventional procedures, often on a mobile basis.

Renal transplantation, carried out on a pre-emptive basis, will increase substantially driven by improvements in short and long term results of allografts. The availability of donors will continue to be a major limiting factor, but the use of "expanded-indication" cadaver donors, non-heart beating cadaver donors and living, unrelated donors will mitigate the shortage of donors to some extent. By 2020 approximately 25,000 renal transplants will be performed annually in the US with a >90% 3 year kidney survival rate and a >75% 10 year kidney survival rate. Surviving transplant recipients with functioning grafts will more than triple between now and 2020, if a source of donors can be expanded. A few centers will begin to perform genetically modified porcine xenografts by 2020 and the procedure will become “routine” by 2040, thus fully alleviating the “donor” shortage. Long-term survival of renal allografts (but not xenografts) without maintenance immunosuppression (operational acquired tolerance) will be achieved by 2040. Pancreas and islet cell transplants will no longer be needed for treatment of diabetes by 2040 because of the development of effective primary preventative strategies for Type 1 diabetes mellitus (genetic and auto-antibody profiling and pre-insulinopenic interventions, such as immunosuppression or stem cell therapy). Recurrence of original disease, death from co-morbidity (e.g. cancer) and the development of chronic viral disease will be the main factors limiting long-term success of renal transplantation.

Several monogenic diseases contributing to the development of ESRD (e.g. autosomal dominant polycystic kidney disease, Fabry’s disease, Alport syndrome) will be prevented and/or treated by genetic or cellular manipulation (gene therapy, stem cell therapy). Many chronic progressive forms of glomerulonephritis (e.g. Lupus nephritis) will be controlled by early identification (genomics, proteomics, auto-antibody profiling) and intervention with mechanism-specific targeted agents.

Type 2 diabetes mellitus will be declining as a cause of ESRD before 2040 due to the application of safe and effective strategies to control obesity and insulin resistance and to preserve (or replace) b-cell function. Progression of microalbuminuria to overt nephropathy will be halted by early detection and selective intervention strategies, involving Angiotensin inhibition, AGE inhibition or cross-link breaking and counteraction of the effects of TGF-b1.

Basic and Clinical Nephrology Research: 2004-2044:

By 2020 the dominant themes in basic nephrology research will be: 1) High throughput mouse mutation models of human disease (cell and tissue specific site directed mutations); 2) Isolation, propagation, selective differentiation and transplantation of embryonic and adult stem cells; 3) computational science involving the analy-
sis and modeling of the three dimensional structure of biologically active molecules leading to an understanding of protein folding, cellular distribution and disposal, structure-function relationships and synthesis of small molecule active compounds; 4) Differential display of genes and proteins in the course of specific diseases. Most of these studies will no longer be carried out in individual investigator laboratories. The collective efforts of larger groups of investigators, often collaborating over long distances (via the Internet), will be the dominant source of new discoveries. Federal and non-federal research funding will gravitate to and facilitate these collaborative group arrangements. The solo investigator will be a relic of the past by 2040.

By 2020 the dominant themes in Clinical Renal Research will be: 1) The identification of the molecular factors involved in susceptibility to specific renal diseases thus permitting early diagnosis and intervention in both hereditary and acquired forms of renal disease; 2) Studies of the molecular basis of variability in the response of individual patients and diseases to treatment (Pharmacogenomics); 3) Testing the safety and efficacy of new products specifically targeted to a defined mechanism of disease susceptibility, development or progression in homogeneous patient populations (somatic gene therapy, gene transcription inhibitors, receptor agonists and antagonists). The dominant disciplines and technologies utilized in clinical renal research will be: 1) Drug delivery systems and vectors; 2) Clinical informatics; 3) Clinical epidemiology and outcomes analysis; 4) “Designer” drug development and testing; 5) Gene, Protein and Auto-antibody profiling for diagnosis and prognosis.

Opportunities will abound for both basic and clinical renal investigation in the next several decades. These opportunities will be present not only in traditional academic pathways in basic science and clinical departments in schools of medicine but will also be present in freestanding research institutes and centers and in pharmaceutical companies with significant commitments for research and development. The latter will increasingly be focused on specific “themes” of research (such as stem cell biology or structural biology). Preparation for a career in basic research will require a PhD (with or without an MD) and at least three years of laboratory training and experience. Preparation for a career in clinical research will require an MD and in some instances an MPH. Expertise and training in clinical trials, clinical epidemiology, outcomes research, database management and analysis will be essential. Most clinical research will be conducted in an interdisciplinary manner by larger groups investigating a common thematic area. Solo clinical investigators will be a relic of the past by 2040 or sooner.

Summary, Conclusions and Further Speculation:

In describing a possible future of the discipline of Nephrology I have tried to allow my imagination to express itself without too many restrictions. Whether any of the resulting predictions prove to be correct is immaterial. Taken literally, they represent the musings of a septuagenarian, partly retired, former Academic who has seen and experienced the remarkable transformation of Nephrology from a nascent discipline to a mature and vibrant specialty in the last four decades. I am very confident that the next four decades will be just as exciting (and unpredictable). It seems likely that many kidney diseases considered untreated or only partially treatable today will come under control in the not too distant future due to the benefits of the revolution in molecular biology. The size and characteristics of the population of patients with CKD and ESRD are also likely to evolve in interesting new directions, with significant differences between the developed and the developing world. The “gaps” in availability and sophistication of care for patients with renal disease that currently exist between the developed and developing nations is likely to increase. Nephrology practice seems likely to differentiate further into “Ambulolist” and “Hospitalist” branches and to require a more team-oriented format for efficient and effective operation. Nephrology research will also be more collaborative and group-oriented. Basic biology has provided powerful new tools to uncover fresh insights into mechanisms of disease. Translation of these insights into innovative new approaches for prevention and treatment of disease is likely to accelerate. While every generation believes that they lived in and experienced a “Golden Era”, for myself I believe that the best is yet to come.

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REFERENCES