ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

ASN 50 years

Kidney News

March 2016 | Vol. 8, Number 3

Living Donor Protections Included in Act Introduced by Congress

A new bill introduced by Congress in February 2016 aims to encourage living organ donations and protect the rights of living organ donors. The bill would also set the stage for education efforts on living organ donation to be instituted by the US Department of Health and Human Services.

The proposed legislation would prohibit providers of life, disability, and long-term care insurance from denying or limiting coverage to living organ donors. It would also prevent insurers from charging higher premiums. In addition, the bill clarifies that living organ donors may use time allotted to them through the Family and Medical Leave Act to recover from donation surgery and thus maintain their job security (Table 1).

"By creating job security for living organ donors and ensuring them time to recover from their donation surgeries, as well as ensuring education concerning these new protections, this important legislation will likely help countless Americans receive the gift of life," said ASN President Raymond C. Harris, MD, FASN.

The number of people affected by kidney disease is staggering. According to the National Institute of Diabetes, Digestive, and Kidney Diseases, 1 in 10 American adults—more than 20 million people—are affected by some level of chronic kidney disease (CKD), and the numbers are increasing. A patient is added to the kidney waitlist every 14 minutes, and despite the fact that this list is always growing, living donation rates are decreasing. In all, 12 Americans die each day waiting for a transplant.

The Living Donor Protection Act of 2016 was introduced with bipartisan support by both houses of Congress, with Reps. Jerrold Nadler (D-NY) and Michael Burgess (R-TX) and Sens. Mark Kirk (R-IL), and Kirsten Gillibrand (D-NY) proposing the legislation.

The American Society of Nephrology was one of 16 kidney health organizations that united to advance the legislation on Kidney Community Advocacy Day in 2015. ASN will continue to work toward

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History of Hemodialysis Could Help Guide Ethical Use of Medical Resources

By Tracy Hampton

Ongoing advances in technology and drug discovery continue to transform numerous aspects of health, but making such breakthroughs available to all who may benefit from them is often not possible, especially in the early days of their use. Furthermore, as society strives to address rising healthcare costs and consider responsible distribution of limited healthcare dollars, many questions arise regarding the most appropriate use of expensive tests and therapies.

A new paper in the *Clinical Journal of the American Society of Nephrology* addresses such questions, using the history of the development and dissemination of maintenance dialysis as a guide (Butler CA, et al. *Clin J Am Soc Nephrol*. doi: 10.2215/CJN.04780515 [published online February 11, 2016]).

"The medical research community is feverishly developing new technologies and drugs offering a plethora of treatment options; however, the existence of these treatments does not direct how and for whom they should be used," said lead author Catherine Butler, MD, of the University of Washington. "Increasingly, medical practitioners, lawmakers, and laypeople take part in debate about this complex distribution. This discourse is best coordinated by participants understanding a common structure of ethical evaluation."

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Inside

Living Donor

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its passage into law.

"Introduction of this bill is very timely since living kidney donation has been in a downward trend for a decade—6647 donors in 2004 compared with 5075 donors in 2015 (Figure 1). Quite paradoxically there has been a significant rise in 'paired-exchange donations' since 2008, accounting for >1700 transplants so far in the US, and without this novel undertaking it is likely that the total number of living donor transplants would have been much worse," said KN Editorial Board member Uday S. Nori, MD, a nephrologist with Ohio State University Wexner Medical Center in Columbus.

"This observation underscores that there are serious systemic problems that need to be addressed urgently," Nori said. "Although the specific causes for this trend remain unclear, it is widely believed that loss of wages during the donation time along with the fear of penalization by insurance providers in the long-term are significant deterrents for living donor candidates. Successful passage of this new legislation would offer important incentives to heighten the interest in living donation."

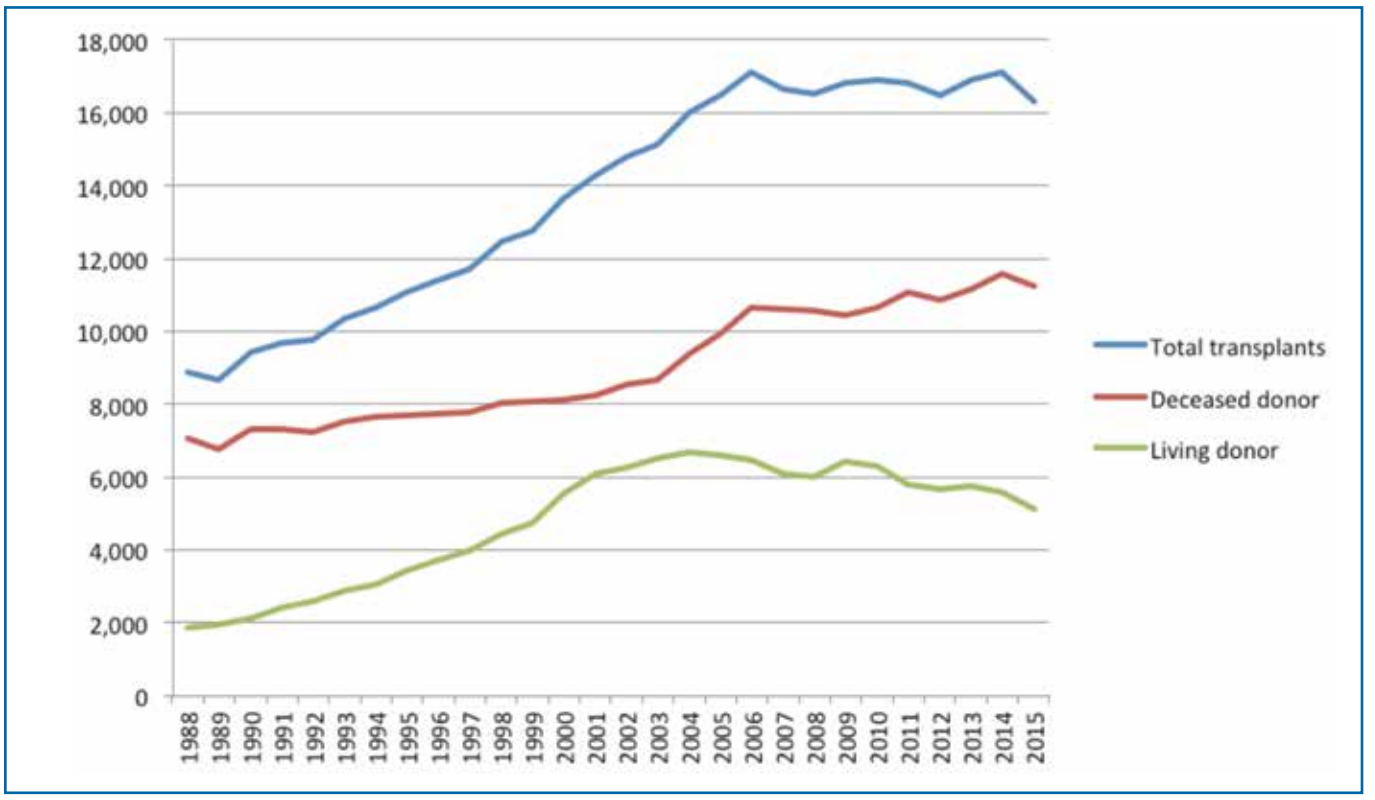
Douglas Keith, MD, of the University of Virginia Medical Center, presented findings at Kidney Week 2015 that showed a much lower living kidney donation rate for African Americans compared with that for Caucasians, Hispanics, and Asians. His study looked at the impact of organ transplant candidates' socioeconomic environment on living kidney or kidney-pancreas donation rates.

Kidney News asked Keith whether provisions of the Living Donor Protection Act might help close the gap in living organ donation rates among those from different socioeconomic environments.

"I think it may have a modest effect on donation in general but I doubt it will have a large effect on African Americans. The gap in donation between Caucasians and African Americans is driven in my opinion by two major issues. One is the African American donor population has high rates of obesity, diabetes mellitus, and hypertension, making them much higher risk for donation and more likely to be found unsuitable for donation and declined as donors. Second, socioeconomic status is much lower on average in the African American population of recipients and donors in the US. I suspect few if any of the donors have life or disability insurance so that is not likely a factor in their decision," Keith said.

"Family leave for donation could potentially help this group since loss of employment due to donation in low socioeconomic populations is an issue," he said. "Many people in low wage jobs cannot be off work for the 6 to 12 weeks required to recover from donation and keep their job—they have no benefits that allow for this. The other issue is the loss of income while recovering from donation. Reimbursing donors for lost wages while recovering from donation may have a larger effect on low socioeconomic groups. Unfortunately, this legislation only prevents job loss but does not compensate employed donors for lost wages, a major factor that may influence donation."

Figure 1. Transplantation rates, 1988–2015



Courtesy: United Network for Organ Sharing, https://optn.transplant.hrsa.gov/

Table 1. Provisions of the Living Donor Protection Act

The bill promotes access to living kidney donations by:

- ***Protecting Donors***: prohibiting insurance companies from charging higher premiums and from denying or limiting life, disability and long term care insurace to living donors
- ***Securing Jobs***: clarifying that living organ donors can use Family and Medical Leave Act time time to recover from donation surgery and maintain their job security
- ***Educating Americans***: directing HHS to improve efforts to educate Americans about living kidney donation

World Kidney Day Puts Spotlight on Kidney Disease in Children

"Kidney Disease and Children" is the focus of World Kidney Day on March 10, 2016.

Each year, World Kidney Day seeks to raise awareness about the importance of the kidneys to overall health and to increase support for reducing the incidence and impact of kidney diseases and associated health problems worldwide.

Kidney diseases can affect children in various ways, ranging from treatable disorders without long-term consequences to life-threatening conditions. Some children are born with kidney diseases and others develop symptoms while very young. These symptoms in children are often nonspecific, and can be missed. Yet the missed symptoms can grow over time and result in adult chronic kidney disease.

"Early detection and a healthy lifestyle in children are crucial to mitigating the incidence of adult chronic kidney disease," said ASN President Raymond C. Harris, MD, FASN. "Kidney disease that manifests in adulthood may occur more often in those with risk factors that could be detected in childhood."

The American Society of Nephrology is working with the American Society of Pediatric Nephrology (ASPN) to recognize the importance of preventing and treating childhood kidney diseases on World Kidney Day in the US. Other events are being held around the world from Japan to Buenos Aires, Argentina.

The ASPN and Congressional Kidney Caucus will host a congressional briefing, "Kidney Disease in Children . . . Act Early to Prevent It," on March 10, 2016. The briefing aims to inform policymakers about the impact on families of having a child with kidney disease and the role Congress and regulatory agencies can play in the pediatric kidney disease population. Among those supporting the event are ASN, the Polycystic Kidney Disease Foundation, National Renal Administrators Association, American Association of Kidney Patients, and Renal Physicians Association. The hearing is provided in cooperation with the American Nephrology Nurses Association.

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History of Hemodialysis

Continued from page 1

Butler noted that because the themes explored in the history of dialysis are common and recurring among newly developed medical technologies, they may serve as a template for future discussion in parallel fields. As an example, the researchers highlight Medicare's recently announced National Quality Strategy, which seeks to build a healthcare delivery system that's better, smarter, and healthier. It includes 3 aims—better care for the individual, better health for populations, and reduced healthcare costs—that can only be reached by addressing multiple, and sometimes conflicting, values.

In their Ethics Series paper that considers the history of hemodialysis, Butler and her colleagues trace the ethical conundrums that arose at various times during the adoption and distribution of dialysis. "The first formal method of medical ethics grew up with the technology and set a precedent for many future medical resources," Butler said.

Hemodialysis was conceived in the 1940s, but it wasn't until 1960, when the Quinton–Scribner shunt (designed by Wayne Quinton and Belding Scribner, MD) allowed repeated vascular access, that maintenance dialysis became feasible. In 1962, a committee of laypeople in Seattle attempted to fairly distribute a limited number of maintenance hemodialysis stations guided by considerations of justice. Later, as technology advanced, dialysis was funded under an amendment to the Social Security Act in 1972, and patients with end stage renal disease were entitled to receive Medicare benefits. With this change, the focus shifted to providing dialysis for all who needed it, which lessened the ethical stress of how to fairly distribute resources but created new questions such as how to balance longevity and quality of life and how to understand and respect patient preferences. Also, with funding available through Medicare, a growing number of older patients with comorbidities began dialysis, and utilization grew to the point that Dr. Scribner suggested the need for a "deselection committee" because the criteria for starting dialysis had become so liberal.

Butler's team found that the 4 principles forming the basis of clinical ethics—beneficence, nonmaleficence, autonomy, and justice—are emphasized to varying degrees over time. In the early days, the survival benefit offered by dialysis provided a strong argument for beneficence in initiating treatment, but it later became clear that the toll of treatment on quality of life sometimes outweighed the benefit, highlighting a role for the concept of nonmaleficence. Also clear is that a well informed and autonomous person is in the best position to consider whether initiating maintenance dialysis will support his or her own values and preferences. Therefore, clinicians must ensure that patients receive adequate information and work together with patients to establish appropriate and individualized treatment plans. Finally, the authors note that recent scrutiny of healthcare spending has put a focus on the just allocation of limited Medicare funds, and the utility of dialysis is not simply being compared among kidney failure patients but also in the context of payments for coronary stent placement, supporting cancer research, or instituting preventive health programs.

"Through the history of hemodialysis, the 4 bioethical principles are weighed differently as forces of technologic innovation, resource limitation, and social values change," said Butler. Because of this variability, creating sustainable ethical solutions may require considering and addressing all 4 ethical principles as fully as possible.

"I found the article very thorough and, to the best of my knowledge, very accurate. It is certainly one of the best expositions of one of the early bioethical dilemmas," said Albert Jonsen, PhD, emeritus professor of Ethics in Medicine at the University of Washington's School of Medicine. He noted that he and the late Dr. Scribner once talked about how commercial dialysis had become, and Dr. Scribner noted that he had often been asked why he didn't patent the shunt. "He said he had never given it a thought, then went on to say that he deplored the formation of so many dialysis centers to exploit patients for whom dialysis was of marginal value," said Dr. Jonsen. "He concluded that he had never made a penny from the shunt or from such profit-making dialysis centers: to do so would be profoundly unethical."

Govind Persad, PhD, a junior faculty fellow in ethics at Georgetown University, added that it may be useful to bring nonclinical components into the discussion. "The article makes the welcome and important point that, at the level of health policy, dialysis must be compared to alternative medical interventions. I would add that dialysis also must be compared to non-medical interventions," he said. "One promising avenue for further research is considering what approach—whether the 4 principles or something else—is best for making these kinds of comparisons." He noted that administrators and policymakers, such as those tasked with implementing Medicare's National Quality Strategy, "frequently employ cost-effectiveness analysis and cost-benefit analysis, but proposals for alternative approaches would be welcome."

Co-authors include Rajnish Mehrotra, MD, MS, Mark Tonelli, MD, MA, and Daniel Lam, MD.

Disclosures: Daniel Lam receives some salary support from the Northwest Kidney Centers as their Palliative Care Medical Advisor.

The article, titled "The evolving ethics of dialysis in the United States: A principlist bioethics approach," is available at http://cjasn.asnjournals.org/content/early/2016/02/10/CJN.04780515.abstract.

Findings

Three new genetic risk factors for kidney disease in type 2 diabetes

Three genetic variables are identified as predictors of chronic kidney disease (CKD) in Chinese patients with type 2 diabetes, according to a study in *Kidney International*.

The study used a new three-stage procedure to test the hypothesis that genetic variants associated with type 2 diabetes, obesity, and fasting plasma glucose might be associated with type 2 diabetes-related CKD. This process was carried out using a large clinicogenomic dataset from a prospective cohort of 2755 patients with type 2 diabetes from the Hong Kong Diabetes Registry.

The model included 25 clinical variables and 36 genetic variants associated with type 2 diabetes, obesity, or fasting plasma glucose. Clinical, genetic, and clinicogenomic models were compared, and the effect of the top selected genetic variants on the clinicogenomic model was assessed. The selected genetic variants were subsequently validated in two independent cohorts.

Of the top six single-nucleotide polymorphisms selected from the clinicogenomic data, three were associated with significant improvement in prediction performance. These were the rs478333 variant of the gene G6PC2 and the rs7754840 and rs7756992 variants of CDKAL1. Patients with the rs478333 variant had a faster decline in eGFR—greater than 4 percent per year. On meta-analysis in replication cohorts, the as-

sociations for rs478333 and rs7754840 remained significant after adjustment for conventional risk factors.

The three implicated gene variants seem to be novel predictors of CKD associated with type 2 diabetes in a Chinese population. Jian et al. believe that their three-step process may be useful for selecting predictors of clinical outcomes in other large datasets including clinical and genetic data [Jian G, et al. Genetic and clinical variables identify predictors for chronic kidney disease in type 2 diabetes. *Kidney Int* 2016; 89:411–420].

Adding insulin to metformin increases hypoglycemia risk

For diabetic patients on metformin who require treatment intensification, adding insulin rather than sulfonylurea is associated with an increased risk of hypoglycemia, reports a study in the *Canadian Medical Association Journal*.

Using the Veterans Health Administration database, the researchers identified 178,341 patients who initiated metformin treatment between 2001 and 2008. Treatment was subsequently intensified using insulin in 2948 patients and sulfonylurea in 39,990 patients. Risk of a first or recurrent hypoglycemia event was compared in propensity score-matched groups: 2436 patients taking metformin plus insulin versus 12,180 patients taking metformin plus sulfonylurea.

At the time of treatment intensification, patients had been taking metformin for a median of 14 months and had a median glycated hemoglobin level of 8.1 percent. The follow-up data included 121 first hypoglycemic events among patients who added insulin and 466 first hypoglycemic events among patients who added sulfonylurea. Outcome rates were 30.9 versus 24.6 events per 1000 person-years, respectively—adjusted hazard ratio was 1.30 with insulin compared with sulfonylurea.

Insulin intensification was also associated with a higher rate of recurrent hypoglycemia: 39.1 versus 30.0 per 1000 person-years (hazard ratio of 1.39). Accounting for competing risk of death, the hazard ratio for initial hypoglycemia in the insulin group was 1.28 [Roumie CL, et al. Risk of hypoglycemia following intensification of metformin treatment with insulin versus sulfonylurea. *CMAJ* 2016; doi:10.1503/ cmaj.150904].

Policy Update

Senate Finance Committee Eyes Kidney Care Components for New Bill

By Rachel Shaffer

Patients with kidney disease may see several positive changes to their ESRD care options in 2016. A bipartisan "Chronic Care Working Group" formed by the Senate Finance Committee recently released a white paper outlining policy changes they are interested in enacting this year—including several components related specifically to kidney care.

After soliciting input in June 2015 from ASN and other stakeholders in the medical community regarding opportunities to improve the care of people with chronic conditions and reduce related Medicare expenditures, the committee received more than 1000 suggestions. The white paper narrowed down the feedback to approximately 20 policy options, which are on the short list for inclusion in a piece of legislation to be introduced later this year. Among the suggestions are two provisions for which ASN advocated that are specific to patients with kidney disease and several that would have direct and positive benefits:

Expanding telehealth access for both home hemodialysis and home peritoneal dialysis

Permitting home dialysis patients to interact with their nephrologist for monthly visits via telehealth would create several benefits. Telemedicine may be valuable for ongoing care of patients residing in rural areas, who could avoid the need to travel in dangerous weather or for prohibitively long distances. Permitting patients and their physicians the option to participate in telehealth visits in some months—with in-person visits at least quarterly (every three calendar months)—may incentivize patients to adopt home dialysis as a treatment option.

In its comments to the committee,

ASN emphasized that patient safeguards are essential for a patient population that requires ongoing, intensive treatment. Both patients and physicians must retain the option to choose to conduct their monthly clinical assessment visit in-person if that more appropriately meets clinical needs in any given month. The committee's proposal is currently limited to permitting telehealth interactions that take place at dialysis facilities, but ASN continues to support allowing patients to interact with their nephrologist for some monthly visits from their own home.

Permitting patients with ESRD to enroll in Medicare Advantage plans

Under current law, people who develop kidney failure are not permitted to enroll in Medicare Advantage plans—ESRD is the only pre-existing condition that renders patients ineligible to participate in this program. ASN encouraged the committee to grant ESRD beneficiaries the same freedom of choice and access to improved care coordination services as other Medicare-enrolled individuals and will continue to support the committee's interest in including it in the final legislation.

Allowing patients with advanced kidney diseases to benefit from new and existing chronic care management (CCM) payment codes

The committee proposed developing a new code that would reimburse physicians who dedicate time to coordinating care for people with multiple high-severity chronic conditions. This concept builds upon a recently created code that reimburses for care of people with multiple chronic conditions (but which are not necessarily high-severity).

More than 50% of patients with chronic kidney disease have 5 or more co-morbid conditions, and CKD is included among 4 of the 5 most costly chronic condition combination triads in the Medicare program. CKD patients could benefit greatly from the proactive, comprehensive care coordination that the newly proposed high-severity codes would offer—providing them superior quality of life, fewer hospitalizations, and better long-term health.

Current CMS policy excludes patients with end-stage renal disease (ESRD) from eligibility for the existing CCM codes during the same 90-day period during which they receive standard—and lifesaving—dialysis care. This exclusion was not legislatively mandated, but rather, implemented during the CMS rulemaking process. ASN strongly believes that patients with kidney disease deserve equitable access to CCM services, and would be among the most likely to benefit from the new high-severity codes.

Among other beneficial policy recommendations the committee may include in its bill are quality measures for chronic conditions and commissioning of a study on medication synchronization. ASN will continue to interact with committee members and staff to build support for these and other policies as they move forward to drafting and introducing a bill. For more details concerning ASN's recommendations, please visit: http://www.asn-online.org/policy/webdocsAmericanSocietyofNephrologyASN.pdf.

President's 2017 Budget Shortchanges Kidney Research

By Grant Olan

On February 9, 2016, President Barack Obama released his budget proposal for 2017, the official start of the congressional budget process. Although the proposal includes increases for the National Institutes of Health (NIH) and other ASN priorities, it relies on budget gimmicks that some congressional appropriators are calling nonstarters.

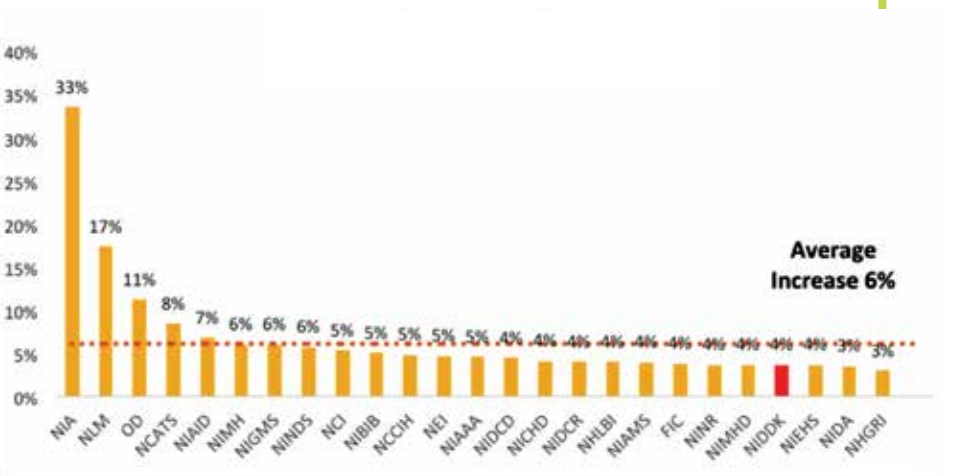
With those budget gimmicks, the President's proposal would increase NIH funding overall by $825 million for a total of $33 billion. However, the entire increase would go to a handful of administration priorities that include the Cancer Moonshot, Precision Medicine Initiative, and BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative. None of the additional funds would go to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and most of the other 26 institutes and centers are similarly shortchanged. Instead, NIDDK's budget for 2017 would remain flat at $1.966 million.

"ASN commended President Obama in 2016 for his bold leadership in securing a budget increase for NIH and NIDDK," ASN President Raymond C. Harris, MD, FASN, recalled. "Regrettably, his 2017 budget proposal would shortchange NIDDK and kidney research. Change is on the way because of advances made through NIDDK-funded kidney research. Additional funding is needed to accelerate these and other novel therapies that could improve the care of patients with kidney disease and result in significant savings to Medicare," Harris said.

ASN, in partnership with more than 200 patient and voluntary health groups, medical and scientific societies, and academic and research organizations, is advocating for a 2017 request for NIH of $34.5 billion, about a 7% increase over 2016. As a leader in Friends of NIDDK, a coalition that advocates collaboratively for increased NIDDK funding, ASN is spearheading the kidney community's efforts to advocate for a 2017 budget request for NIDDK of $2.165 billion, about a 10% increase over 2017. NIDDK ranked near the bottom of the list of NIH 2016 funding increases by institute and center (Figure 1).

"The story of cancer, heart disease, and HIV/AIDs is clear. Researchers go where the dollars are and funding increases drive innovation," ASN Research Advocacy Committee Chair Frank "Chip" Brosius, MD, commented. "HIV/AIDs went from a death sentence in the 1980s to essentially a chronic disease today. That kind of progress is possible with kidney disease if we are visionary enough to provide NIDDK sustainable funding increases for kidney research."

Figure 1. NIH funding increase by institute and center



Statement on President Obama's 2017 Budget Proposal

By ASN President Raymond C. Harris, MD, FASN

Looking back to this time last year, ASN was commending President Obama for his bold leadership in securing a budget increase for NIH and NIDDK in 2016. Regrettably, his 2017 budget proposal would shortchange NIDDK and kidney research. Kidney disease affects more than 20 million Americans and costs Medicare $80 billion. The Medicare End-Stage Renal Disease Program alone costs $35 billion, more than NIH's entire budget. Yet federal investments in kidney research are less than 1% of total kidney care costs.

There have been several major breakthroughs in the past several years thanks to NIDDK-funded research. For example, geneticists focused on the kidney have shaped our understanding of the pathogenesis of nephrotic syndrome and chronic kidney disease. Just last year, scientists announced a method for growing new kidneys in a laboratory as well as a rapid method for screening new prescription medications using kidney cells that would spare the expense and time of conducting human clinical trials.

Change is on the way because of advances made through NIDDK-funded kidney research. Additional, sustained funding is needed to accelerate these and other novel therapies that could improve the care of patients with kidney disease and result in significant savings to Medicare. A failure to maintain and strengthen NIDDK's ability to support the groundbreaking work of researchers across the country carries a palpable human toll, denying hope to the millions of patients awaiting the possibility of a healthier tomorrow.

Practice Pointers

Kidney Stones: New and Not So New Issues

This month, Alex Constantinescu, MD, of the American Society of Nephrology Practicing Nephrologists Advisory Group speaks about the latest on kidney stones. Dr. Constantinescu is associated with the Joe DiMaggio Children's Hospital, pediatric nephrology, in Hollywood, FL.

KN: Are we facing a higher incidence of nephrolithiasis?

Recent evidence suggests that over the past 4 decades, the incidence of kidney stones has increased in adults from 3.8 percent to 8.8 percent (1). In children, over the past 25 years, it has increased at a rate of 6 percent to 10 percent annually, reaching 50 cases per 100,000 adolescents (2).

KN: What may be the reason(s) for this increase, and is it reflected in stone composition?

Over the past 50 years, a few notable changes have taken place: a rise in body mass index, a higher rate of obesity, and a higher purine intake. Several studies have found significant correlations between these factors and the higher incidence of kidney stones but could not conclude that they were the only responsible culprits. An analysis of 11,099 kidney and ureteral stones between 1990 and 2010 revealed gender differences in the biochemical composition of calculi (3). Although calcium-containing stones remained the most common, females had an increase in total kidney stones from ~30 percent to ~40 percent and a significant increase in the incidence of uric acid stones. By contrast, males had a stable rate of uric acid stones (~11 percent) and showed an increase in the incidence of cystine and struvite stones, along with a higher percentage of apatite per stone.

KN: Who is at high risk for the development of renal calculi (i.e., ethnicity, race, disease states, diet, medications)?

Although known genetic factors contribute to ~50 percent of all kidney stones (i.e., in hyperoxaluria, cystinuria, Dent's disease, medullary sponge kidney, polycystic kidney disease, in total, 30 known kidney stone genes), not all genes have been identified, which suggests that epigenetic factors play a significant role. Surprisingly, 14 monogenic genes account for only 15 percent of cases of nephrolithiasis and nephrocalcinosis (4).

In the United States, an analysis of data from the National Health and Nutrition Examination Survey from 1974 to 2010 found a correlation between stone prevalence and increased caloric intake, as well as with diets rich in dark green vegetables, flour or cereal products, fish or shellfish, corn products, and added sugars, and an inverse correlation with a high intake of citrus fruits, as expected (1).

In Europe, the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition consisted of 51,336 participants and identified vegetarians as the subgroup with a lower risk for kidney stones, in particular those with high intakes of fresh fruits, wholegrain cereals, and magnesium-rich foods. The higher-risk group was characterized by a diet high in meat, meat products, and zinc-rich foods, such as seafood, dairy products, nuts, and beans, consistent with the role of zinc in mineralization and calcification processes (5).

A kidney stone risk of 5.5 percent was found after chemotherapy in patients with lymphoproliferative disorders, and the stone formers had higher serum uric acid, calcium, and potassium concentrations. Also, diabetes mellitus, hypertension, and hyperlipidemia were common in patients with de novo kidney stones (6). The known risk factors for urolithiasis also include medications such as topiramate (causing calcium phosphate stones), protease inhibitors (leading to various stone compositions, including drug-containing crystals), with excess calcium supplementation (some is good; too much is bad), loop diuretics, steroids, and ketogenic diet being among the most common causative agents (7).

KN: Are there new studies to identify the presence of, and complications from, kidney stones?

Most patients with renal colic undergo radiologic studies in the emergency department. Although a radiologic study of the kidneys, ureters, and bladder can identify calcium-containing radiopaque stones but not radiolucent ones, such as those composed of uric acid, ultrasonography and non–contrast medium computed tomography cannot differentiate between the various types of calculi, even though they can detect smaller stones. The Image Gently campaign was the origin of the quest for safer and more accurate imaging studies that can identify, and even attempt to differentiate, the composition of the stones. The use of a reduced dose of radiation appears not to diminish the ability to diagnose a ureteral stone larger than 5 mm (8). In addition, dual-energy computed tomography (9) appears to be able to differentiate between calcium oxalate and hydroxyapatite stones as well as the supersaturation values do. If the imaging study cannot only identify the stone but also give information about the stone composition with acceptable certainty, a specific therapy plan can be established much sooner, preventing complications from the long-standing calculus. In children, the stones are smaller, and such imaging studies may expose them to higher radiation doses. Therefore, the quest for the ideal diagnostic imaging test continues. In women, a history of urolithiasis has been associated with a higher risk of chronic kidney disease, even the need for dialysis (10).

KN: What are the benefits and limitations, if any, of minimally invasive techniques for the treatment of urolithiasis?

Some calculi smaller than 5 to 10 mm in both children and adults can pass spontaneously, or with help of hydration, diuretics, β-blockers, or a combination thereof. Unfortunately, some other calculi require surgical intervention. The discomfort caused by renal stones and their possible complications (e.g., infections, decrease in kidney function) have made early therapy a necessity. In addition, the need for faster recovery with the least tissue damage created an impetus for using endoscopic procedures, with less frequent extracorporeal shock wave lithotripsy and open surgical procedures for nephrolithiasis being very rarely needed. An analysis of this shift in surgical management confirmed this observation, with more than double the use of ureteroscopy and a decline in the use of extracorporeal shock wave lithotripsy over the past 20 years (11). Because this approach contributed to a decline in readmission rates, this trend may continue.

KN: What can be done to prevent the recurrence of renal calculi?

There is no doubt that patients who have experienced one kidney stone want to avoid a recurrence. This requires an accurate identification of the factors that led to the formation of the calculus and represent significant risk factors for its formation again. Stone composition is helpful, although it may not be available in all cases. Supersaturation values in 24-hour urine collection are helpful in adults, whereas in children, either ratios with urine creatinine as the common denominator, or values based on body weight and surface area are more frequently used. The American Urological Association published evidence-based guidelines for medical management of kidney stones in 2014. Increasing fluid intake, limiting sodium intake, and maintaining a normal calcium diet are recommended, independently of the stone composition. Specific dietary restrictions are based on stone composition or the biochemical abnormality noted. Lifestyle changes should be monitored closely, and drug therapy (i.e., thiazide diuretics, allopurinol, alkali) may be needed in carefully selected cases (12). Rule et al. (13) and colleagues identified younger white men with a family history of kidney stones, and uric acid composition of either symptomatic or asymptomatic calculi, to have the highest risk for recurrence, and they suggested a nomogram that can be the start of prevention trials.

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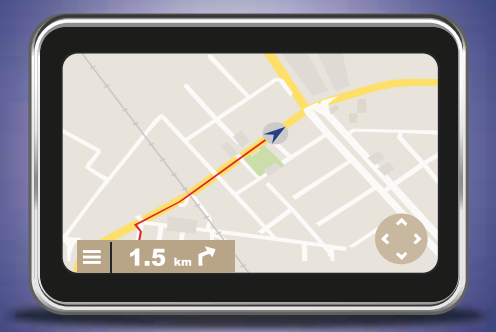

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Distinguished Conversations: *Keeping Nephrology Great*

It is a pleasure to introduce a new series at *Kidney News*, "Distinguished Conversations: Keeping Nephrology Great." We have asked established leaders in nephrology to invite their mentors, heroes, or most esteemed colleagues for a discussion of their opinions and recollections about the field of nephrology, especially how it has been great in the past and how we can continue to improve in the future. It is wonderful and fitting that this series coincides with the celebration of ASN's 50th anniversary. We hope you will enjoy it greatly. Please let us know at kidneynews@asn-online.org.

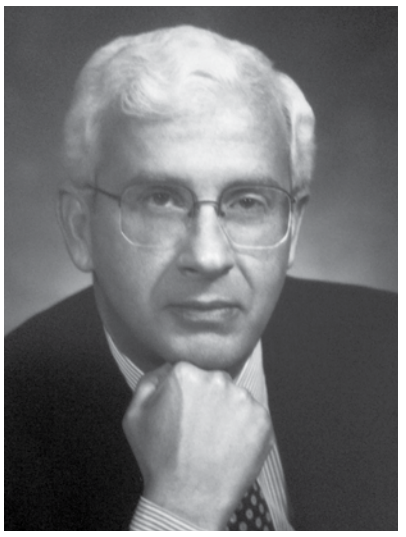
For the first installment of the series, ASN President Raymond C. Harris, MD, Chief of Nephrology at Vanderbilt University School of Medicine, chose to interview his early mentor at Harvard Medical School, Barry M. Brenner, MD, Director Emeritus of the renal division at Brigham and Women's Hospital, Samuel A. Levine Distinguished Professor of Medicine at Harvard Medical School, and an inimitable leader in nephology.

Dr. Brenner earned his MD degree from the University of Pittsburgh School of Medicine in 1962 and completed his internal medicine residency at the Bronx Municipal Hospital Center, Albert Einstein College of Medicine, in 1966. He did his kidney research training at the National Heart Institute (precursor to the National Heart, Lung, and Blood Institute) and then moved to the University of California, San Francisco, in 1969, before arriving at Harvard in 1976 to join its distinguished nephrology division. During the period from 1979 to 2001, when he was director, Brigham's renal division was named America's leading nephrology program by *U.S. News and World Report*.

A former president of ASN, this true triple threat has won the ASN Homer W. Smith Award for basic science, the John P. Peters Award for clinical science, and the Robert G. Narins Award for education and teaching. He also has been honored by the National Kidney Foundation, International Society of Nephrology, American Heart Association, and the Royal College of Physicians, among many others. He has held at least 25 editorial board appointments, published more than 700 scientific articles, edited 49 books, and participated in well more than 300 visiting lectures and/or professorships. We are delighted he agreed to be the first individual interviewed for this series.

Richard Lafayette, MD, editor-in-chief, ASN Kidney News

Raymond C. Harris, MD



Barry M. Brenner, MD

Dr. Harris: Dr. Brenner, how did you end up becoming a nephrologist?

My early life is a study of a bright boy, self-motivated and driven to advance by studying 15 hours per day, 6 or 7 days a week. This "deep work," a form of intense, undistracted, and undisturbed study, is something I have engaged in throughout my life. Still, any success that flowed to me was because of the many people who gave me encouragement and boosts along the way.

In my youth, I was very intrigued by the natural sciences. When I was a young teenager, I already had a microscope and was looking at pond water and identifying all the different unicellular organisms moving through the field. This filled me with great delight. I did lots of chemistry experiments at home, and my parents gave me as gifts pure compounds and glassware; the latter I broke repeatedly. I also burned myself and made some explosions that stained the ceilings.

I attended Long Island University in Brooklyn, which gave me a scholarship. I came from a poor family where no one had been educated. My greatest advantage in growing up is that I was disadvantaged in terms of our modest family background and little external guidance regarding career development.

The person who helped me the most was a man named J. Robert Oppenheimer, who was head of the Manhattan Project, responsible for making the atomic bomb. He was a brilliant atomic physicist, who, although not known to me personally, intrigued me greatly with his story and spurred me to read extensively about atomic physics and his contributions to this evolving field.

When Oppenheimer graduated from Princeton, he wrote in the class yearbook under his photo, "undergraduate school—3 years," and when I went to college I was driven to do better. By that I mean I graduated with honors in 32 months, with many of my course credits at the graduate level. So I beat him by a few months, which was my target, and I think this said something about my drive and ambition at the time.

"I was enamored by the research process"

I interviewed at several medical schools, but it was the University of Pittsburgh that most interested me. There I was interviewed by Harold Segal, a young assistant professor of biochemistry. At the end of a lengthy discussion about anti-matter and fundamental atomic physics, he said, "You will get a letter of acceptance later this week, and if you come here, I want you to work in my laboratory."

When I started medical school at Pitt in September 1958, I also started in Segal's laboratory. He had identified a new enzyme—a 5'-nucleotidase—and since Pitt was renowned for enzymology because Maud Menten, of Michaelis–Menten fame, had been on the faculty, Segal assigned me the task of working out the Michaelis–Menten kinetics for this new enzyme, which I did. We published the paper on the results in the *Journal of Biological Chemistry* a year later.

I was enamored by the research process. The scientific method to me was the Holy Grail.

I continued to work in research while going to medical school. At that time, 50% of the freshman class at the end of the year stayed over the summer to do bench research. The school provided funds for 2 months of summer research and half the class was involved—something I think is unheard of today.

The second year of medical school involved the study of pathology. Segal contacted the chairman of that department, Frank Dixon, the father of immune complex–mediated diseases, and like Segal, he urged me to work in his lab. "Work with me during the day in my lab, but you still have to be responsible for the slide sets and take the exams along with your class," he said. I worked with him for 6 months and also did very well on the exams.

Thus Segal and Dixon redesigned the curriculum to fit me rather than slot me in as just another student. It served me extremely well. These were opportunities that I don't think are offered to young people today, and I think that's a tragedy.

Dr. Harris: Yes, I think that you're exactly right. We need to be open to opportunities within or outside the curriculum for those who are creative and driven.

When I did my medical residency at Albert Einstein in New York, I also was blessed with a unique opportunity. Instead of having morning report for your residency to discuss the cases that came in the night before, we had what were called "morning prayers," where each of the 30 residents in rotation was responsible for giving a talk on a scholarly topic of their choice. It had to be scientifically oriented and you were expected to bring to the session the person on campus most knowledgeable about the topic you were presenting. Department Chair Irving London presided over the session.

One day I gave a talk on a *PNAS* paper by George Porter and Isidore Edelman on the mechanism of induction of sodium current by aldosterone in toad urinary bladder. They showed that it was a DNA-dependent RNA synthesis step that took 90 minutes to unfold before the sodium current increased, and they could block it with an inhibitor of RNA synthesis. I drew all the figures on the blackboard because in those days there were no funds for us to make photocopies or slides. As an expert, I invited Robert Davis. He showed up with somebody I didn't know.

I presented the material over the course of 45 minutes. Davis led the discussion and the person he brought with him also asked me some questions. When the session was over I felt good about it and left to supervise the care of patients and my interns. At lunch, Davis came back with this person I didn't know…it turned out to be Robert Berliner, director of kidney research at NIH.

"Three to four uninterrupted years of laboratory experience"

Although I had already been accepted for fellowship training with Alex Leaf, Frank Epstein, Arnold Relman, and William Schwartz, Berliner said, "Those are programs that will dilute your energy because you will have clinical responsibilities. Come to NIH and we will give you 3 or 4 uninterrupted years of laboratory experience." I joined his lab because I was intrigued with the delicacy of the micropuncture technique, with the micro-analytical skills that needed to be applied—like the intrigue of a watchmaker for his craft.

At NIH, I worked with a young woman, Julia Troy, who was leading the micropuncture technical team. Within a month of my joining the lab, Berliner came to me and said he had been invited to Stanford to be the discussant at a clinicopathological conference. He asked me to look over the case protocol they had sent him, and after I had done so, I told him, "I think I've seen this case before." I didn't remember where but I went home that night and scoured my unbound issues of the *New England Journal of Medicine* that I had meticulously saved. There, about a year earlier, was the protocol of the same patient with medullary cystic disease. I showed the article to Berliner and said, "All you need to do is talk about the concentrating mechanism and how it's not working well when there are cysts in the medulla," which is what he did at the Stanford conference. For the next 6 months, every time he saw me he asked, "Did I ever thank you for helping me with that protocol?" I had entered his inner sanctum.

Then I had the good fortune of doing the micropuncture experiment that disproved the geometry hypothesis. That hypothesis came out of Gertz's laboratory in Germany and then Floyd Rector and Donald Seldin (University of Texas Southwestern Medical School, Dallas) picked it up. The hypothesis stated that the more the tubule was dilated, the greater the absorption rate. So the square of the radius of the proximal tubule was proportional to the isotonic fluid flux across the tubule. The experiments were done by dilating the proximal tubule by producing intratubular obstruction with an oil block, similar to how blocking the ureter would raise intratubular pressure. What they didn't do, and I did, was I realized that unless I had a very long oil block below where I was sampling the fluid, there was retrograde flow from more distal portions of the nephron into the pipette. They did not estimate the tubule fluid-to-plasma concentration ratio and the volume per minute collected because if they did and multiplied the two, which gives you the single nephron GFR, it would come to about 300 nL/min, which if multiplied by 30,000 nephrons per kidney would be nearly10 mL/min GFR in a rat—an impossible result. The rat doesn't have much more than 10 mL of blood volume!

So by putting in these very long oil blocks, there was no retrograde backleak, and the estimated single nephron GFR was approximately 30 nL/min, the normal physiologic value for the rat. Under these circumstances where the tubule was dilated, the reabsorption rate did not increase, so it was insensitive to the square of the radius of the tubule. On the other hand, when I used short oil blocks, I obtained the artificially high estimates reported by the Dallas group.

I tell you this story because then something that never happens did happen. Berliner told me to write up the results for *Journal of Clinical Investigation*. I said I was happy to do so but also wanted to share the results with Rector and Seldin before we published. He thought that unnecessary but I thought it was essential. So I paid my airfare to Dallas and showed the draft manuscript to them. Rector looked at the data and immediately said to me, "You're right and we're wrong."

A year later, I was back in Dallas meeting again with Rector and Seldin. Fred Wright and I failed to obtain evidence showing that volume expansion with saline led to the release of a natriuretic third factor, whereas the Dallas group had already published several papers and had a half-dozen in press about this so-called third factor. (Third factor meaning not GFR, not aldosterone, but something else.) We brought them unknown plasma samples from some dogs that we volume expanded, some that we didn't, and they got only half right—and, more important, half wrong! Their studies suggesting a third factor were the result of an artifact in the shrinking droplet technique that they employed.

These two examples of sharing data prior to publication are, I believe, uncommon practices in today's scientific community, but in my early career development, these interchanges proved very beneficial.

Dr. Harris: Right, and taking advantage of the opportunities and having mentors who both helped you and allowed you to take advantage of those opportunities.

Actually, our work on the square of the radius geometry hypothesis was done in 1967, the year of the first ASN meeting. And do you know the three state-of-the-art lecture titles at the first meeting in Los Angeles? One was called "Renal Physiology" and was given by Berliner. Another was called "Dialysis," and the third, "Transplantation."

Berliner presented my data and talked about Barry Brenner 5 or 6 times in his lecture, so that at the end of the first ASN meeting and the end of my first year as a fellow, everybody in nephrology knew my name. Talk about pure good fortune.

I had to pay to go to the meeting because Berliner would only send one person and it was a more senior person. My salary as a fellow at NIH (I was not part of the military) paid me $2000 a year. Yet my wife Jane, a schoolteacher, said, "Barry, you're going to do this," and paid for the trip.

I listened to Berliner give his talk, then on my own I flew up to San Francisco at the height of Haight-Ashbury in the 1960s. I wanted to see what it was all about. So I took a walk across the Golden Gate Bridge. The fog came in, and I could actually touch it. I looked toward the city and it was most beautiful thing. I said to Jane when I got home, "I don't know where we're going to live after we finish here, but it's going to be San Francisco. I won't open any envelope with a job offer unless the return address is San Francisco." And of course it was.

"I took an offer because I could grow a clinical service slowly while doing research"

I received invitations from Larry Earley, head of renal at UCSF, and from Marvin Sleisenger, chief of medicine at the VA. I took the latter offer because I wanted so much to protect my personal research time as I did not want to inherit a big clinical service. In this way I could grow it slowly at my own pace while doing research.

Julie Troy and I both moved to San Francisco in 1969. While at NIH, we had built a device that allowed for real-time measurement of pressures in the renal microcirculation. The NIH basically made a long-term loan of this servo-null transducer system because we were now working at another government institution.

Continued on page 16

Continued from page 15

We were using the device to measure pressures in peritubular capillaries and for experiments looking at peritubular capillary control of proximal reabsorption when at a meeting in Munich, I was talking to Klaus Thurau, who said, "We don't have any interest in this but you might, Barry. We have some rats that are showing cherry red spots on the surface of the kidney. We assume they are arteriovenous malformations." I knew instantly that these were surface glomeruli.

I asked him to send me a dozen rats so I could take a closer look. A week or so later, I got a call from Lufthansa cargo at San Francisco airport telling me a box of rats had arrived. I went down to the airport to fetch the rats and sign whatever documents were needed, and counted not 12 but 11 rats, whereas the manifest said 12. So one rat escaped through a small hole. After that, I would never let my family fly Lufthansa, for fear the sole escapee might be eating through the cables that connect the wings to the body of the plane.

We quickly confirmed that the red spots on the surface were indeed glomeruli, and the pulse contours were highly refined.

We sent half the rats for breeding to the people who took care of animals at the VA hospital. We labeled them "Munich Wistar Rats" in honor of the city in which they were discovered, the way people would at that time name hemoglobins—for the city where a particular mutation in a hemoglobin molecule was identified. The name stuck—they are still called Munich Wistar Rats.

So we recorded the glomerular capillary pressures, and from there we were able to do the biophysics of the glomerular circuit. In collaboration with Bill Deen and Channing Robertson from the Chemical Engineering Department at Stanford, we were able to do the quantitative assessment of the ultrafiltration coefficient and a lot of the regulatory steps.

"A finding that led us in the direction of understanding progression of renal disease"

We prepared several papers on the dynamics of glomerular ultrafiltration, and in the eighth paper, which was intended to examine the effect on the dynamics of the reduction in renal mass surgically created, we were struck by the increase in single nephron GFR and the rise in glomerular capillary pressure that drove that rise in GFR. It dawned on me, "Well, maybe this rise in GFR as an adaptation to reduced renal mass is not a good thing because over time, the remnant kidney deteriorates and capillaries, like blood vessels in general, don't tolerate high pressure." We have no trouble comprehending how arterioles are damaged by hypertension, so why would there not be damage in capillaries if hypertension is imposed at that level? That led us in the direction of understanding progression of renal disease and the interruption of disease progression by lowering of those glomerular pressures. First we lowered glomerular pressures by dietary protein restriction and this proved to be beneficial long-term. Then we needed a pill—because who is going to give up their beefsteak?

The pill had to be something other than a pill that only lowered systemic blood pressure because up to that time, every antihypertensive drug was a vasodilator, and although they lowered systemic pressure, they opened up the afferent arteriole and the glomerular pressure did not decline. Therefore there was no renal benefit to be expected. But we had been working on the effect of angiotensin II, which we showed constricted the efferent arteriole, not the afferent, and believed that if there was something that could relax the efferent arteriole, that would be a way to lower intraglomerular pressure selectively. And then came the ACE inhibitors captopril and enalopril, both of which indeed lowered intraglomerular pressure dramatically and thereby minimized progressive glomerular injury.

"Bringing molecular biology to the renal division at Brigham"

In 1976, I along with a number of our San Francisco VA team accepted positions at Brigham and Women's Hospital in Boston. An early recruit to our new program, Steve Hebert, was at that time perfusing isolated tubules. I also recruited Matthias Hediger, who, with Ernie Wright, had used expression cloning to identify the sodium-glucose cotransporter-1 and show that mutation of the transporter resulted in glucose-galactose malabsorption. His work was beautiful—I admired it and I got him to come to Brigham. I also recruited another molecular biologist, Jonathan Lytton, so I had these two young scientists doing pure molecular biology in our renal division.

Hebert was so taken with their work that he took an intramural sabbatical. He stopped perfusing tubules and learned how to do the molecular biology. His first success, with a fellow named Kevin Ho, was to clone renal outer medullary potassium channel (ROMK1). He then cloned the thiazide-sensitive NaCl cotransporter, and then NKCC2, the thick ascending limb transporter, and then the calcium-sensing receptor, all in a period of 3 years. Hebert went on to Yale, was elected to the National Academy of Sciences and, sadly, died suddenly at the age of 61. Hediger went off to Zurich, and then to Bern, where he directs an institute of molecular research. Jonathan Lytton went home to Calgary, Canada, where he is now chairman of the department of biochemistry. It was a very special time—a Camelot for us at Brigham, with these people adding an enormous dimension to the research.

So you now have a sense of how I got into nephrology and how my early career was bolstered by very good fortune, being given very important problems to work on (e.g., the existing hypothesis for explaining proximal absorption), exploiting those unique rats with surface glomeruli, doing the pure basic science drill on glomerular ultrafiltration, but then leap-frogging it into a clinical context and showing how the glomerular hypertension plays a role in the progression of kidney disease.

In the latter sense, what we did was take the various renal diseases, all of which progress, and say there is a final common pathway that underlies the progression of all of them. It doesn't mean that this is the sole mechanism. It doesn't mean that everything is explained by this hypothesis, but it went a long way toward unifying disparate entities into something that made a more coherent story. For me, it was one of the major milestones of my career.

Dr. Harris: I think your career is a paradigm of someone who has been interested in basic science and has always been willing and able to translate it into clinically relevant issues.

Well, for me, it was following a single thread. The nephron GFR is driven more by plasma flow than by hydraulic pressure. It's a low pressure system, whereas when we made the first measurements and I looked in Robert Pitts' book, *Physiology of the Kidney and Body Fluids*, the estimate of glomerular pressure was assumed to be 90% of the systemic pressure, not 40% as we had demonstrated. When you think about it, how could a capillary endure such pressure? But the single thread took those pressure measurements from low to higher values when nephron reduction occurred, whether by disease or by surgical reduction of renal mass. Now I am preoccupied with more of the same thread. What if you are born with fewer nephrons? Isn't that like renal reduction by surgery and doesn't that constitute a potential risk for progression of renal disease?

As you know, it does. But I have been unsuccessful in 30 years at getting physicians to use the simple surrogate for low nephron number, namely low birth weight. Question number one: What was the endowment of nephrons a patient started with? Instead, everyone starts at the same place—it is wrongfully assumed that everyone starts out with 1 million nephrons in each kidney. It's the number every student remembers. Not a million **plus or minus 30%**, which is the reality.

Dr. Harris: You're right. What I think we should be doing is getting a better birth history, but also finding better ways to image and actually count glomeruli. I think that's the next frontier.

Yes, and to make that a clinically feasible assessment in toddlers and young people as a baseline. Anyway, I've been frustrated with my inability to convince our renal colleagues that these steps must be taken. But I have reason to be encouraged. At Giuseppe Remuzzi's invitation, I gave a plenary lecture on nephron endowment at the last ISN meeting in Cape Town in March 2015. The audience seemed impressed. I am pleased that a symposium on the theme of this lecture will be held under Remuzzi's leadership in Bergamo, Italy, in April 2016.

Dr. Harris: So I think that your work is not done.

Well, it's what keeps me on the younger side of my 78 years. It keeps me going. I remain deeply immersed in the issues that fascinate me, and I continue to devote myself to my favorite indoor hobby, deep work.

One final thing. I would like to express my unbounded gratitude and love to my wife, Jane, our children, Rob and Jen, and our grandchildren, Sam, Max, Elliott, and Abigail. I also thank all the fellows who taught me so much. I especially thank Julia Troy, the most able technical assistant the micropuncture field has ever known. When I bound all the articles she and I wrote together over the years into a book, I inscribed in the front cover, "To Julia Troy. With you, the voyage has been wonderful. Without you, I would never have left the shore."

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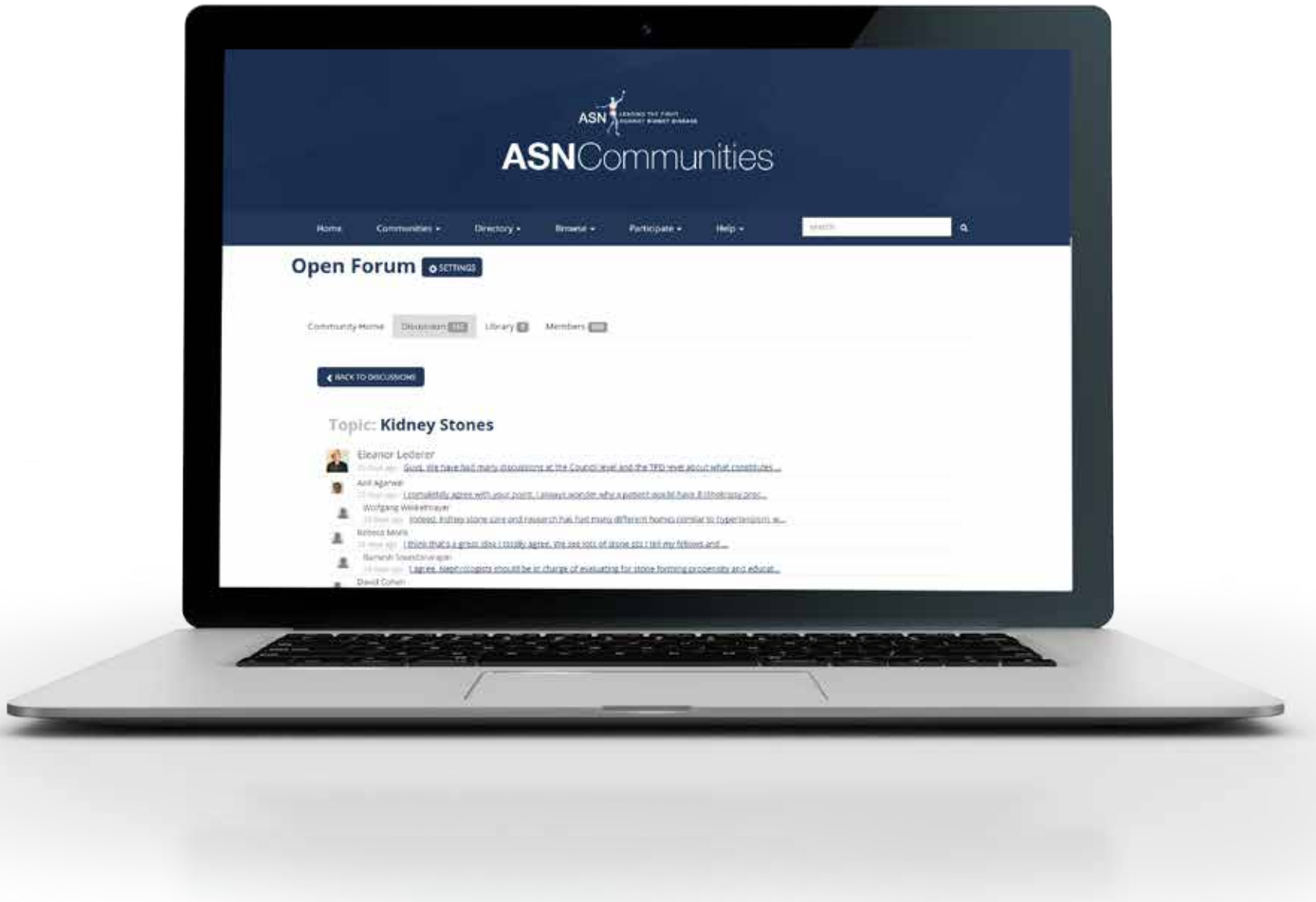

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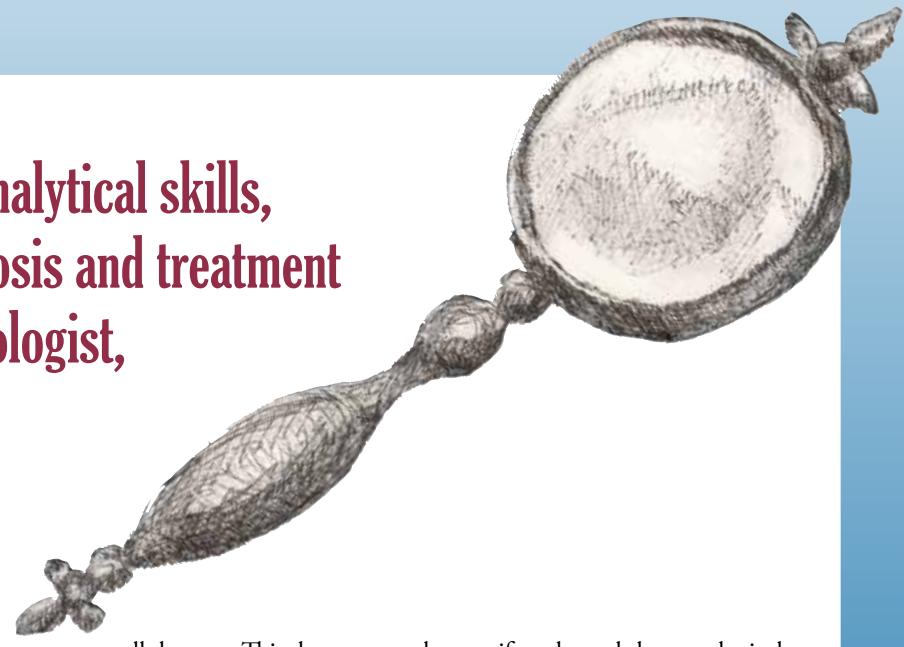

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Nephron What do you have for me today Henle?

Henle looks at Glom

Glom I have a 65-year-old man with a serum sodium concentration of 112 mEq/L.

Nephron Hyponatremia! My favorite electrolyte disorder. What is the first question you need to ask?

Henle Whether the patient has symptoms?

Nephron Exactly. Given the severity of this hyponatremia, we need to know if we need to treat immediately with hypertonic saline to avoid life-threatening cerebral edema. Severe symptoms such as seizures and coma indicate significant cerebral edema and require the use of NaCl 3% 100 mL IV bolus, which you could repeat twice if symptoms persist. Moderate symptoms such as confusion indicate a lesser degree of cerebral edema but still significant enough to be dangerous and also require the use of NaCl 3% but in slow infusion. Remember, severely symptomatic or moderately symptomatic hyponatremia are medical emergencies and need to be treated with hypertonic saline.

Henle I interviewed the patient and did a full neurological exam. The patient is asymptomatic.

Nephron *(upset)* That is not entirely true, is it? Evidence has emerged over the last several years suggesting that all hyponatremias are symptomatic to a degree. Even mild chronic hyponatremia in the range of 125 to 135 mEq/L is not only associated with increased mortality but also increased morbidity in the form of subtle attention deficits, gait disturbances, falls, fractures, and osteoporosis.

Glom I did not know that.

Nephron *(smiling)* Are you familiar with the concept of regulatory volume decrease or RVD?

Henle & Glom *(looking at each other)* No.

Nephron Regulatory volume decrease is the process by which cells adapt to swelling. In the brain, astrocytes do swell under hypotonic conditions, and neurons do not because they lack aquaporin 4, the water channel responsible for cerebral edema. Astrocytes achieve regulatory volume decrease by extruding osmoles to the extracellular compartment, therefore reducing intracellular tonicity to avoid further water entry. Initially, during the first 3 hours of this process, K+ and Cl- are the main osmoles extruded, but after that, organic osmoles, such as glutamate and myoinositol, take a primordial role. Glutamate is the main excitatory neurotransmitter in the brain. It is hypothesized that glutamate released in large amounts during this process can cause excitotoxicity and neuronal cell damage. This damage may be manifested as subtle neurological symptoms such as gait disturbances that can only be detected by special neuropsychometric testing.

Glom Amazing!

Nephron Well, getting back to our case, since our patient is apparently asymptomatic, there is no need to use hypertonic saline. Mildly symptomatic and the so-called "asymptomatic" (*looking at Henle*) hyponatremia reflect almost complete adaptation to hypotonicity with mild degrees of cerebral edema. Full adaptation takes 48–72 h and that is where the difference lies between acute and chronic hyponatremia. Hypertonic saline is not needed in this case and we have more time to focus on the underlying pathophysiology causing hyponatremia.

Nephron Glom, why don't you tell me more about this patient?

Glom He is a 65-year-old homeless man with a significant history of alcohol abuse. He was found down in the street by the police who brought him to our emergency department. It seemed the patient was inebriated initially but was alert and oriented for me. On exam, his BP = 100/60 mm Hg, heart rate = 79 bpm, RR = 20. He looked disheveled and malnourished. Cardiopulmonary exam was unremarkable. Abdominal exam was benign. Neurological exam was normal, as Henle said. Overall, he seemed euvolemic. His initial laboratory examination revealed a Na = 112 mEq/L, K = 2.5 mEq/L, Cl = 95 mEq/L, TCO_2 = 25 mEq/L, Glucose = 75 mg/dL, BUN = 3 mg/dL, Cr = 0.3 mg/dL, Alb = 3.2 g/dL. POsm = 280 mOsm/kg. So, it seems he has pseudohyponatremia, but I thought we don't see this anymore since the way the laboratory measures sodium concentration has changed?

Nephron *(shocked)* That is a common misconception. Two-thirds of all clinical laboratories in the US still use indirect ion selective electrode technology to measure sodium concentration on a routine basis. This technology is prone to error in the presence of high protein or lipid levels in the blood. So we still need to be alert for those, however, pseudohyponatremia does not seem to be the problem here. Do you have a serum ethanol level from his initial laboratory examination in the emergency department?

Glom Sure, it was 192 mg/dL.

Nephron Mmmm …. It seems we need to go over the concepts of osmolality and tonicity. Henle?

Henle Tonicity is effective osmolality. Tonicity does not take into account the contributions of solutes that cross cell membranes and therefore do not exert an osmotic effect. Urea is one of these solutes. But the BUN is low in this patient?

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Nephron Can you think of another solute that crosses cell membranes and does not contribute to tonicity but does contribute to osmolality?

Henle *(jumps in)* Ethanol!

Nephron Precisely, and this is what happened to this patient. The ethanol level was high enough that it made the plasma osmolality normal, but if you discard its effects, the tonicity will still be low, roughly 228 mOsm/kg. This is really a hypotonic hyponatremia. Classically, this is seen in hospitalized ESRD patients with hyponatremia associated with normal osmolality. Let's stop expensive workups looking for hypertriglyceridemia and multiple myeloma without realizing that what makes osmolality normal in these patients is the contribution of high urea levels.

Glom *(blushing)* Thanks for telling me. I will cancel my orders for a SPEP and a lipid profile. So following the algorithm, then, this patient has hypotonic euvolemic hyponatremia.

Nephron You like algorithms, don't you Glom? Clinicians use algorithms as a way of chunking separate pieces of information and to increase space in their working memory. That is a valid and effective cognitive technique, but when algorithms are abused and used as cookbook medicine without understanding the underlying pathophysiology they fail miserably. There are several issues with the classic hyponatremia algorithm: first, clinicians' assessment of volume status in hyponatremia has been studied and found to have a low sensitivity and specificity. Second, the effectiveness of the classic algorithm only enables 10% of clinicians to correctly diagnose hyponatremia. Finally, the classic algorithm suggests you could arrive to a single diagnosis; however, hyponatremia is usually multifactorial.

Henle Understood. What is your approach then?

Nephron In a series of pivotal studies done by Dr. Edelman and reported in a landmark paper published in the *Journal of Clinical Investigation* in 1958, he described what is known now as the Edelman equation by which the serum sodium concentration could be viewed as a function of total body contents of sodium, potassium, and water. The equation goes like this: $[Na^+] = (Na_E + K_E)/TBW$. Where $[Na^+]$ is the plasma sodium concentration, Na_E and K_E are the total body exchangeable sodium and potassium respectively, and TBW is total body water.

Henle Exchangeable sodium and potassium?

Nephron Exchangeable sodium and potassium represent the total body sodium and potassium that exert an osmotic effect. For instance, bone tissue can store almost a third of total body sodium, but it is non-exchangeable, meaning it does not exert an osmotic effect and therefore does not contribute to plasma sodium concentration. It is hypothesized that movement of sodium from bone to plasma during chronic hyponatremia is responsible for osteoclast activation and subsequent osteoporosis.

Henle Very interesting.

Nephron Following the Edelman equation, then, hypotonic hyponatremia is produced when total body water is increased relative to total body exchangeable sodium and potassium, or simply put, when there is excess solute-free water.

Glom Is that why you always said hyponatremia is mainly a water disorder, and not a sodium disorder?

Nephron Yes. By the way, what are the sodium disorders?

Glom Mmm ….

Henle Hypovolemia and hypervolemia.

Nephron Excellent! Then an excess of solute-free water can develop as a consequence of either increased water intake or decreased water excretion.

Glom This is finally making more sense for me.

Nephron Patients can ingest large amounts of water without developing hyponatremia because kidneys can handle huge water loads, but there is a limit as to how much the kidneys can excrete…

Pause… and the limit is about 18 liters per day.

Glom I see.

Nephron We said most hyponatremias are due to an increase in water compared to total exchangeable cations. We talked about increase in water intake. What about decrease in renal water excretion? What pathophysiological mechanisms do contribute to a decrease in renal water excretion?

Henle High antidiuretic hormone (ADH).

Nephron Yes! High ADH activity is the most common mechanism of hypotonic hyponatremia.

Nephron And what stimulates ADH to be released in large amounts?

Glom Hypertonicity and hypovolemia.

Nephron Hypertonicity is a well-known stimulus for ADH release, but remember true hyponatremia is hypotonic so this does not really apply here.

Glom What about hypovolemia?

Nephron To be more precise, you should say "decreased effective arterial blood volume." Hypovolemia refers to decreased extracellular fluid (ECF) volume. Remember, extracellular fluid volume can be divided into 2 compartments, interstitial and intravascular. The intravascular compartment can also be divided into a venous sub-compartment that contains 85% of the blood volume, and an arterial sub-compartment that contains only 15% of the blood volume. The baroreceptors are located in the arterial portion of the intravascular space and sense changes in this compartment. When the volume of this compartment goes down, the baroreceptors are activated and the end result is the release of ADH from the posterior pituitary. Baroreceptors do not sense changes in ECF volume. ECF volume changes can parallel changes in the arterial compartment such as in individuals who develop hemorrhage, vomiting, or diarrhea, the so-called hypovolemia, but sometimes not. That is why you could have patients with low effective arterial blood volume despite an expanded ECF volume. Can you think of clinical scenarios where this happens?

Glom Liver cirrhosis and heart failure.

Nephron Very good! What about other non-physiological causes for ADH release?

Henle & Glom *Mmm….*

Nephron What do you call the condition where ADH is secreted autonomously in the absence of a physiologic stimulus?

Henle SIADH (syndrome of inappropriate antidiuretic hormone secretion)!

Nephron Exactly! Any other mechanism by which ADH could be high?

Henle Adrenal insufficiency?

Nephron Primary, secondary, or tertiary?

Henle I don't know.

Nephron *(surprised look)* All! But by different mechanisms. Cortisol exerts a negative feedback loop on ADH release. So, in the absence of cortisol, ADH is uninhibited. This occurs in any adrenal insufficiency. In the specific case of primary adrenal insufficiency where the problem is the adrenal gland, aldosterone secretion is also compromised, and aldosterone regulates renal sodium excretion. In the absence of aldosterone, you have renal salt wasting and decreased effective blood volume causing ADH release as well.

Glom Fascinating!

Nephron What other mechanisms of decreased renal water excretion do you know?

Henle Decreased GFR.

Nephron Very well. This is a very common problem in our AKI, CKD, and ESRD patients. They don't need to drink 18 L of water to develop hyponatremia. With much less water intake they will be in trouble because their kidneys cannot excrete the extra water load. When you see an anuric ESRD patient with hypotonic hyponatremia, it is almost always due to this. Don't do a million dollar workup looking for another cause.

Nephron Any other mechanisms of decreased renal water excretion?

Glom I don't know any other.

Nephron Low solute intake. The amount of solutes excreted in the urine, also known as urine solute load, determines the volume of urine being produced. Under steady state conditions, the amount of solutes you eat is equal to the urine solute load. So, if you eat a low solute diet, then you will excrete a small urine solute load and therefore your urine volume will be low, and with low urine volumes the ability to excrete water will be limited.

Glom *(confused)* What is considered a low solute intake?

Nephron The normal diet contains 600 to 900 mOsm per day of solutes.

Glom I must be eating a good amount of solute because I love spaghetti.

Nephron That is a common misconception; carbohydrates do not produce any meaningful solutes. Most solutes are derived from either proteins because they metabolize to urea, or salt.

Henle I guess this occurs in the so-called tea and toast diet?

Nephron Exactly. These patients eat toast, which is mainly carbohydrates, with very little solute intake, and drink tea all day, which is mainly water, exceeding the capacity of their kidneys to excrete water. Any other clinical scenarios?

Henle Not sure.

Nephron Have you heard of beer potomania?

Henle Oh yes!

Nephron This condition occurs in alcoholics. They usually do not eat enough solute and therefore they have a limited capacity to excrete water. On top of that, they drink beer all day and beer is 90% water. They usually end up retaining water and developing hyponatremia. I am afraid this is what is happening to this patient. How much does he drink? Does he eat enough solutes?

Glom Yes, I asked him. He said he drinks 2 six packs of beer every day and eats very little food. He looks very malnourished.

Henle Yes, his BUN is only 3!

Nephron Do you have a urine osmolality in this patient?

Glom It is 79 mOsm/kg.

Nephron That is very diluted urine with suppressed ADH, which can only be explained by drinking in excess of the kidney's ability to excrete water. You can see low urine osmolality in patients with primary polydipsia who drink huge loads of water, or patients who drink a normal amount of water but their kidneys have a limited ability to excrete water due to non-ADH mechanisms such as low GFR or low solute intake. Given his normal kidney function, the history of alcohol abuse, and his nutritional status, I say this is likely low-solute-intake hyponatremia caused by beer potomania.

Glom What is the treatment?

Nephron Increase his solute intake, give him a hamburger! I mean, give him regular hospital food.

Henle Any other recommendations?

Nephron I am glad you asked. Patients with low-solute-intake hyponatremia will overcorrect once dietary solute is increased. These patients usually start having a brisk urine output due to massive water diuresis, so the primary team needs to be aware of this and ready to act.

Glom Act?

Nephron *(with confidence)* Overcorrection of hyponatremia is a medical emergency. Overcorrection is the main risk factor for osmotic demyelination syndrome.

Glom OK, I will tell them the correction rate should be 0.5 mEq/L/h.

Nephron That is the classic teaching in medical school but there is actually not much evidence to support the notion of correction rates. There are, however, correction limits that when you cross put your patient at risk for osmotic demyelination syndrome. The limits have traditionally been 10–12 mEq/L in 24 h. The 0.5 mEq/L/h is an extrapolation of this, i.e., 12 mEq/L divided by 24 h. The absolute magnitude of correction is more important than the rate. You could theoretically correct the sodium by 10 in the first hour as long as you keep the sodium the same in the next 23 hours. There are animal studies that support this concept.

Henle So, should we tell the team our goal is no more than 10 mEq/L in 24 h?

Nephron No. 10 mEq/L in 24 h is a limit, not a goal. When you use digoxin or phenytoin, you do not aim for one minus the toxic dose, right? You aim for a smaller level that is effective but also

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safe. The same happens in hyponatremia. We do not aim for 10 mEq/L; 10 mEq/L is our limit. Case series have demonstrated that correcting the sodium concentration by 6 mEq/L in any 24-h period is a safe and effective goal.

Glom OK, so aim for 6 mEq/L but definitely no more than 10 mEq/L?

Nephron *(in teaching mode)* Also incorrect. 10 mEq/L is the limit for patients with average risk of osmotic demyelination syndrome. Patients with liver cirrhosis, malnutrition, alcoholism, and hypokalemia are at high risk of osmotic demyelination syndrome and the limit should be no more than 8 mEq/L.

Glom What happens if the sodium corrects too fast? What can we do?

Nephron They need to carefully monitor his urine output and once they see an increase in urine output or a rapid elevation of serum sodium concentration they need to relower the serum sodium. Relowering serum sodium concentrations has been proven to be an effective prevention strategy to avoid osmotic demyelination syndrome in case series and animal studies. I recommend using D5W at 3 mL/kg IV over 1 hour and repeat sodium right after. We can also add desmopressin 2–4 µg subcutaneously if it seems that D5W is not enough. Some clinicians follow a protocol where they start with NaCl 3% along with desmopression Q8h from the get-go, creating a state of artificial SIADH and avoiding water diuresis, which is the main state responsible for overcorrection. In that way, they are able to correct the hyponatremia very nicely without complications.

Glom I will also tell them to replace the potassium of 2.5 mEq/L.

Nephron Hold on! You have to be very careful about replacing potassium in patients with hyponatremia. Following the Edelman equation, any addition to the total body potassium will increase serum sodium concentration. In other words, correcting hypokalemia will also correct hyponatremia. So, I will try to minimize the potassium correction for now unless the patient has arrhythmias or muscle weakness until the sodium concentration is at a safer level.

Henle *(yawning)* It looks like I might need to be awake all night to monitor the sodium concentration in this patient.

Nephron That is a good idea Henle but also it is part of being a good nephrologist. We always do the best for our patients. Make sure you bring your coffee with you Henle, as you will need it!

Special thanks to Dr. Helbert Rondon, Assistant Professor of Medicine, Renal-Electrolyte Division at the University Of Pittsburgh School Of Medicine (writer and submitter for this case).

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