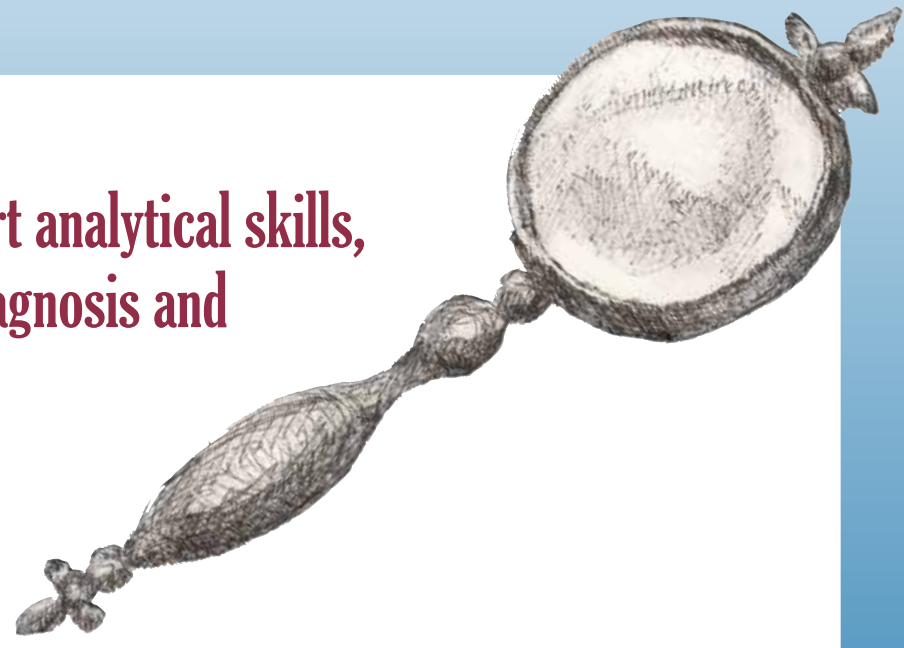
Detective Nephron



Detective Nephron, world-renowned for expert analytical skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases.

Wildly waving a stack of paper records, budding nephrologist L.O. Henle and medical student Ms. Curious Tubule run down the hall toward Detective Nephron's office.

Henle *(with a smile):* A case, a case!

The detective sits facing the window. He is silent for a moment, then quickly turns around.

Nephron *(curious):* Finally, something that might put an end to this utter boredom.

Henle It's a case of metabolic acidosis.

Nephron *(smiling):* Ah yes. My 8th favorite acid-base abnormality.

Ms. Tubule appears confused. Henle chuckles knowingly and subtly shakes his head.

Tubule *(curious):* 8th?

Nephron *(smiling):* You forget about mixed double and triple acid base disturbances. But please, continue.

Tubule So this is a young female—rather healthy, with only a history of migraines and depression—who presented with one week of progressive shortness of breath, generalized malaise, and loss of appetite.

Nephron How . . . nonspecific! I like that . . . go on . . . .

Tubule She was found to have a serum bicarbonate of 12 mmol/L. Her sodium was 143 mmol/L, chloride was 120 mmol/L. That gives her a serum anion gap of . . . .

Nephron *(surprised look):* . . .

Tubule . . . an anion gap of 11. So this is a normal anion gap metabolic acidosis.

Henle Her serum pH was 7.25.

Nephron Interesting. So we have a hyperchloremic metabolic acidosis. I'm guessing she doesn't have diarrhea, or else you wouldn't be bothering me with this.

Tubule Well, for hyperchloremic metabolic acidosis, you want to see whether there is a kidney-related cause or an extrarenal cause.

Nephron Remember there are only two body systems in my nephrocentric mind . . . renal and extrarenal.

Tubule Well, the patient hasn't complained of any diarrhea, otherwise . . . I don't know.

Henle *(stepping in):* We calculated the urine anion gap. It was +12 and her urine pH is 6.5.

Nephron I see. Ms. Tubule, Let's take it one step at a time. If you have acidemia, what should the kidney be doing? Should the urine be acidic or alkaline?

Tubule Acidic! The kidney needs to dump that acid to help us cope with this acidemia.

Nephron Good. So if the kidney is able to dump acid and get rid of it, the kidney is doing the right thing, right? In other words, it's not a distal nephron problem (where the fine tuning of acid–base is headquartered). So if you are dumping acidic urine, your problem lies in the gut or the proximal tubule most of the time. If you are having alkaline urine, your problem lies in the distal tubule most of the time. Because if the kidney is the problem and you truly have a nephrogenic tubular acidosis (my term for renal tubular acidosis), it's really a distal tubule problem and you cannot acidify the urine.

Tubule *(happy):* Well said!

Nephron How is the urine anion gap calculated?

Tubule Urine anion gap . . . Oh! So that would be the urine sodium plus potassium, minus the urine chloride. If there is more chloride than sodium and potassium—that is, the urine anion gap is negative—then we presume that extra chloride is balancing high ammonium excretion, which is the proper renal response to acidemia, implying an extrarenal cause of acidosis.

Nephron Right. More precisely, urine anion gap is a surrogate marker for the ability of the kidneys to excrete acid in the form of $NH4^+$. What about the urine pH?

Henle It also represents decreased $NH4^+$ excretion in the kidney.

Nephron *(jumping in):* Careful with that quick reflex thinking. Let's think this through. The kidney can excrete acid in 3 ways: $NH4^+$, titratable acids, and free protons. $NH4^+$ is the main way the kidneys excrete acid and grossly represents about two-thirds of the total acid excretion load. $NH4^+$ excretion requires 3 things: proximal tubular synthesis, medullary recycling, and intraluminal trapping by free H^+ excreted in distal nephrons. We measure $NH4^+$ excretion indirectly with urine anion gap. Free protons represent less than 0.01% of the total acid excretion load. Free protons depend on the activity of the H^+-ATPases in type A intercalated cells. We measure free H^+ with urine pH. So a high urine pH does not really represent problems with $NH4^+$ excretion.

Now, where were we? We have a hyperchloremic metabolic acidosis that we now suspect is nephrogenic in etiology. I presume the patient has normal renal function?

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Tubule Yes.

Henle So now we're entering the land of renal tubular acidoses or in your words—nephrogenic tubular acidosis. Serum potassium is normal. Her urine pH was 6.5. Her urine anion gap is positive. Her fractional excretion of bicarbonate was 17%.

Nephron I take it this was after she was given IV sodium bicarbonate?

Henle Yes.

Tubule They were initially giving her sodium bicarbonate when she first came in the emergency department.

Nephron The clinical characteristics of proximal nephrogenic tubular acidosis will vary depending on whether the patient is at steady state or is actively receiving treatment with bicarbonate. They will also vary depending on if the proximal nephrogenic tubular acidosis represents an isolated problem with bicarbonate reabsorption or is part of a generalized proximal tubular disorder.

Tubule What?

Nephron Remember that with proximal RTA (the way you like it), the defect is a decreased capacity to reclaim filtered bicarbonate in the proximal tubule. The renal bicarbonate losses continue until steady state is reached where the serum bicarbonate—and thus the filtered bicarbonate load—has decreased so much that it is able to be completely reabsorbed. When proximal RTA is in steady state or not treated, and the problem is isolated to bicarbonate reabsorption in the proximal tubule, then there will be no problems with $NH4^+$ production in proximal tubule, so therefore the urine anion gap will be negative. Also, there will be no problems with the H^+ pumps in the distal nephron, so the urine pH should be less than 5.5. However, when the proximal RTA represents rather a generalized proximal tubular problem such as Fanconi syndrome, then the ability of the proximal tubule to synthesize $NH4^+$ will be compromised, and therefore the urine anion gap will be positive and the urine pH will still be < 5.5 since there are no issues with distal acidification. If the patient is actively receiving bicarbonate, the bicarbonate not reclaimed in the urine will be eliminated along with Na^+, which will increase the urine anion gap and make it positive. Also, the bicarbonate in the urine will buffer H^+ in the urine from distal acidification and make the urine pH > 5.5.

In this case, another extra piece of information we need to consider is the elevated fractional excretion of bicarbonate (FE bicarbonate), which only occurs in the presence of bicarbonate supplementation.

Tubule *(relieved):* I see…

Nephron Is there other evidence of generalized proximal tubular dysfunction?

Henle She has no hypophosphatemia or hypouricemia; also no glucose in the urine.

Nephron What do we think?

Tubule I think this is a proximal or type 2 RTA actively treated with bicarbonate, hence the positive urine anion gap and urine pH of 6.5 as she does have the elevated urinary bicarbonate excretion. But I don't know from what.

Nephron Let's stay away from calling thing types 1 and 2. Rather using terms such as proximal and distal is more illustrative of the location and pathophysiology. Numbers confuse physicians – especially nephrologists . . . .

—looking over to Henle: Et tu, Henle?

Henle Well, given the evidence so far, I have to agree with Ms. Tubule that there's definitely some element of proximal RTA. However, the severity of her acidosis is what perplexes me. Normally with proximal RTA, at steady state, the serum bicarbonate is in the 12–20 mEq/L range. Her serum bicarbonate is borderline low and her presentation quite severe for what I would expect.

Nephron Agreed!

Henle So I'm not sure. But in the differential for proximal RTA, we think of congenital transport defects–doubtful for it to present in a middle-aged woman. Lead, mercury, cadmium, copper could also do it, but I don't think she's had any exposure to heavy metals. I don't think she has Wilson's disease, either. Infiltrative conditions–multiple myeloma, amyloidosis–are a possibility as well . . . And your favorite test–serum free light chains–had a normal ratio for her kidney function.

Nephron Are there medications she is taking that are associated with proximal tubular dysfunction?

Henle She's not on acetazolamide, tenofovir, or any chemotherapy agents as she has no cancer.

Tubule Her only medicine is topiramate.

The detective's eyes brighten as he suddenly looks up at Ms. Tubule for a split second, then looks down again.

Nephron Fascinating.

Henle and Ms. Tubule appear puzzled.

Henle and Tubule, in unison What?

Nephron Do we have the pH of the original urine sample? Before bicarbonate infusion?

Ms. Tubule flips frantically through her index cards as though the world were looking on.

Tubule It was 6.1.

Henle Why do you ask?

Nephron So this patient demonstrates the inability to acidify her urine also in steady state conditions. In the face of severe acidemia one would expect her urine to be maximally acidified, and yet this young patient with otherwise normal renal function is unable to get the urine pH lower than 5.5.

Henle A problem with distal acidification. So you're thinking about a distal RTA also?

Nephron Exactly. In fact, a mixed proximal and distal nephrogenic tubular acidosis caused by topiramate. When was the medication started?

Tubule It was for migraine prophylaxis, started several months ago, and why, the dose was recently increased!

Nephron As I suspected.

Henle Let me make sure I understand. To summarize, we have a patient who presented with a hyperchloremic metabolic acidosis, symptomatic for 1 week, with bicarbonate initially of 12. The

history and urine studies suggested a nephrogenic cause of the acidosis. Potassium was normal. Her urine was consistent with a distal acidification defect, but she also demonstrated increased FE bicarbonate after receiving bicarbonate supplementation. And all of these findings are consistent with adverse effects related to topiramate.

Nephron Indeed. And these derangements typically improve with stopping the medication. In addition, topiramate has also been associated with an increased incidence of calcium phosphate nephrolithiasis and osteoporosis.

Tubule Fascinating...

One week later...

Tubule Do you remember the patient we suspected of having mixed RTA secondary to topiramate?

Nephron Of course.

Tubule Right, so on our recommendation the primary team discontinued the medication. She did well with bicarbonate supplementation in the short term and was discharged from the hospital; follow-up labs have completely normalized.

Nephron Very well then. And so, yet again, from a diagnosis of hyperchloremic metabolic acidosis, you have identified an easily reversible cause, and I hope one you will never forget. Let's have some NY style coffee . . . I have a headache!

Special thanks to Dr. Chi Chu, Nephrology Social Media Collective intern and resident at California Pacific Medical Center for submitting this case. A special thanks to Dr. Helbert Rondon, Assistant Professor of Medicine, Renal-Electrolyte Division at the University Of Pittsburgh School Of Medicine and Dr. Rimda Wanchoo, Assistant Professor of Medicine, Nephrology Division, Hofstra Northwell School of Medicine for content editing.

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Policy Update

ASN Promotes Additional Federal Investments in Kidney Research

By Grant Olan

On Thursday, July 7, the ASN Research Advocacy Committee participated in meetings at the U.S. National Institutes of Health (NIH) and Department of Veterans Affairs (VA) during the society's annual Kidney Research Advocacy Day (Table 1). ASN Research Advocacy Committee Chair Frank C. Brosius, MD, and ASN Public Policy Board Chair John R. Sedor, MD, FASN, also participated in a first-ever ASN meeting with the White House Office of Management and Budget on Friday, July 8.

The Research Advocacy Committee urged the NIH and VA to pool resources and knowledge toward uncovering new discoveries and innovations for preventing and treating kidney diseases. Meeting topics also included continued collaboration and partnerships with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to eliminate kidney health disparities and increase interest in kidney research careers.

"Kidney Research Advocacy Day is a rewarding opportunity to encourage more kidney research collaborations and initiatives among federal research stakeholders," Dr. Brosius remarked. "Cancer, HIV/AIDS, and other diseases have had great success in part because stakeholders worked together to revolutionize care. ASN hopes to do the same thing for kidney diseases. We've seen too few advances in care, and patients with kidney diseases deserve more and better treatments than the limited options available today."

The Research Advocacy Committee began annual visits to NIH in 2012 to raise the profile of kidney diseases, promote more kidney-related research, and encourage more cross-institute collaboration. In addition to NIDDK, the committee met with leaders of the National Heart, Lung, and Blood Institute (NHLBI); National Institute of General Medical Sciences (NIGMS); National Institute of Minority Health and Health Disparities (NIMHD); National Institute of Biomedical Imaging and Bioengineering (NIBIB); and National Institute on Aging (NIA).

At the VA, the Research Advocacy Committee learned that the highest number of grants during the last funding round went to kidney research, including one of the first five Million Veteran Program grants. The VA Office of Research and Development expressed interest in continued collaboration with ASN and the society's members who are VA clinician-investigators. ASN is a member of the Friends of VA Medical Care and Health Research (FOVA) advocacy coalition. FOVA was founded over 25 years ago to ensure that America's veterans receive high-quality healthcare.

While meeting with the White House Office of Management and Budget, Dr. Brosius and Dr. Sedor discussed the importance and need for more federal investments in kidney research, as well as the status of the Government Accountability Office's (GAO) investigation on the adequacy of federal investments in kidney research. Rep. Barbara Comstock (R-VA), Rep. Tom Marino (R-PA), Sen. Ben Cardin (D-MD), and Sen. Bill Nelson (D-FL) requested the GAO study given the significant societal burden of kidney diseases.

An internal ASN study of kidney research revealed that less than 1% of total Medicare expenditures on care for patients with kidney diseases is invested in kidney research. Altogether, Medicare spends $99 billion annually. The Medicare End-Stage Renal Disease Program—the only disease-specific entitlement program—annually costs $35 billion alone, more than the entire NIH budget. Yet federal investment in kidney research pales in comparison, totaling only $650 million.

The GAO is on track to complete and release the results of its study by the end of 2016. "The GAO report is a crucial first step in understanding the current kidney research landscape, and I anticipate it will confirm what ASN has suspected all along—that kidney research is underfunded," Dr. Sedor said. "I believe the report will pay dividends for research funding down the line. Once complete, ASN looks forward to sharing the results with the entire kidney community."

In the meantime, ASN is working with other stakeholders in the research community to continue building support for another NIH and VA research funding increase in 2017. In 2016, Congress increased the NIH budget by $2 billion to a total of $32 billion, as well as the VA Research Program's budget by $41.8 million to a total of $630.7 million.

Table 1

ASN Research Advocacy Committee

Frank C. Brosius, MD, Chair
Josef Coresh, MD, PhD, FASN
Susan T. Crowley, MD, FASN
William H. Fissell, MD
Jeffrey L. Garvin, PhD
Susan B. Gurley, MD, PhD
David S. Hains, MD
Benjamin D. Humphreys, MD, PhD, FASN
Edgar A. Jaimes, MD
Jordan A. Kreidberg, MD, PhD
John R. Sedor, MD, FASN
Bradley K. Yoder, PhD
Bessie A. Young, MD, FASN, MPH