

Kidney News

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Wintertime and Hypoalbuminemia Mean Vitamin D Deficiency for Hemodialysis Patients

By Tracy Hampton

Vitamin D deficiency is nearly universal in patients who have hypoalbuminemia (≤ 3.1 g/dL) and who start dialysis during the winter, a new study has found (Bhan I, et al. Clinical measures identify vitamin D deficiency in dialysis. *Clin J Am Soc Nephrol* 2010; 5:460-467).

“We were hoping to see if clinical data that are readily available to clinicians taking care of patients starting dialysis could identify individuals likely to have vitamin D deficiency,” said first author Ishir Bhan, MD, of the Massachusetts General Hospital in Boston. “While we cannot predict this with 100 percent accuracy, we did identify a subpopulation at extremely high risk of deficiency.”

Bhan’s study looked at parameters that can reveal which kidney disease patients starting hemodialysis will al-

most certainly be vitamin D deficient (defined by serum levels of 25-hydroxyvitamin D).

Vitamin D levels in kidney disease patients

Impaired metabolism of vitamin D is among the most recognized disorders associated with chronic kidney disease (CKD), and 50–90 percent of patients with end stage renal disease (ESRD) are vitamin D deficient. Although low levels of 25-hydroxyvitamin D in the blood are associated with increased mortality in patients with ESRD, testing for the vitamin is expensive and not routinely performed in these individuals. If commonly collected clinical characteristics could be used to predict the risk of vitamin D deficiency in

Continued on page 3



Kidney research depends on robust inquiry at all levels of our perception and imagination. See special section, p. 7.

Inside

7 Our special section

“Translational Research: Where do We Go From Here?” considers the road ahead for kidney research

14 Kidney specialists

on the ground in Haiti after the quake



16 Fellow's Corner

Remembering Nathan Hellman

16 Industry Spotlight

An update on drugs for renal cancer

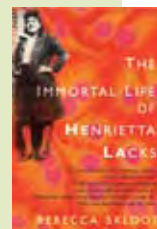


17 Journal View

Blood lead linked to teens' kidney function

18 Book Review

The Immortal Life of Henrietta Lacks



ESRD Bundling Rule Garners Many Comments

By Caroline Jennette and Bradley Layton

Almost everyone in the renal community has heard the steady grumbling about the new Prospective Payment System (PPS) or “bundle” set to change the landscape for dialysis reimbursement in 2011. Reactions to the proposal have run the gamut from enthusiastic to outraged. A number of stakeholders, including patient advocates, health care providers, and professional

organizations, added their voice to the federal comment submission process that ended late last year.

Before a final rule is created, Congress is legally mandated to have an open submission period to garner ideas, suggestions, and concerns from the public on proposed regulations. Submitted comments are used by the rulemaking body to justify how decisions are made for the

final rule.

In many cases, the public doesn’t scan the Federal Register and provide comments—this process is usually left to interest groups and paid lobbyists. But the creation of a new payment system for dialysis—a financially and emotionally charged subject—brought many to the rulemaking process for the first time.

As comments started pouring in to the Centers for Medicare and Medicaid Services (CMS) through the federal regulations website (www.regulations.gov), Bill Peckham, a home dialyzer, advocate, and creator of the blog “Dialysis from the sharp end of the needle” began to catalog

Continued on page 4

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Indication: Renvela® (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis.

Important Treatment Considerations

Renvela is contraindicated in patients with bowel obstruction • Caution should be exercised in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery • Uncommon cases of bowel obstruction and perforation have been reported • Serum bicarbonate and chloride levels should be monitored • Vitamins D, E, K (coagulation parameters), and folic acid levels should be monitored • The most frequently occurring adverse reactions in a short-term study with sevelamer carbonate tablets were nausea and vomiting • In a short-term study of sevelamer carbonate powder dosed three times daily, adverse events were similar to those reported for sevelamer carbonate tablets • In long-term studies with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, the most common adverse events included: vomiting, nausea, diarrhea, dyspepsia, abdominal pain, flatulence, and constipation • Cases of fecal impaction and, less commonly, ileus, bowel obstruction, and bowel perforation have been reported • Drug-drug interactions may occur with some medications and should be taken into consideration when instructing patients how to take Renvela • Patients should be informed to take Renvela with meals and to adhere to their prescribed diets

Please see Brief Summary of Prescribing Information on adjacent page.

Reference: 1. Renvela [package insert]. Cambridge, MA: Genzyme Corp; 2009.

Wintertime

Continued from page 1

CKD patients, only those most likely to be affected could be tested and treated.

With this goal in mind, Bhan and his colleagues analyzed data from 908 patients in the Accelerated Mortality on Renal Replacement (ArMORR) cohort, a nationally representative group of U.S. hemodialysis patients. The ArMORR cohort contains a variety of demographic and clinical data including medical problems and laboratory

results, as well as serum and plasma samples. Data from 60 percent of the patients were used as a training set to determine potential predictors of vitamin D deficiency, and data from the other 40 percent of patients were used to validate the predictors.

Bhan’s team found that 79 percent of the study population was vitamin D deficient, with 25-hydroxyvitamin D levels less than 30 ng/mL. Black race, female sex, initiation of hemodialysis during the winter season, and hypoalbuminemia were the strongest predictors of vitamin D deficiency. In

the validation set, hypoalbuminemia and initiation of hemodialysis during winter increased the likelihood of vitamin D deficiency in black females (from 90 percent to 100 percent), black males (from 85 percent to 100 percent), white females (from 82 percent to 94 percent), and white males (from 66 percent to 92 percent).

The presence of hypoalbuminemia, particularly in females and black males, may reduce the need to measure 25-hydroxyvitamin D in patients initiating dialysis between October and March, the authors suggest. Be-

cause testing is much more costly than treatment, empiric therapy with a nutritional form of vitamin D such as ergocalciferol could be considered for these individuals. The authors noted that additional studies should be done to validate their findings.

Biological clues revealed

The research not only identifies which hemodialysis patients are at the highest risk of vitamin D deficiency, but also provides some potential biological explanations as to why. The link between hypoalbuminemia and the deficiency suggests that at-risk patients excrete large amounts of protein—perhaps including vitamin D binding protein—in their urine. The loss of vitamin D binding protein, the main carrier of vitamin D, would inevitably cause the loss of vitamin D as well.

Earlier studies showed that patients on dialysis have an impaired ability to generate vitamin D from sun exposure. But the association between initiating hemodialysis during the winter season and vitamin D deficiency found in Bhan’s study suggests that skin-based production of the vitamin is important even in patients with ESRD.

While this study identified clinical factors that can be used to predict low 25-hydroxyvitamin D levels, it is unclear whether correcting these levels is clinically beneficial for patients with ESRD. Other experts in the field, however, stress the negative health consequences that can arise from vitamin D deficiency.

“Very low vitamin D levels can cause osteomalacia, a serious bone disease. Based on these findings, nephrologists should consider use of vitamin D supplements in most dialysis patients during winter at least,” said Daniel Coyne, MD, who was not involved with the research and is professor of medicine in the renal diseases section at Washington University School of Medicine in St. Louis.

Previous studies have shown a correlation between 25-hydroxyvitamin D levels and factors such as cardiovascular health and infection in ESRD patients. The authors noted that more research is needed to determine if supplements can have any effect on these conditions.

“The authors are correct that low vitamin D levels may just be a marker for illness, rather than mediating other adverse outcomes,” Coyne said. “We need prospective trials to prove vitamin D supplements improve patients’ health and survival.”

Study co-authors include Sherri-Ann Burnett-Bowie, MD, Jun Ye, PhD, Ravi Thadhani, MD (Massachusetts General Hospital), and Marcello Tonelli, MD (University of Alberta, Edmonton, Canada). Thadhani has received research support from Abbott Laboratories and honoraria from Abbott Laboratories and Genzyme. The other authors have no disclosures.

Renvela[®]

sevelamer carbonate

[se vel' a mer]

See package insert for full prescribing information.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Renvela[®] (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis.

DOSAGE AND ADMINISTRATION

Because of the rapid reaction with the hydrochloric acid in the stomach, the dosing of Renvela powder or tablet is anticipated to be similar to that of the sevelamer hydrochloride salt or tablet.

General Dosing Information

Patients Not Taking a Phosphate Binder. The recommended starting dose of Renvela is 0.8 to 1.6 g, with meals based on serum phosphorus level. Table 1 provides recommended starting doses of Renvela for patients not taking a phosphate binder.

Table 1. Starting Dose for Dialysis Patients Not Taking a Phosphate Binder

SERUM PHOSPHORUS	RENVELA [®] 800 MG	RENVELA POWDER
> 5.5 and < 7.5 mg/dL	1 tablet three times daily with meals	0.8 g three times daily with meals
> 7.5 mg/dL	2 tablets three times daily with meals	1.6 g three times daily with meals

Switching from Sevelamer Hydrochloride Tablets. For patients switching from sevelamer hydrochloride tablets to sevelamer carbonate tablets or powder, use the same dose in grams. Further titration may be necessary to achieve desired phosphorus levels. The highest daily dose of sevelamer carbonate studied was 14 grams in CKD patients on dialysis.

Switching between Sevelamer Carbonate Tablets and Powder. Use the same dose in grams. Further titration may be necessary to achieve desired phosphorus levels.

Switching from Calcium Acetate. In a study in 84 CKD patients on hemodialysis, a similar reduction in serum phosphorus was seen with equivalent doses (approximately mg for mg) of sevelamer hydrochloride and calcium acetate. Table 2 gives recommended starting doses of Renvela based on a patient's current calcium acetate dose.

Table 2. Starting Dose for Dialysis Patients Switching From Calcium Acetate to Renvela

CALCIUM ACETATE 667 MG (TABLETS PER MEAL)	RENVELA [®] 800 MG (TABLETS PER MEAL)	RENVELA POWDER
1 tablet	1 tablet	0.8 g
2 tablets	2 tablets	1.6 g
3 tablets	3 tablets	2.4 g

Dose Titration for All Patients Taking Renvela. Titrate the Renvela dose by 0.8 g TID with meals at two-week intervals as necessary with the goal of controlling serum phosphorus within the target range.

Sevelamer Carbonate Powder Preparation Instructions

The entire contents of each 0.8 or 2.4 g packet should be placed in a cup and mixed thoroughly with the amount of water described in Table 3.

Table 3. Sevelamer Carbonate Powder Preparation Instructions

RENVELA POWDER PACKET STRENGTH	MINIMUM AMOUNT OF WATER FOR DOSE PREPARATION (EITHER OUNCES, mL, OR TEASPOON/TABLESPOON)		
	ounces	mL	tsp/tbsp
0.8 g	1	30	6 teaspoons/2 tablespoons
2.4 g	2	60	4 tablespoons

Multiple packets may be mixed together with the appropriate amount of water. Patients should be instructed to stir the mixture vigorously (it does not dissolve) and drink the entire preparation within 30 minutes or resuspend the preparation right before drinking.

Based on clinical studies, the average prescribed daily dose of sevelamer carbonate is approximately 7.2 g per day.

DOSAGE FORMS AND STRENGTHS

Tablets: 800 mg white oval, film-coated, compressed tablets imprinted with "RENVELA 800".

Powder: 0.8 g and 2.4 g pale yellow powder packaged in an opaque, foil lined, heat sealed packet.

CONTRAINDICATIONS

Renvela is contraindicated in patients with bowel obstruction.

WARNINGS AND PRECAUTIONS

Use Caution in Patients with Gastrointestinal Disorders. The safety of Renvela has not been established in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery. Uncommon cases of bowel obstruction and perforation have been reported.

Monitor Serum Chemistries. Bicarbonate and chloride levels should be monitored.

Monitor for Reduced Vitamins D, E, K (clotting factors) and Folic Acid Levels. In preclinical studies in rats and dogs, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, reduced vitamins D, E, and K (coagulation parameters) and folic acid levels at doses of 6-10 times the recommended human dose. In short-term clinical trials, there was no evidence of reduction in serum levels of vitamins. However, in a one-year clinical trial, 25-hydroxyvitamin D (normal range 10 to 55 ng/mL) fell from 39 ± 22 ng/mL to 34 ± 22 ng/mL (p<0.01) with sevelamer hydrochloride treatment. Most (approximately 75%) patients in sevelamer hydrochloride clinical trials received vitamin supplements, which is typical of patients on dialysis.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

There are limited data on the safety of Renvela. However, based on the fact that it contains the same active ingredient as the hydrochloride salt, the adverse event profiles of the two salts should be similar. In a cross-over study in hemodialysis patients with treatment durations of eight weeks each and no washout the adverse reactions on sevelamer carbonate tablets were similar to those reported for sevelamer hydrochloride. In another cross-over study in hemodialysis patients, with treatment durations of four weeks each and no washout between treatment periods, the adverse reactions on sevelamer carbonate powder were similar to those reported for sevelamer hydrochloride.

In a parallel design study of sevelamer hydrochloride with treatment duration of 52 weeks, adverse reactions reported for sevelamer hydrochloride (n=99) were similar to those reported for the active-comparator group (n=101). Overall adverse reactions among those treated with sevelamer hydrochloride occurring in > 5% of patients included: vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), flatulence (8%), and constipation (8%). A total of 27 patients treated with sevelamer and 10 patients treated with comparator withdrew from the study due to adverse reactions.

Based on studies of 8-52 weeks, the most common reason for withdrawal from sevelamer hydrochloride was gastrointestinal adverse reactions (3-16%).

In one hundred and forty-three peritoneal dialysis patients studied for 12 weeks using sevelamer hydrochloride, most adverse reactions were similar to adverse reactions observed in hemodialysis patients. The most frequently occurring treatment emergent serious adverse reaction was peritonitis (8 reactions in 8 patients [8%] in the sevelamer group and 2 reactions in 2 patients [4%] on active-control). Thirteen patients (14%) in the sevelamer group and 9 patients (20%) in the active-control group discontinued, mostly for gastrointestinal adverse reactions. Patients on peritoneal dialysis should be closely monitored to ensure the reliable use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

Postmarketing Experience: Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post-approval use of sevelamer hydrochloride, which has the same active moiety as sevelamer carbonate: pruritus, rash, abdominal pain, fecal impaction, and uncommon cases of ileus, intestinal obstruction, and intestinal perforation. Appropriate medical management should be given to patients who develop constipation or have worsening of existing constipation to avoid severe complications.

DRUG INTERACTIONS

Sevelamer carbonate has been studied in human drug-drug interaction studies with warfarin and digoxin. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in human drug-drug interaction studies with ciprofloxacin, digoxin, warfarin, enalapril, metoprolol, and iron.

Ciprofloxacin: In a study of 15 healthy subjects, a co-administered single dose of 2.8 grams of sevelamer hydrochloride decreased the bioavailability of ciprofloxacin by approximately 50%.

Digoxin: In 19 healthy subjects receiving 2.4 grams of sevelamer hydrochloride three times a day with meals for 2 days, sevelamer did not alter the pharmacokinetics of a single dose of digoxin. In 18 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily, sevelamer did not alter the pharmacokinetics of a single dose of digoxin.

Warfarin: In 14 healthy subjects receiving 2.4 grams of sevelamer hydrochloride three times a day with meals, sevelamer did not alter the pharmacokinetics of a single dose of warfarin. In 14 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily with meal, sevelamer did not alter the pharmacokinetics of a single dose of warfarin.

Enalapril: In 28 healthy subjects a single 2.4 gram dose of sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of enalapril.

Metoprolol: In 31 healthy subjects a single 2.4 gram dose of sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of metoprolol.

Iron: In 23 healthy subjects, a single 2.8 gram dose of sevelamer hydrochloride did not alter the absorption of a single oral dose of iron as 200 mg exsiccated ferrous sulfate tablet.

Other Concomitant Drug Therapy: There are no empirical data on avoiding drug interactions between Renvela and most concomitant drugs. During postmarketing experience, very rare cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Monitor TSH levels and signs of hypothyroidism in patients receiving both medications.

When administering an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, there is no information suggesting a dosing regimen that would be universally appropriate for all drugs. One may, however, administer the drug one hour before or three hours after Renvela, and when important, monitor blood levels of the drug. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Sevelamer products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effect of sevelamer hydrochloride on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy. In pregnant rats given doses of sevelamer hydrochloride during organogenesis, reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D, occurred at a dose approximately equal to the maximum clinical trial dose of 13 g on a body surface area basis. In pregnant rabbits given oral doses of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred at a dose approximately twice the maximum clinical trial dose on a body surface area basis [See *NONCLINICAL TOXICOLOGY* (13.2)].

Labor and Delivery: No sevelamer hydrochloride treatment-related effects on labor and delivery were seen in animal studies [See *NONCLINICAL TOXICOLOGY* (13)]. The effects of sevelamer carbonate on labor and delivery in humans is unknown.

Pediatric use: The safety and efficacy of Renvela has not been established in pediatric patients.

Geriatric use: Clinical studies of Renvela did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

OVERDOSAGE

Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to normal healthy volunteers in doses of up to 14 grams per day for eight days with no adverse effects. In CKD patients on dialysis, the maximum dose studied was 14 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. There are no reports of overdosage with sevelamer carbonate or sevelamer hydrochloride in patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Rats were given sevelamer hydrochloride by diet at 0.3, 1, or 3 g/kg/day. There was an increased incidence of urinary bladder transitional cell papilloma in male rats of the high dose group (human equivalent dose twice the maximum clinical trial dose of 13 g). Mice received dietary administration of sevelamer hydrochloride at doses of up to 9 g/kg/day (human equivalent dose 3 times the maximum clinical trial dose). There was no increased incidence of tumors observed in mice.

In an *in vitro* mammalian cytogenetic test with metabolic activation, sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay.

Sevelamer hydrochloride did not impair the fertility of male or female rats in a dietary administration study in which the females were treated from 14 days prior to mating through gestation and the males were treated for 28 days prior to mating. The highest dose in this study was 4.5 g/kg/day (human equivalent dose 3 times the maximum clinical trial dose of 13 g).

Developmental Toxicity: In pregnant rats given dietary doses of 0.5, 1.5, or 4.5 g/kg/day of sevelamer hydrochloride during organogenesis, reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D, occurred in mid- and high-dose groups (human equivalent doses approximately equal to and 3.4 times the maximum clinical trial dose of 13 g). In pregnant rabbits given oral doses of 100, 500, or 1000 mg/kg/day of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

HOW SUPPLIED/STORAGE AND HANDLING

Tablets: Renvela[®] 800 mg Tablets are supplied as white oval, film-coated, compressed tablets, imprinted with "RENVELA 800", containing 800 mg of sevelamer carbonate on an anhydrous basis, microcrystalline cellulose, hypromellose, diacylated monoglycerides, sodium chloride, and zinc stearate.

1 Box of 30 ct 800 mg Tablets (NDC 58468-0130-2)

1 Bottle of 270 ct 800 mg Tablets (NDC 58468-0130-1)

Powder: Renvela[®] for Oral Suspension is supplied as opaque, foil lined, heat sealed, packets containing 0.8 g or 2.4 g of sevelamer carbonate on an anhydrous basis, natural and artificial citrus cream flavor, propylene glycol alginate, sodium chloride, sucralose, and ferric oxide (yellow).

1 Box (NDC 58468-0131-2) of 90 ct 2.4 g packets (NDC 58468-0131-1)

1 Box (NDC 58468-0132-2) of 90 ct 0.8 g packets (NDC 58468-0132-1)

1 Sample Box (NDC 58468-0131-4) of 90 ct 2.4 g packets (NDC 58468-0131-3)

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ESRD Bundling

Continued from page 1

and code all submitted comments as a way to track and review the issues being talked about most. A total of 1165 comments collected by Peckham were coded according to type of commenter (if available) and main themes mentioned in each comment.

Who commented?

Health care providers and consumers submitted the most comments (28.4 percent and 14 percent, respectively) of the 60 percent of comments that could be coded by commenter type (Table 1). Dialysis facilities and their staff accounted for 10 percent of comments. Twenty-five professional, research, or advocacy organizations submitted comments on behalf of their constituents.

Physicians and nurses submitted over half of health care provider comments, while those on dialysis submitted the overwhelming majority of consumer comments (Table 2). The majority of comments from consumers came from those on home modalities who wrote to testify that they felt healthy and were satisfied with their care.

The Renal Support Network (RSN) spearheaded much of the effort to involve patient consumers and their family members in the commenting process. RSN's Kidney Public Policy 101 web site created an avenue for patients to learn from each other while interpreting the guidelines, an often intimidating process.

"We attempted to provide a forum where patients could exchange thoughts, ideas, and concerns about the bundled payment system rather than simply soliciting comments," said Lori Hartwell, RSN president and founder and long-time patient advocate. "This way, patients are able to understand this complex subject and share how the proposed system may impact their quality of life."

The Medical Education Institute (MEI), a nonprofit social marketing firm headed by Dori Schatell, also provided resources and tools for patients and providers wanting to comment.

"We pulled together literature to back up concerns and disseminated this information widely to other advocacy and renal organizations," Schatell said.

MEI's own submitted comments systematically went through each element, offering research and recommendations to improve patient-focused regulations.

In addition to submitting a comment, the American Society of Nephrology (ASN) was one of only a few organizations allowed to testify at a town hall meeting about bundling hosted by CMS. The ASN's Public Policy Board, in conjunction with a task force specifically created by ASN to study the new PPS, wrote a detailed letter on behalf of members, which can be read on the ASN's web site.

What types of comments were submitted?

The two themes that received the most comment were inclusion of oral drugs in the proposed bundle (65.8 percent) and issues related to home dialysis (30.1 percent). Other topics garnering top mention were inclusion of laboratory services into the bundle (22.8 percent), concerns about the amount of the adjusted composite rate (19.7 percent), suggestions for the Quality Improvement Projects (16.3 percent), and changes to the case-mix adjusters (14.3 percent). Table 3 lists the 12 themes mentioned most often in submitted comments.

Bundling oral drugs

The proposed ESRD PPS bundle is slated to include all drugs and biologics that are currently separately billable for ESRD patients under Medicare Parts B and D, regardless of the route the drug or biological is administered. Under the proposed rule, ESRD facilities would be responsible for providing these drugs—CMS would no longer be able to pay anyone but the facilities after the new PPS is phased in.

Health care providers and dialysis facilities submitted the majority of comments related to bundling oral drugs. Administrators expressed a fear that facilities would be forced to shut down due to reduced reimbursement, and many health care providers are concerned that physicians will be forced to choose cheaper medications versus the most effective for their patients as a way to keep costs down. There were also many questions regarding the logistics of having dialysis facilities act as medication dispensaries, especially for small dialysis organizations, and the feasibility of complying with variable state pharmacy laws.

Consumers shared stories of their own struggles to pay for medications, especially during the Part D "donut hole," and expressed worries that bundling oral drugs may increase co-payments that are already financially overwhelming.

Many comments suggested that CMS take more time to review the feasibility of bundling oral drugs or at least try to slowly phase in Part D and B rules to be sure the new rules comply with state laws. Another suggestion was to mandate that pharmaceutical companies supply facilities with drugs at a set minimal charge over cost and then have facilities contract with pharmacies to "decrease competition, provide the necessary oral medications to the patients, and improve care to the ESRD patient."

Advocates concerned about bundling oral drugs may already have a reprieve in the Senate version of House health reform legislation that passed in November. Section 10336 of the "Patient Protection and Affordable Care Act" (H.R. 3950) outlines a request for the Government Accountability Office to conduct a feasibility study on the inclusion of oral drugs into the PPS and the ability of dialysis providers to comply with state laws in providing oral drugs. The provision also asks for a report on the presence of safeguards to protect Medicare beneficiaries. Although chances of current health reform legislation getting through are looking slim, this section could be removed and placed in another bill.

Table 1
Types of commenters

Connection of commenter	Number	Percent
Congressman	2	0.2
Consumer	163	14.0
ESRD network	2	0.2
Dialysis facility/administrator	117	10.0
Family member	64	5.5
Foundation	2	0.2
Health care provider	331	28.4
Industry	22	1.9
Network	2	0.2
Patient advocacy organization	4	0.3
Professional/research organization	19	1.6
Unknown	437	39.5

Table 2
Health care provider and consumer commenters

Types of health care providers who commented	Count	Percent
MD	131	40.1
Nurse	66	20.2
Dietician	36	11.0
Pharmacist	1	0.3
Social worker	28	8.6
Staff	27	8.3
Unknown	38	11.6
Types of consumers who commented		
Dialysis patient	140	86.4
Transplant patient	19	11.7
Pre-ESRD patient	3	1.9

Table 3
Main themes mentioned in comments

Comment theme	Number of comments	Percent of total comments
Home training	315	30.1
Amount of payment	229	19.7
Labs	265	22.8
Oral drugs	766	65.8
QIP	190	16.3
Case mix adjustment	166	14.3
Race adjuster	45	3.9
Method II	38	3.3
Small volume facility	156	13.4
IV meds	78	6.7
Blood transfusions	24	2.1
Copays	119	10.2


Home training payments

Thirty percent of comments mentioned home dialysis training and payments for home services. The proposed rule has several provisions related to home dialysis including: 1) removing the option for home dialysis patients to order their own supplies and equipment from a supplier, 2) bundling the payment for training patients to do home dialysis into the adjustor payment for the first four months of dialysis, and 3) continuing to only pay for three dialysis treatments per week unless more treatments are ordered by a physician. Many commenters proposed a separate payment adjustor for home dialysis training instead of including it in the adjustor, with the reasoning that many patients come to home dialysis after the first four months of reaching ESRD. The majority of family member and consumer comments focused

on home dialysis, with many commenters explaining the importance of home dialysis and how it had changed their lives and their families' lives for the better. Consumers also expressed a worry that facilities would begin to de-incentivize home therapies if training were included in the bundle. This concern was echoed in the comments of small dialysis facilities; their administrators noted that the adjustor does not adequately cover the time spent and materials required to train patients for home modalities. Both health care providers and consumers applauded CMS for keeping the payment to a per treatment basis versus a weekly or monthly payment bundle. Although only covering three treatments per week, this provision allows those on dialysis the opportunity to more easily travel for work and vacation.

What's next?

The proposed rule is expected to come out sometime during the summer of 2010. The new PPS is slated by law to begin in January 2012 with a phase-in period of four years. Facilities can opt out of the phase-in period if they wish to fully implement the new system. Any facilities opening after January 2011 will be required to utilize the full PPS. As part of the new bundle, CMS is required to also implement a Quality Improvement/Incentive Program (QIP), which will tie dialysis payments to how well facilities perform on certain clinical care measures. A comment submission period focused specifically on QIP measures is forthcoming. If you'd like to submit a comment on this topic, stay tuned and visit www.cms.hhs.gov/ESRDpayment/ for upcoming dates and deadlines. ●



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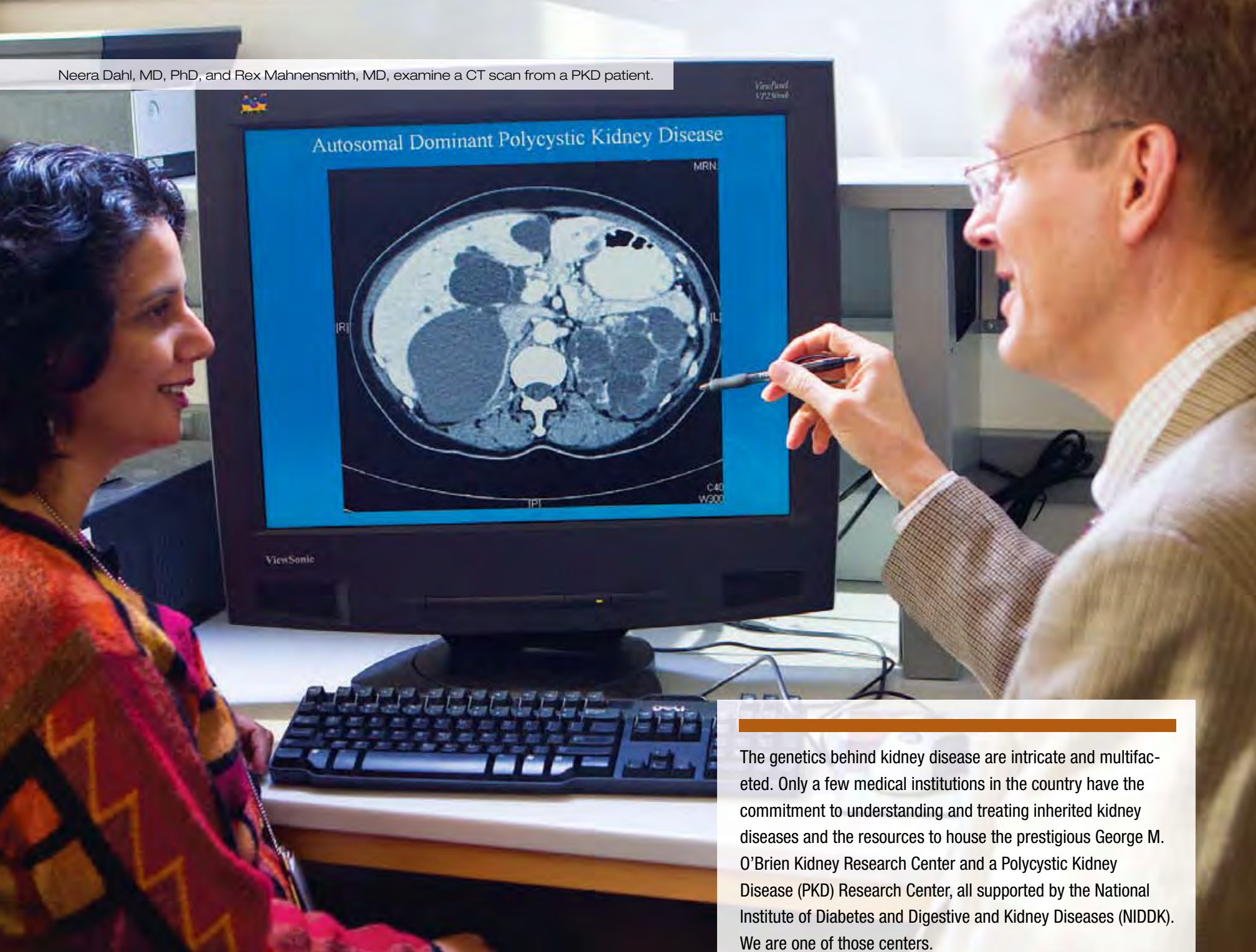
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LEADING THE FIGHT
AGAINST KIDNEY DISEASE

Neera Dahl, MD, PhD, and Rex Mahnensmith, MD, examine a CT scan from a PKD patient.



The genetics behind kidney disease are intricate and multifaceted. Only a few medical institutions in the country have the commitment to understanding and treating inherited kidney diseases and the resources to house the prestigious George M. O'Brien Kidney Research Center and a Polycystic Kidney Disease (PKD) Research Center, all supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). We are one of those centers.

Research Excellence, Clinical Leadership and a Commitment to Our Patients

Our researchers have discovered over fifteen genes for human diseases affecting the kidney and blood pressure. These discoveries cover the gamut from rare disorders of blood pressure regulation through sodium and potassium handling such as Liddle's syndrome, pseudohypoaldosteronism type II and Bartter's and Gittelman's syndromes to such common inherited kidney diseases as polycystic kidney disease (PKD). While our researchers are now seeking to translate these findings to treatments for PKD and other disorders, our nephrologists are using these discoveries to help our patients lead healthy and fulfilling lives.

Being at the forefront of clinical research and treatments means that our physicians and surgeons are furthering the current understanding of kidney disease. Most importantly, it means they are positioned to provide the best care possible to our patients.



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Translational Research: Where Do We Go From Here?



Nephrologists do a lot to improve and prolong the lives of their patients, but we all wish we could do more. No magic fairy will grant our wishes. They will only be fulfilled through painstaking research.

In this section, Speth and Wood speak as scientist and patient about the importance of animal models in the development of therapies for chronic kidney disease. Animal research is still a key component of procedure and drug development that benefits people and animals. Barker,

Story, and Wathen present their thoughts on statistical evaluations and the conflict between Frequentists versus Bayesian analyses. Take heed: there is a sec-

tion of hard-core mathematics, but the differences will be otherwise apparent. Mahan and Smoyer examine a common disorder, pediatric nephrotic syndrome, and

the need for multicenter study groups to change its long-term outcomes. They specifically review their own experience with the Mid-West Pediatric Nephrology Consortium and other clinical study groups.

Solving kidney problems requires better understanding of basic processes of biology, new therapeutic targets and the drugs to modulate them, and studies of populations with and without kidney disorders. Research is a complex dance of ideas from the clinic to the laboratory bench and then back to the bedside. Progress depends on robust inquiry at all levels of our perception and imagination. ●

Pascale Lane, editor in chief, ASN Kidney News

Animal Research in the Development of Kidney Transplantation

...A Professional Perspective

By Robert Speth

The kidney maintains a proper fluid and electrolyte balance in our body, plays a major role in regulating blood pressure, and filters out waste products from the bloodstream for excretion from the body as urine. In addition, it is the source of the hormone erythropoietin and the active form of vitamin D. How has animal research contributed to treatment of kidney failure?

the kidney (2).

During World War II, injuries to soldiers demanded new therapies to heal wounds. Joseph Murray, MD, found himself at a Veterans Administration hospital facing the challenge of treating a badly burned airman who needed skin grafts but did not have enough intact skin to provide these grafts. Knowing that allografts of cadaver skin would soon be rejected by

Harvard kidney transplant group (3).

In his autobiography (3), Murray takes great pains to acknowledge the importance of animal models in perfecting the kidney transplant technique. To overcome difficulties with hemostasis, denervation, and other surgical issues, Murray first did autotransplants, fully removing the kidneys from dogs and relocating them in another optimal location. After autotransplanted dogs had survived for three years, Murray and his colleagues carried out the first successful human kidney transplant using identical twins as donor and recipient.

The problem of rejection made the operation unattainable for everyone other than identical twins. E. Donnal Thomas, another Nobel Prize winner, attained some success by using radiation to kill the lymphocytes that carried out the immunological rejection of the transplanted organ; however, there were more failures than successes. A better procedure was still needed.

The breakthrough came five years later. Drs. Robert Schwartz and William Dameshek used an anticancer drug, 6-mercaptopurine (6-MP) to stop immunological rejection of a foreign protein in rabbits (4). Soon thereafter Drs. Murray and Roy Calne used 6-MP concomitantly with transplantation of an allograft kidney in a dog. The transplant was a success!

Additional kidney transplant experimentation in dogs with analogs of 6-MP

synthesized by Drs. George Hitchings and Gertrude Elion of Burroughs-Wellcome, Ltd., led to the development of azathioprine (IMURAN) as a superior agent for prevention of rejection of the transplanted kidney. Further tests of the kidney transplant dogs showed that they retained normal immune function, indicating that the effects of 6-MP and azathioprine were short-lived, just long enough to allow the body to accept the foreign antigens that characterized the transplanted organ. This research ultimately led to the first successful cadaveric kidney transplant into a human in 1962 by Dr. Murray (5), a success soon repeated in hospitals worldwide.

While the success rate for kidney transplants soared, there was still room for improvement. Azathioprine did not always prevent rejection of the transplanted kidney. It had toxic side effects and could be lethal. Indeed, the first human transplant patient treated with azathioprine died from its toxicity.

Once again biomedical researchers used animals to develop drugs with greater efficacy and fewer adverse side effects. Orthoclone, OKT3 (generic name: muromonab-CD3), the drug that Patty was treated with, was the first monoclonal antibody drug to be approved by the Food and Drug Administration (FDA) in 1986 (see article on facing page). Monoclonal antibodies are produced by fusing a single precursor cell from a mouse spleen with a

All who benefit from animal research, who work for the betterment of humankind and animals, must make our voices heard . . .

Galen first identified the kidney as the source of urine based on his studies of nonhuman primate anatomy. In the 19th century, Sir William Bowman (for whom Bowman's capsule is named) greatly expanded our knowledge of renal function based on his studies of kidneys that included exotic animals such as boa constrictors and parrots (1) (Figures 1 and 2). Subsequent discoveries of renal function also relied heavily upon animal studies. Historical reviews of kidney research provide considerable detail of the elegant physiological studies that led to our present understanding of the workings of

the airman's immune system, Murray did them anyway to buy time for the airman to recover sufficiently so that autografts of his skin could be made to heal his wounds (3).

Ultimately this success led Murray to his interest in developing the kidney transplant technique, for which he ultimately received the Nobel Prize in Physiology or Medicine in 1990. A colleague and good friend discouraged Murray from taking on this challenge, saying "... you may ruin your whole future." Despite opinions among nephrologists that this was a "fools' errand," Murray joined the

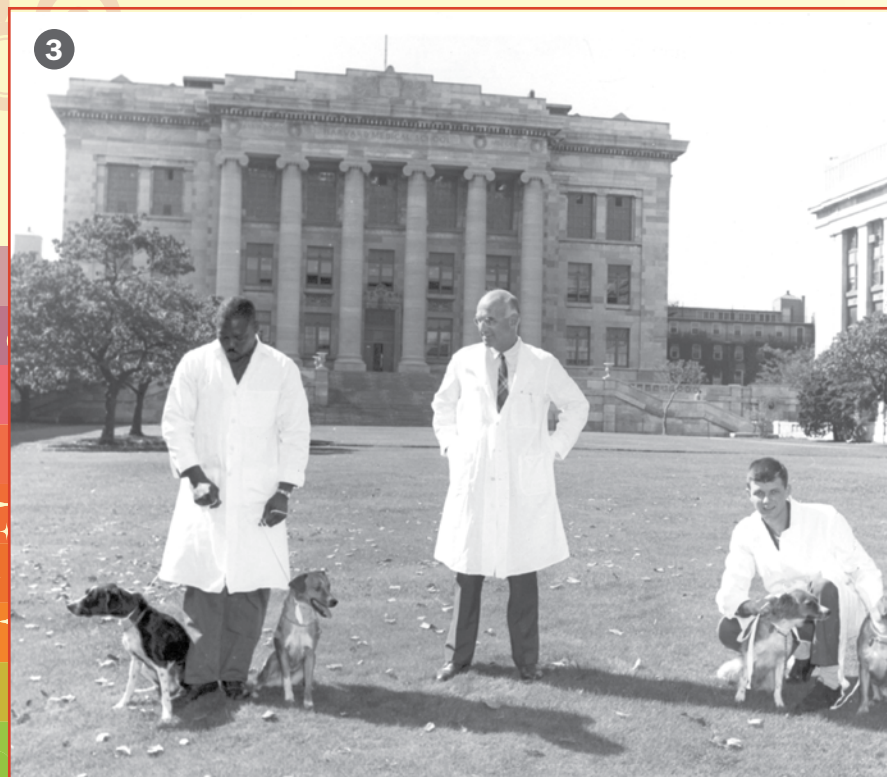
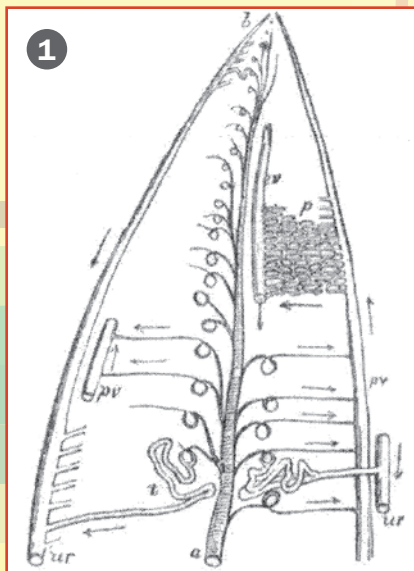


Figure 1

Drawings of a boa constrictor kidney by Sir William Bowman (from Eknoyan, *Kidney Int* 1996, 50: 2120-2128).

Figure 2

Drawings of a parrot kidney by Sir William Bowman (from Eknoyan, *Kidney Int* 1996, 50: 2120-2128).

Figure 3

Picture of Dr. Joseph Murray with dogs that had kidney transplants.

human myeloma cell, allowing the cells to proliferate and produce a single, specific antibody to CD3 T cells. Initially these were then grown in the peritoneal cavity of other mice, although now they can be cultured and harvested in vitro.

Orthoclone OKT3 targets a specific antigen (CD3) on T cells (the type of blood cell responsible for mounting an immunological attack on foreign antigens such as those of transplanted kidneys). When the monoclonal antibody binds to CD3 on the surface of the T cell, it initiates an immune attack on the T cell leading to its destruction. This drug has a short-term effect to prevent acute organ rejection, but also has long-term effects that fundamentally alter the immune system to make it tolerant of the transplanted organ.

The other drug that Patty credits with saving her life, erythropoietin (EPO, EPOGEN) came about through research in sheep. Patty's physician, Joseph Eschbach, in collaboration with John Adamson demonstrated that EPO is a hormone produced by the kidney that acts upon the bone marrow to stimulate the production

of red blood cells. Without this hormonal stimulation, red blood cell production may not be adequate to meet the needs of oxygen transport in the bloodstream, leading to anemia and chronic weakness. Patty was one of the many patients in whom this Phase II clinical trial (6) established the efficacy of EPOGEN, leading to its approval for use in humans in 1989.

Animal research, from its primitive underpinnings to modern-day molecular biological advances, played an essential role in the development of kidney transplantation and other tools for the management of chronic kidney disease. As we face the ongoing challenges of human and animal health, animal research continues to play a pivotal role.

A former Secretary-General of the United Nations, Dag Hammarskjöld, once wrote, "The madman shouted in the market place. No one stopped to answer him. Thus it was confirmed that his thesis was incontrovertible."

All who benefit from animal research, who work for the betterment of human-

kind and animals, must make our voices heard so as not to be shouted down by those who would deny us progress against the diseases that shorten and impair our lives. ●

Robert Speth is a professor of pharmaceutical sciences at Nova Southeastern University in Fort Lauderdale, Fla. He is a member of the board of directors of the National Animal Interest Alliance and a former president of the Society for Veterinary Medical Ethics.

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Animal Research in the Development of Kidney Transplantation

... A Personal Perspective

By Patty Wood

In 1971, I was diagnosed with kidney failure. Although I didn't know it, my life had taken a new path. With a husband to love and support me, and a new baby daughter to raise, I had to pull myself together and get on with life.

My blood pressure was much too high, and soon I entered a clinical trial at the University of Washington in Seattle. The new blood pressure medicine being tested in the trial worked well for me. It slowed my kidney failure and kept me off dialysis for several years, much longer than had been projected.

That blood pressure drug had recently emerged from animal testing. At the time, I didn't realize how close I would be to the little mice used in most animal research, and I didn't know how I would eventually defend their role in biomedical research.

I began dialysis in July 1978 and adapted well. The following April my brother gave me a kidney, and it worked immediately. I felt like a new person. It gave me freedom. I was curious about the history of my medications and was amazed at how researchers took their ideas from the bench to animal testing. After demonstrating new therapies using animal models, the therapies were then tested in human clinical trials. What seemed so fitting to me was that,

in many instances, these therapies came back to the animals for use in their own health care.

I lectured to schools, colleges, civic groups, and even churches about kidneys, transplants and, of course, the part that animal research plays in all of our lives. I also became aware of a new dissenting group called People for the Ethical Treatment of Animals (PETA), which had connections to a local group called "PAWS" and a more extreme version called "NARN." I tried to communicate with these groups, but they had no interest in reasoning and were very rude. In one instance they were very aggressive and began pushing me. Fortunately my husband was there and stepped in.

In 1986, I lost my brother's kidney and went back on dialysis, which was complicated by severe anemia. My doctor, Joseph Eschbach, was also a researcher studying erythropoietin (EPO). His research was to the point of clinical trials. I felt at death's doorstep when he put me into the trials, but within four weeks I could run up four flights of stairs and had the strength to withstand the stress of another transplant surgery. The kidney I received was in "trauma" and to save it, I received another new drug called Orthoclone OKT3. Within

four days I could sense that the kidney was working. It worked well for 21 years—what a life, what freedom!

My recovery was so dramatic that Amgen, the company that had developed recombinant human erythropoietin as a drug, invited me to give lectures to its employees. This gave me the opportunity to thank them for their part in saving my life. Organizations throughout the United States invited me to talk about my experiences and what I had learned about animal research. Somehow I feel that by standing up to animal extremists, it gave me a way to "give back" and say thank you to the people who devote their lives to saving others.

In March 2000, Research America! honored me for my contributions to biomedical research. My husband, daughter, and Dr. Eschbach were by my side in Washington, DC, as I received the award.

I worked at a local veterinary clinic for six years, and found it interesting to learn that EPO and many other medications given to animals were tested on human guinea pigs like me! I've also consulted for many Seattle area biomedical companies and love being close to the starting point of the miracles brought to us by so many mice.

In October 2007, I received a new kidney. Miraculously, it matched perfectly and kicked right in, but fate stepped in and caused other problems. Ultimately a blood clot destroyed the kidney, and it had to come out. Many other complications necessitated a six-month hospital stay. Because of the blood clot, I had to learn to walk again, which took a lot of hard work, but I've made it back.

Biomedical research has saved my life over and over. I'm now on dialysis three times a week. I can hardly believe the changes that have taken place in dialysis in the last 33 years—in the procedures, the medicines, and the machine itself. Of course I'm also back using EPO, and it is keeping me strong.

I thank God every day for my life, my husband, our family, and our grandchildren. It's breathtaking to have lived this long and see the goodness medical research has done for everyone.

As for transplant number four? I'm still pondering that possibility while I play with my grandchildren. ●

Patty Wood is a kidney transplant recipient and has been an outspoken advocate for biomedical research using animal models for more than 20 years.

Advancing the Care of Children with Renal Diseases

Moving to a Children's Oncology Group-Oriented Approach for Children with Idiopathic Nephrotic Syndrome and Other Kidney Diseases

By John Mahan and William Smoyer

Idiopathic nephrotic syndrome (INS) affects 16 per 100,000 children and is one of the most common acquired childhood kidney diseases. INS often runs a relapsing course in children, even in the children who respond to prednisone therapy. As a result, these children often have a prolonged clinical course. Because of the burden of this condition—augmented by the significant complications associated with INS and its treatments in children—childhood INS remains an intimidating challenge for children, families, and medical professionals.

Remarkably, the present-day approach to childhood INS is still based on a series of foundational studies that are limited in their application to the clinical challenges faced by families and pediatric nephrologists today. These important studies were published between 1970 and 1993 and began with an international collaborative effort sponsored by the International Study of

decades. Some examples of the changing nature of INS in children include the increasing recognition of genetic factors that underlie nephrotic syndrome in children, the rising incidence of focal segmental glomerular sclerosis (FSGS) in children with INS, the increasing prevalence of obesity and type II diabetes mellitus that may be exacerbated by standard INS treatments with glucocorticoids, and the importance of family status and treatment compliance in patient outcomes.

In 2008, Gipson and colleagues performed a survey regarding treatment of childhood INS among North American pediatric nephrologists at 10 U.S. centers (3). Great disparities in even the most fundamental aspects of care, such as the management of initial clinical presentations, relapses, and steroid resistance in children with INS were identified among the 30 participating practitioners. In response to these

Another concern is the paucity of studies in children with INS that address important long-term issues. In the consensus conference report, only a handful of studies involved more than 10 years of follow-up outcomes. A recent report from Kyrieleis (5) addressed long-term steroid responsiveness in children with INS and highlights the value and impact of detailed long-term observational studies in these children. Because the vast majority of children with INS now survive to adulthood, there is a real need for studies of the long-term outcomes (and complications) of our therapies to help define the lifelong consequences of INS and INS treatment in children. For too long, studies of treatment of children with INS have been limited to single centers and short-term perspectives, which inherently preclude insight about important long-term issues.

Careful prospective multicenter observational and interventional studies that address evaluation and treatment and incorporate comprehensive follow-up of children with INS are required to provide the basis for improvements in consistent and effective care. We have designed a prospective evaluation of new incident children with primary nephrotic syndrome in conjunction with the Mid-West Pediatric Nephrology Consortium (MWPNC). In doing so, we hope to begin the systematic evaluation of appropriate approaches for evaluating and treating children with steroid-sensitive and steroid-dependent/resistant nephrotic syndrome.

In our evaluation, we have relied on the methods and lessons of the Children's Oncology Study Group (COG). COG (www.curesearch.com) began in the United States and is now a worldwide clinical trial cooperative group comprised of investigators from 238 institutions who are supported by the National Cancer Institute to study childhood cancers. COG was formed in 2000 from the merger of four independent cooperative cancer study groups that date back to 1956 in conducting prospective randomized clinical trials to study best treatments, quality of life, and impact of cost on families of children with cancer. We have been particularly struck by these lessons learned from the COG experience:

1) Improved patient outcomes can be derived from sequential comparisons of standard-of-care versus novel treatments in prospective clinical tri-

als. The basis for all improvements is the comparison of new therapies to the existing standard care.

2) Successful studies can be obtained by combining patient results from multiple institutions; this is necessary to overcome the challenges of low patient numbers for most pediatric diseases.

3) An established clinical trial infrastructure must exist to enable repeated clinical trials that can perform sequential comparisons with consistent methods and participation among member centers. There are tremendous advantages to having an existing study group and not having to construct a new study group for each study.

4) Networks and defined study groups can develop relationships that promote collective efforts, dedication to mutual goals, and accountability to projects. Relationships especially matter in collaborative clinical research endeavors.

Under the stewardship of the MWPNC steering committee (Denis Geary, Larry Greenbaum, John Mahan, Tej Mattoo, and William Smoyer), the MWPNC has held a members meeting every six months since 2003 to develop collaborative research projects and present the results of existing and completed MWPNC studies. Member centers elect to sign on to studies of interest, and authorship is offered to all participants who are involved in at least two of three essential study elements: design, execution, and analysis/publication.

At this point the MWPNC has published 11 pediatric nephrology studies in several areas of investigation and has 15 approved studies underway. From an initial group of 20 collaborating centers located in the Midwest, the MWPNC has grown to involve 30 participating centers in the United States and Canada that are centered in, but not limited to, the Midwest. A prospective trial of standardized therapy for children with INS that leads to subsequent testing of alternate strategies and provides patient data and samples that help define complications and outcomes in children with INS is now approved. The study will soon be underway in the MWPNC (www.MWPNC.org).

Study networks in pediatric nephrology have evolved over time to carry out the important work of advancing the care of children with kidney disorders.

Kidney Disease in Children (ISKDC).

From 1967 to 1974, 521 children with new-onset INS underwent renal biopsies and standard prednisone treatment. The investigators demonstrated that response to therapy with cessation of abnormal proteinuria within eight weeks of corticosteroid therapy was predictive of minimal change nephrotic syndrome (MCNS) (1). As a result, pediatric nephrologists began to rely on the initial therapeutic response to glucocorticoids to guide subsequent evaluation and therapy for children presenting with INS.

A series of important studies by the Arbeitsgemeinschaft für Padiatrische Nephrologie also helped define practice management of children with INS (2). While these landmark studies have been critical in our approach to these children, they are now almost 20 years old, and the clinical characteristics and challenges of the children presenting with INS have clearly changed over recent

challenges, we participated in a Children's Nephrotic Syndrome Consensus Conference for North American pediatric nephrologists. The conference was convened to develop updated evidence- and opinion-based recommendations for the evaluation and management of children with INS (4).

In the consensus conference report, only a limited number of treatment recommendations were based on Class 1 evidence. Recommendations related to extent of evaluation, monitoring for complications, and treatment for steroid-dependent and steroid-resistant INS were almost all based on small case series and expert opinion. Thus, in many clinical situations, pediatric nephrologists are dependent on well designed but older randomized trials. These trials have led to continued variations in clinical approach among practicing physicians with little data beyond anecdotal evidence to guide further clinical decision-making for these patients.



The Southwest Pediatric Nephrology Group (SWPNG), founded in 1980, was the first successful North American collaborative pediatric nephrology study group. SWPNG now consists of over 70 participating centers and is still active today; it has published 27 papers since its inception. The SWPNG provided important evidence of the power of collaborative networks in this area.

The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Registry was founded in 1987 and has pioneered the process of translating a pediatric nephrology registry into an opportunity for collaborative clinical research. NAPRTCS now includes 110 participating institutions in the United States and Canada and has a distinguished track record of registry descriptive studies that have done much to advance our understanding of clinical issues in children with chronic kidney disease and posttransplant. NAPRTCS has now developed a number of multicenter collaborative trials devoted to these populations.

Other examples of collaborative clinical research networks in pediatric nephrology include the Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry, a study group founded in 2001 that is devoted to advancing care of children who require continuous renal replacement therapy. In addition, study groups devoted to a single, yet many times multifaceted, study have helped move the care of children with kidney disease forward. These include the Prospective Cohort Study of Kidney Disease in Children (CKiD) study, the Novel Therapies for Resistant FSGS (FONT) Study Group, the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) Study, and the now completed NIH FSGS trial group. Efforts devoted to providing continuous quality improvement (CQI) models appear to be another useful approach to improve the practice of care but are limited in the ability to generate new evaluation tactics and therapies.

Important lessons can be derived from the COG experience and our experience in pediatric nephrology. We propose that any attempts to test new evaluation strategies and therapies in children with kidney disease should include:

- 1) the power of relationships to motivate individual practitioners and investigators to work together to address important clinical issues.
- 2) the need for investigators to be willing to put aside their own cherished patterns of care and beliefs to enroll patients in studies that prove the value of therapies.
- 3) the absolute value and need to question the established standard of care and/or try to improve our therapies and assess short- and long-term outcomes.
- 4) the need to consider each patient with a pediatric renal disease as a study patient.

It is only in these ways that we will be able to keep the focus where it belongs: the child with kidney disease. We believe so strongly in the power of the COG-like model that we are attempting to develop this in the MWPNC as an enduring mechanism to conduct and deliver prospective multicenter collaborative studies that will advance the care of childhood INS, as well as other pediatric kidney diseases. ●

John Mahan, MD, and William Smoyer, MD, are with the department of pediatric nephrology at Nationwide Children's Hospital, the Ohio State University College of Medicine, in Columbus.

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Statistics in Medicine: I Don't Need a p Value ... What's a p Value Anyway?

By Kerry Barker, Ken Story, and J. Kyle Wathen

Would you bet \$25 to win \$100?

We would gladly take the bet if the chance of winning were 96 percent. We certainly would not change our minds if the odds dropped to 94 percent. However, many scientists make different decisions on the basis of the p values inherent in this example—whether $p = 0.04$ or $p = 0.06$.

Most scientists utilize Frequentists statistics to prevent abuse of data. Frequentists require that you specify your hypothesis, statistical test, and the criteria of success in advance. Often this criterion is a “significant” p value, especially in medical studies. While $p \leq 0.05$ is often the criterion of choice, one may also choose 0.01/0.001 for “definitive studies” or 0.10/0.15 for “exploratory studies.”

Much has been written about why this is a flawed strategy. Most statisticians admit the strategy is flawed in hallway conversations or even in articles such as this one. Clients of statisticians will state that they know this is only part of the conclusions from a data analysis. Yet, at the end of the day, $p = 0.08$ is deemed a failure and $p = 0.04$ is a success.

In this article, we will informally present the Frequentists dilemma and describe differences between the Frequentists and Bayesian schools of statistical thought.

The Frequentists dilemma

You are asked to analyze a study upon completion. Even though you get an interim data set, you wait until the study is done before analyzing because, a priori, you decided to wait until the study is done. You find significance, $p = 0.05$. However, in another analysis scheme, we a priori decided to perform an interim analysis. We tell you that significance was not obtained after adjusting for multiple looks. Who is right? Luckily, since both of our analytic strategies were stated “a priori,” we are both right, even though our conclusions from the same data are completely different.

You and your friend develop a program for predicting winners in college basketball. It is only 50 percent accurate (a coin toss). Your friend looks further into the data and e-mails you stating that if you adjust for which team was at home and use only major conferences, the accuracy is now 99

percent. You smile at the foolishness of your friend, violating two important principles of statistics: adding a post-hoc analysis and analysis on a subgroup. Your friend decides to use the scheme to bet on games anyway. You meet one month later and remind your friend of his statistical foolishness. You also tell him that paying cash for a new Porsche with his winnings seems extravagant.

Have multiple looks at data been used inappropriately to declare significance? Yes. Have post-hoc analyses been used inappropriately? Yes. Have subgroup analyses been grossly misused? Yes, more times than we care to remember! Based on the cases above, the problems with Frequentists statistics seem obvious.

Bayesian methodology, disdained for years by Frequentists, uses prior information and subjective data. Worse, it is hard to do. However, in real life everyone uses prior information and subjectivity in making decisions. Buying a

house? Hiring a person? Marrying? All use prior information and subjectivity. Given the housing bubble, human resource issues, and the divorce rate, many people are not good at this type of analysis. The solution is not to eliminate the use of this information, but to make better use of it.

Frequentists versus Bayesian analyses

Let \mathbf{X} represent the observed data from a study comparing a placebo (P) and an experimental (E) treatment and Θ be an unknown parameter of interest. Assume that the larger the value of Θ , the bigger the improvement E provides over P and a value of zero when E and P are equivalent.

Both Frequentists and Bayesians have a common goal, making a statement about Θ .

For Frequentists, one calculates the probability of observing X or, more severely, assuming $\Theta = 0$, which can be

represented as $P(\mathbf{X} \text{ or more extreme} \mid \Theta = 0)$. If this probability is small (0.05), then the conclusion is that Θ is some value that is not zero. If the probability is not small, the conclusion is not that $\Theta = 0$; rather the conclusion is that there is not enough evidence to conclude $\Theta \neq 0$. Note neither statement is telling us much about Θ . A Bayesian analysis gives us the probability of Θ based on the observed data, which can be represented as $P(\Theta \mid \mathbf{X})$, for example, the probability that $\Theta > 0$ given X is 0.95, or in notation $\Pr(\Theta > 0 \mid \mathbf{X}) = 0.95$.

While the goals of Frequentists and Bayesian analysis are the same, there is a big difference between

$$P(\mathbf{X} \text{ or more extreme} \mid \Theta = 0) \text{ and } P(\Theta \mid \mathbf{X})$$

The Frequentists make a conclusion about Θ by assuming it is a particle value (here $\Theta = 0$) and calculate the probability of observing more extreme data under that assumption. This is a very roundabout way of analyzing Θ , and one must specify what is meant by “or more extreme.” A Bayesian analysis is more straightforward, and the resulting probability directly references Θ , the parameter of interest. So why is not everyone a Bayesian? One reason is that $P(\Theta \mid \mathbf{X})$ is calculated using the following equation

$$P(\Theta \mid \mathbf{X}) \approx P(\Theta \mid \Theta) * P(\Theta)$$

Where $P(\Theta \mid \mathbf{X})$ is called the posterior, $P(\mathbf{X} \mid \Theta)$ is called the likelihood (sampling distribution), and $P(\Theta)$ is called the prior. The prior is what Frequentists have an issue with and what Bayesians devote much of their time to. Just as the name suggests, “the prior” is based on all knowledge prior to the data collection and may include historical data or “expert” opinion. There are many types of priors. Given that the choice of priors is based on judgment, a Frequentist would state that this introduces bias into the analysis.

Two Frequentists would obtain the same results analyzing a data set (if they used the same method), while two Bayesians could get different results using different priors.

Bayesian methodology is not as well known, even to statisticians, and seems more complex. However, new software tools are making common Bayesian analysis more accessible.

Points to remember

- Using Bayesian methods should be methodological, not ad hoc.
- Statistical methodology is not a substitute for planning. Careful consideration of practical issues that may influence the design should be discussed with the statistician at the early phase of product development. Under the Bayesian paradigm, these practical issues can easily be included and their impact studied via simulation.
- In the Bayesian paradigm, you are not penalized for looking at the data and can easily include external data that arise during a study. This makes Bayesian particularly useful for performing adaptive designs.
- Stopping rules have no consequences for a Bayesian, but make a world of difference for Frequentists.
- There is no silver bullet—increasing sample size is still the best way to improve a study.

Operating characteristics of Bayesian analysis: are you a closet Bayesian?

In the Frequentists paradigm, one often obtains the operating characteristics (OCs) of a design that includes simple summaries such as the average number of patients enrolled, false positives, and power without considering potential departures from the assumptions made when designing the trial.

Bayesian statisticians routinely perform evaluations under varied and realistic scenarios taking into account a multitude of practical aspects involved before a study begins. In general, Bayesians use simulation to better understand the decision-making process and to study the impact that deviations from assumptions will have on product development. Due to technical difficulties, the impact of deviations from model assumptions are rarely investigated under Frequentists methods even though departures can seriously degrade the properties of the design.

These are critical components contributing to the superior performance of Bayesian methods. While the gain in terms of OCs may not always be substantial, one gains a much clearer understanding of how the design will perform in practice. In addition, the resulting analysis and conclusions from a Bayesian analysis are much simpler to interpret and are often how the non-statistician interprets a Frequentist's results.

Subjectivity is pervasive in everyday life. And although scientific objectivity is crucial in separating science from intuition, that does not mean subjective opinion does not also arise in the scientific literature. Even if only the "planned" Frequentists analysis is presented, many other analyses have probably been done. It is important to note that there are real costs to waiting for more data—sometimes in lives lost or lives spared. We must also consider the value of rejecting the null hypothesis unless it is in favor of some alternative. Finally, full disclosure of what was done before, during, and after is important regardless of method. ●

"The human understanding, once it has adopted an opinion, collects any instances that confirm it, and though the contrary instances may be more numerous and more weighty, it either does not notice them or else rejects them, in order that this opinion will remain unshaken" – Francis Bacon, 1620.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

AFTER THE QUAKE

Bernard Jaar, MD, FASN, describes his recent trip to manage acute kidney injury following the earthquake in Haiti. Jaar is assistant professor of medicine and epidemiology at Johns Hopkins Medical Institutions and staff nephrologist at the Nephrology Center of Maryland at the Good Samaritan Hospital in Baltimore.

By Bernard Jaar

I was born and raised in Port-au-Prince and attended medical school at the State University of Haiti. My father was from the Dominican Republic. I know Haiti very well and speak fluent Creole, French, and English, and have a good working knowledge of Spanish. As a nephrologist, I know too well the possible consequences of crush injuries with acute kidney injury (AKI). I believe that I was in a unique position to help in the Haiti earthquake. I brought with me 10 acute hemodialysis catheters and 900 grams of kayexalate.

My efforts focused on Jimani, a small town in the Dominican Republic, only 1 kilometer from the border with Haiti. Many Haitian patients were transferred to Jimani or brought by family members seeking medical care.

Surgeons on site communicated to me the early death of several patients after surgery for crush injury. There were no screening activities for AKI in this region, but Doctors without Borders with the International Society of Nephrology Disaster Relief Task Force were already in Port-au-Prince. Hundreds of Haitian patients fled to the Dominican Republic in the first few days after the earthquake to seek medical care.

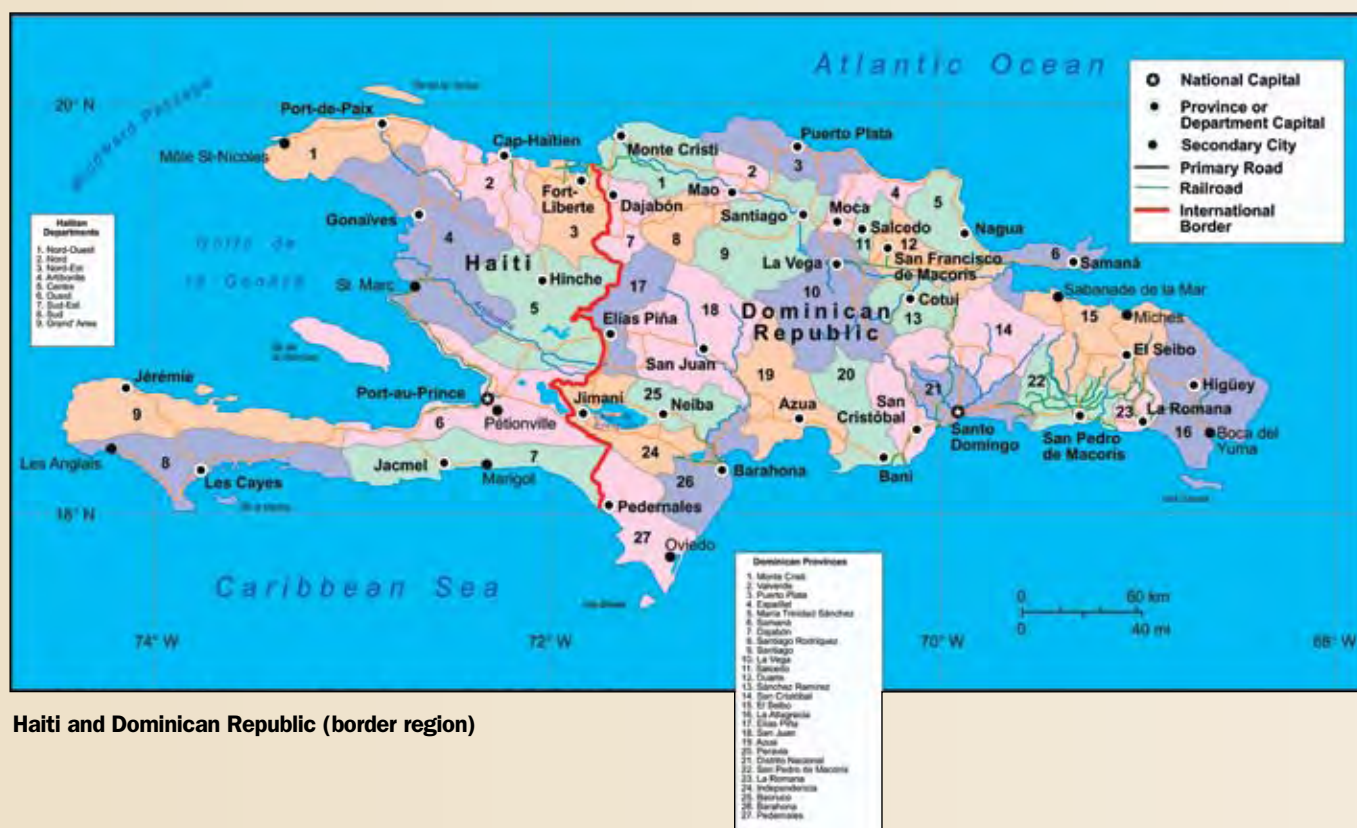
January 21: Contact

I arrived in Santo Domingo and made contact with Dr. Sandra Rodriguez, president of the Dominican Republic Nephrology Association. Dr. Rodriguez knew about my visit and had been in close contact with the ASN Disaster Relief Task Force (Dr. Didier Portilla). I drove to Barahona, the largest town near Jimani, and met with Dr. Julio Cesar Caro, the local nephrologist, that evening. We made plans to drive together to Jimani in the morning.

Dr. Caro is a trained nephrologist from the Dominican Republic. He completed his medical training in Santo Domingo in the late 1990s and has been in Barahona for four years. He is the only nephrologist in that region of the country and is well known and well respected in the community.

January 22: Assessment

Dr. Caro and I visited the Dominican Hospital in Barahona and then drove for another two hours to Jimani. There we visited both the local Dominican Hospital, called Hospital Provincial “General Melenciano” and the makeshift American hospital called “Buen Samaritano.”



Haiti and Dominican Republic (border region)

First we met with the medical director of the Barahona hospital and decided to use this hospital as a regional referral center for acute hemodialysis treatments. The medical director received a copy of the protocol for management of crush injuries.

At both Melenciano and Buen Samaritano in Jimani, we went over the protocol for management of crush injuries and discussed the urgent need to update the hospital laboratories for chemistry measurements, particularly serum potassium and creatinine. We left phone numbers to contact for any local cases of AKI.

At the makeshift hospital in Jimani, we met with Dr. Dale Betterton, medical director of the International Medical Alliance, which runs the Buen Samaritano facility. I went over the protocol for management of crush injuries, and we discussed the urgent need to update the lab for chemistry measurements, particularly serum potassium and creatinine. We were expecting four i-STAT machines from the United States to start AKI screening. Physicians here reported more than 70 major amputations in the first week after the earthquake with “several” deaths. Exact numbers were not available, but hyperkalemia may have played a role in some of the deaths. They were not aware of the nephrologist in Barahona with dialysis capabilities.

January 23: Screening

Our first stop was Melenciano Hospital, where we met again with Dr. Moquette, who reported that they now had 47 patients. Most stable patients were transferred out to Fond Parisien, a border town in Haiti. There was still no systematic screening for AKI, and no capability for chemistry measurements. The reagent for creatinine testing was ordered. At this point they were seeing fewer than five new patients per day, none with severe injuries, and none with crush injuries.

At Buen Samaritano, there were still many patients housed in tents. I delivered a supply of kayexalate to their pharmacy, and we identified a room with tap water and electricity to set up local hemodialysis machines. As the “consultant” for nephrology, I reminded the staff to avoid aminoglycosides, NSAIDs, or Cox-2 inhibitors as much as possible in cases of crush injuries and volume depletion. Unfortunately, we were still awaiting the arrival of i-STAT machines. Screening for AKI started with history and physical exam. Patients identified with crush injury, major limb trauma, “dark” urine, or decreased urine output had serum creatinine checked since this assay was now available.

A 23-year-old female in the ICU with crush injuries to three limbs requiring fasciotomies was transferred to the USS Comfort because of suspected AKI and EKG changes consistent with hyperkale-

mia. She was treated with kayexalate, D50, insulin, and IV bicarbonate. We were unable to obtain serum creatinine because of difficult venous access, given the extent of her injuries.

January 24 to 26: Screening

Buen Samaritano remained very busy. Dr. Caro and I continued to assess patients by history, vital signs, physical exams, urine characteristics, and volume output. Creatinine was measured in several patients, and some cases of AKI were identified. Most were mild and resolved with intravenous hydration. One 23-year-old male had a serum creatinine of 8.1 mg/dL with BUN of 135. One i-STAT machine became available, and his measured serum potassium was 7.3. He was started on a bicarbonate drip, given D50, insulin, calcium gluconate IV, and kayexalate. He was transferred the same afternoon to Dr. Caro’s care in Barahona, where he received his first hemodialysis that same afternoon.

By Jan. 26, the number of new cases presenting to the triage area had significantly decreased. Most surgeries were redos of previous amputations or plastic surgeries for flap closures. Physicians at Buen Samaritano and Melenciano Hospital also had a high level of awareness for crush injury and AKI, as evidenced by their ordering serum creatinine on a more regular basis. They were also aware of Dr. Caro’s availability and dialysis capabilities in Barahona.

Afterward

First, my week on Hispaniola was an amazing experience. Dr. Caro and I screened 250 to 300 patients during that week. Challenges included the makeshift nature of the Buen Samaritano facility, which made it difficult to find patients as they moved from one part of the campus to another. The high turnover of medical providers (who had an average stay of five days) made care more difficult as well. Many medical providers were not trained for disaster medicine, particularly identification of AKI associated with crush injuries. With high turnover of providers and no real charts for documentation, tracking care of patients was challenging. Available medications changed constantly based on supply received, so a course of treatment often included several agents.

Initially, coordination between Dominican physicians and medical providers at Buen Samaritano was suboptimal, with neither aware of the others' capabilities. I arrived 10 days after the earthquake, a bit late to screen for AKI. I suspect many patients had died or recovered spontaneously from AKI before either clinical or biochemical screening capabilities were in place.

On the positive side, there was excellent collaboration among Dr. Caro, myself, and the Dominican Department of Health. I believe this occurred because of the early contact and collaboration between ASN and the Dominican Republic Nephrology Association. We did not need dialysis in

Jimani, as the severe AKI patients were referred to Barahona and the USS Comfort. With Dr. Caro available and the Department of "Salud Publica" sending three Dominican nephrologists to the Jimani area to continue the screening process, there is no longer a great need for foreign nephrologists in the area.

Looking ahead

From my experience in the border region with Haiti, I make the following suggestions to help physicians in future disasters.

Early on, we should send a couple of nephrologists to assess the needs on site. I believe I had a much better understanding of local needs after my arrival despite several conversations about this with local nephrologists. Unfortunately, systematic AKI screening started only after my visit with Dr. Caro to the local hospitals in Jimani and distribution of the protocol. AKI develops early after an earthquake, and earlier intervention may have saved people. Establishing early contact with local nephrologists should also be a priority. Distribution of a crush injury protocol to medical providers who may not be trained for these situations is essential. Finally, rapid deployment of i-STAT machines for rapid diagnosis of biochemical disorders is likewise essential. ●

I would like to thank Didier Portilla, MD, chair of the ASN Disaster Relief Task Force, and my colleagues at the Nephrology Center of Maryland in Baltimore for their staunch and ongoing support during my stay in the border region.

Local Hospitals in Dominican Republic

Barahona Hospital

- ~200 bed hospital
- No chemical tests available (no potassium)
- 2 Braun hemodialysis machines for 12 chronic dialysis patients and 2 chronic peritoneal dialysis patients
- Six dedicated nurses for hemodialysis. No dialysis technicians
- New area under construction to expand unit 8 or 9 hemodialysis machines
- Center has 10 adult and 5 pediatric acute hemodialysis catheters in addition to the 10 adult catheters I brought with me

Jimani: Melenciano Hospital

- About 32 beds
- Now with 107 patients, heavy cases already referred to Buen Samaritano in Jimani or Santo Domingo
- No systematic screening for AKI
- No chemistry tests available but able to do CBC, HIV, Hepatitis B and C Blood type, UA with micro

Jimani: Buen Samaritano (makeshift hospital)

- Capacity up to 300 beds
- A bit better organized with different wards, such as 3 ORs, ICU, Post-op, Med-Surg, ED for triage
- No real charts kept but documentation system improving with manila folders
- Staffed mostly by American physicians, including orthopedic surgeons, anesthesiologists, and intensivists, but none with apparent crush injury experience
- No systematic screening for AKI
- No chemistry tests are available but able to do CBC, HIV, Hepatitis B and C, Blood type, UA with micro through lab run by Melenciano Hospital's staff



Patients in a makeshift ward

ASN Members, Partner Organizations Collaborate in Disaster Relief

A catastrophic 7.0 magnitude earthquake struck near Port-au-Prince, Haiti, in January. Within hours of the quake, ASN's Disaster Relief Task Force (ASN DRTF), led by Didier Portilla, MD, FASN, contacted the nephrology community worldwide to begin coordinating relief efforts.

ASN convened daily conference calls in collaboration with the Kidney Care Emergency Response (KCER) Coalition, other kidney-related organizations, and industry partners. Participants included Doctors without Borders, the International Society of Nephrology, USNS Comfort nephrologists, the Sociedad Latino-Americana de Nefrologia y Hipertension (SLANH), and the Society of Nephrology of the Dominican Republic (SNDR).

"Daily conference calls were vital to assess the situation and identify needs," said Mark Okusa, MD, FASN, chair of the ASN Acute Kidney Injury Advisory Group. "Because the earthquake severely damaged Haiti's telephone and internet infrastructure, communicating with providers on the ground was challenging. Bringing together multiple organizations to share information on Haiti in these calls facilitated a coordinated, more com-

prehensive response."

To track identified needs for supplies and volunteers, ASN developed a central registry and contacted nearly 25 additional kidney care companies regarding donations. Collaborating with Fresenius Medical Care, the society coordinated a shipment of over 10,000 pounds to the Haiti region. "The Port-au-Prince airport was almost impossible to access," said Dr. Portilla, "so ASN partnered with SLANH and with the SNDR President Sandra Rodriguez, MD, to establish an alternate supply chain through the Dominican Republic to deliver the items of greatest need to providers including Doctors Without Borders in Port-au-Prince." ASN also supported Dr. Rodriguez and the SNDR in establishing screening for crush syndrome and acute kidney injury (AKI) on the Haiti-Dominican Republic border, where hundreds of Haitians sought medical care.

"Developing a concise protocol for identifying and treating crush injury was an urgent priority," explained Ricardo Correa-Rotter, MD, SLANH president and ASN member. "We quickly identified a widespread lack of awareness and screening for kidney injury in initial relief

efforts, and therefore developed a concise document on AKI screening, hydration, and triage procedures to disseminate in the region."

As screening operations expanded in both Haiti and the Dominican Republic, so too did the need for related diagnostic and treatment supplies. ASN responded to requests from the SNDR and Port-au-Prince-based Partners in Health by arranging delivery of four i-STAT® machines and cartridges, thanks to a generous donation from Abbott. The society also coordinated shipment of over 400 catheters, donated by Covidien, and 200 bottles of Kayexalate®, donated by KVK-Tech, via the supply chain established in the Dominican Republic.

"The outpouring of support from ASN members for Haitians following the earthquake was phenomenal," said ASN Councilor Bruce Molitoris, MD, FASN. "The society identified more than 70 members willing to travel to the region to provide care, many of whom were fluent in Haitian Creole and French." ASN staff built a database cataloging volunteers' clinical skills, language ability, and availability, and collaborated with the pediatric nephrology community—led by the

American Society of Pediatric Nephrology and the International Society of Pediatric Nephrology—to incorporate such data on pediatric specialists.

ASN member Bernard Jaar, MD, FASN, as well as Talha Imam, MD, traveled to Haiti and the Dominican Republic to provide care shortly after the earthquake, and were in constant contact with the ASN DRTF during their time in the region. "Dr. Jaar and Dr. Imam were instrumental in providing much-needed nephrology care in the disaster area, and also in supplying needs assessments to ASN regarding demand for supplies, medicines, and volunteers," said Rajnish Mehrotra, MD, FASN, chair of the ASN Dialysis Advisory Group.

As demand for emergency nephrology relief in Haiti began to decrease nearly a month after the earthquake, full-time relief organizations such as USAID and the Pan American Health Organization initiated long-term recovery efforts. Continuing to monitor the situation in collaboration with partner organizations in Haiti and the Dominican Republic, ASN remained available to direct these organizations to available nephrologists or additional supplies if a need is identified. ●

Fellows Corner

Remembering Nathan Hellman



Nathan Hellman

Nathan Edward Hellman, talented physician, and beloved father, husband, and son, died on February 13, 2010, from a stroke. Nathan was born in Houston, Texas, on December 8, 1973.

Nathan inaugurated the Renal Fellow Network blog and was the newest member of the *ASN Kidney News* editorial board. He was on staff as a scientist physician at Massachusetts General Hospital and authored numerous scientific publications.

Nathan grew up primarily in Duluth, Minn., where he was editor of the high school newspaper and member of the math, basketball, and track teams. He graduated Magna Cum Laude from Yale University with a degree in molecular biology and biophysics. He received his MD, PhD, from Washington University in St. Louis and then did a residency in internal medicine at the University of Pennsylvania. After his residency, Nathan received a Fullbright Scholarship to study the molecular biology of cystic kidney disease at the Hôpital Necker in Paris, where he grew to love French culture.

He became a member of the division of nephrology at Harvard in 2007 as a clinical fellow in nephrology, and was completing his fellowship as a research fellow and member of Iain Drummond's research group.

Nathan is survived by his wife, Claire; children, Sophie and Maxime; parents, Patricia (Gregorich) and Richard N. Hellman, MD; sisters, Susan Jean Hellman and Catherine O'Malley; brother-in-law, Timothy O'Malley; nephews, Henry and James O'Malley; and uncles, Joseph and Robert Gregorich.

Nathan loved ideas and the written word. In his own communication, he had a knack for matching his message with the medium, whether it be the popular Renal Fellow Network, or peer-reviewed journal articles. He was a kind and compassionate person and will be missed by all who knew him. ●

ASN Kidney News shares some thoughts from Nathan's colleagues and postings from the Renal Fellow Network

Nathan's passion for understanding kidney disease was infectious. He has inspired many people to continue this search.

—Matt Sparks, nephrology fellow, Duke University

Nate's blog was inspiring to me personally and to others in the renal community. Even without meeting him, I felt that we all knew him from his blog. We have lost a great in nephrology who had made it big even at such an early phase in his career.

—Kenar Jhaveri, Great Neck, NY

Nate inspired many of us all around the country. He'll never know how far his enthusiasm, intellect, and inspiration reached.

—resident, Indiana University, future renal fellow

I was so impressed by his website and the person he obviously was—bright, inquisitive, a lover of knowledge and teaching.

—anonymous

Industry Spotlight

Renal Cancer Drug Update

Drug researchers' efforts to come up with new approaches to cancer are beginning to pay off, according to Research and Markets' *Renal Cancer Drug Pipeline Update 2010*.

Nearly 150 companies plus partners currently have in active development more than 160 drugs targeting renal cancer. The report notes the "high existing unmet need in the treatment of renal cancer ... reflected by the poor prognosis of patients with advanced stage disease, five-year survival rates with existing cytokine therapy being less than 20 percent." The report predicts that identification of new biomarkers will significantly help to achieve better staging of renal cancer and more accurate prognoses, and could lead to more individualized treatments and novel drug targets.

Centerwatch.com, a clinical trials and drug approvals site, listed several new drugs for renal cell carcinoma, the most common form of kidney cancer, that were approved in 2009:

- Afinitor® (everolimus), Novartis, approved March 2009
- Avastin® (bevacizumab), Genentech, approved August 2009
- Votrient® (pazopanib), GlaxoSmithKline, approved October 2009.

In early February, GlaxoSmithKline announced Phase III trial results that showed that the time it took for a patient's disease to progress was more than double for the group receiving Votrient (9.2 months), compared with the placebo group (4.2 months). The most dramatic effect was seen in previously untreated



patients (11.1 months for the pazopanib group vs. 2.8 for the placebo) and persisted among those previously treated (7.4 vs. 4.2 months, respectively). The study is ongoing to determine how the drug impacts overall survival.

In late January, Health Canada approved Afinitor, a once-daily oral cancer treatment for patients with metastatic renal cell carcinoma, after failure of initial treatment with VEGF-receptor targeted therapies Sutent® (sunitinib) or Nexavar® (sorafenib).

Also in late January, Novartis announced that Japan's health authorities had approved Afinitor in tablet form for treating patients with non-resectable, metastatic renal cell carcinoma. Japan is now the Swiss-based company's second largest pharmaceutical market after the European market.

The FDA approved the use of Genentech's Avastin in combination with interferon alpha (IFN-alpha) for the treatment of metastatic renal cell carcinoma. FDA approval hinged on Phase III trial data showing that progression-free survival was nearly twice as long (10.2 months) in previously untreated patients who received Avastin in addition to IFN-alpha compared with patients receiving IFN-alpha alone (5.4 months), according to Genentech. The company is a wholly owned member of the Roche Group and is headquartered in South San Francisco, Calif. ●

Journal View

Pretransplant Hemodialysis Doesn't Affect Graft Function

In patients awaiting kidney transplant, performing hemodialysis immediately before transplantation does not adversely affect early graft function, concludes a randomized trial reported in *Transplantation*.

The study included 220 recipient candidates awaiting deceased-donor kidney transplantation. Those with serum potassium levels of 5.0 mEq/L or less were randomly assigned to receive dialysis or no dialysis before transplantation. Patients with serum potassium of greater than 5.0 mEq/L were assigned to undergo dialysis with heparin or citrate anticoagulation.

Estimated glomerular filtration rate (eGFR) at 5 days was not significantly different for patients receiving dialysis or no dialysis: 12 versus 13 mL/min/1.73 m². Rates of delayed graft function were 22 percent and 27 percent, respectively. Rates of cellular rejection, C4d-positive dysfunction, or 1-year graft survival were similar as well.

There was also no difference in 5-day eGFR between patients receiving heparin versus citrate anticoagu-

lation. The two groups had comparable rates of delayed graft function, cellular rejection, and graft survival. Patients receiving citrate anticoagulation had a lower rate of C4d-positive rejection, as well as a higher eGFR at 1-year follow-up.

Previous reports have suggested that performing hemodialysis immediately before kidney transplantation may adversely affect early graft function, increasing the risk of delayed graft failure. It has also been suggested that the anti-inflammatory effects of citrate anticoagulation might positively affect allograft performance.

The new report finds no effect of pretransplant hemodialysis on early allograft function. This argues against routine hemodialysis immediately before transplantation in normokalemic patients. There is no evidence that dialysis anticoagulation with citrate reduces reperfusion/ischemia injury [Kikić Z, et al. Effect of hemodialysis before transplant surgery on renal allograft function—a pair of randomized controlled trials. *Transpl* 2009; 88:1377–1385]. ●

New Insights Shed Light on Decisions for Treating CKD

Other patients' experiences, the timing of information, and a strong preference for the status quo are among the key factors affecting treatment choices for chronic kidney disease (CKD), according to a report in the *British Medical Journal*.

The researchers performed a systematic review of 18 qualitative studies of decision making regarding the choice of dialysis method, transplantation, or palliative care for CKD. The studies used methods such as focus groups and interviews to elicit the views of 375 patients and 87 carers.

Thematic analysis identified four major themes. The theme of "confronting mortality" included dealing with the possibility of death, concerns about being a burden to loved ones, and the feeling of "living in limbo" because of prognostic uncertainty. "Lack of choice" was another key theme, with patients or carers feeling that some alternatives were not available to them or that they lacked desired information on treatment options. Resource constraints were another important factor.

Under the theme of "gaining knowledge of options," patients were greatly influenced by the experiences of other

patients, whether the outcomes were favorable or otherwise. Many patients felt they did not receive needed information in a timely fashion. The fourth theme of "weighing alternatives" included the wish to maintain present lifestyle and family members' input. However, once a decision was made—and particularly after vascular access was created—patients were reluctant to change treatments.

Few previous studies have looked at the factors affecting preferences for CKD treatment from the viewpoint of patients. The authors discuss the implications of their findings for the care of CKD, including the use of peers to help in orientation for newly diagnosed patients; measures to ensure timely information about treatment options when stage 4 disease develops; and the development of formal care pathways for preemptive transplantation, home dialysis, and palliative management [Morton RL, et al. The views of patients and carers in treatment decision-making for chronic kidney disease: systematic review and thematic synthesis of qualitative studies. *Brit Med J* 2009; 340: c112]. ●

Lead in Blood Linked to Kidney Function in Teens

Higher blood lead levels are associated with lower estimated glomerular filtration rates (eGFR) in a nationwide sample of U.S. adolescents, reports a study in *Archives of Internal Medicine*.

The analysis included data on 769 adolescents, age 12 to 20, from the Third National Health and Nutrition Examination Survey, 1988–94. The relationship between whole blood lead level and eGFR—estimated using cystatin C- and creatinine-based equations—was assessed.

Median blood lead level was 1.5 µg/dL and median eGFR (estimated by cystatin C) was 112.9 mL/min/1.73 m². Linear regression analysis showed a consistent inverse relationship between blood lead levels and eGFR. For adolescents with lead levels in the highest quartile (3.0 µg/dL or greater), eGFR was 6.6 mL/min/1.73 m² lower than for those in the lowest quartile (less than 1.0 µg/dL). Doubling of lead level was associated with a 2.9 mL/min/1.73 m² decrease in eGFR. When eGFR was calculated using the creatinine-based equation, the associ-

ation with lead level was weaker and not statistically significant.

Long-term exposure to high lead levels is a known risk factor for kidney disease, but the renal effects of current low-level environmental exposure to lead are unknown. The current study addresses this question in a population of young patients free of kidney disease risk factors such as high blood pressure and diabetes.

The results suggest that American teenagers with higher exposure to lead have lower levels of kidney function. This is so even at blood lead concentrations under the Centers for Disease Control and Prevention's 10 µg/dL "level of concern." The authors call for further study to assess the contribution of lead exposure to chronic kidney disease, particularly in high-risk racial/ethnic and socioeconomic groups [Fadrowski JJ, et al. Blood lead level and kidney function in US adolescents: the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2010; 170:75–82]. ●

Acetaminophen May Protect Kidneys after Muscle Injury

Acetaminophen reduces oxidant injury and resulting kidney damage in rats with rhabdomyolysis-induced renal injury, according to a report in *Proceedings of the National Academy of Sciences*.

The study builds on previous research into the mechanism of rhabdomyolysis, which showed that myoglobin deposits induce oxidative damage to the kidney. Previous studies using a rat rhabdomyolysis model found that the oxidative damage results from heme redox cycling between ferric and ferrous states, generating radical species that induce lipid peroxidation.

In a new series of experiments, the researchers found that acetaminophen inhibits hemoprotein-induced lipid peroxidation by reducing ferrous myoglobin to ferric myoglobin. Through this mechanism, acetaminophen quenches the myoglobin protein radical while preventing formation of heme-to-protein cross-links.

In rats with induced rhabdomyolysis, therapeutic levels of acetaminophen inhibited lipid peroxidation and sharply reduced the extent of kidney damage and decline in renal function. The protective effect was observed whether acetaminophen was given before or after muscle injury.

Crush injuries and other types of muscle damage can lead to rhabdomyolysis, and thus to renal failure. Based on these experimental findings, acetaminophen might provide a new approach to preventing kidney damage after skeletal muscle injury. It could also have applications in other conditions involving blood cell lysis, such as sickle cell disease, malaria, and myocardial ischemia/reperfusion injury. A clinical trial in patients with subarachnoid hemorrhage is underway [Boutaud O, et al: Acetaminophen inhibits hemoprotein-catalyzed lipid peroxidation and attenuates rhabdomyolysis-induced renal failure. *Proc Natl Acad Sci USA*. 2010; doi: 10.1073/pnas.0910174107]. ●

Book Review

The Immortal Life of Henrietta Lacks

The last time I submitted an application to our Internal Review Board, I complained a lot about the process. The questions seemed redundant at times, and so many of them dealt with loss of privacy. Sure, I had taken the required training for working with “human subjects,” but I was not proposing anything harmful like injecting cancer cells or leaving a disease untreated.

After reading *The Immortal Life of Henrietta Lacks* by Rebecca Skloot, I better understand the need for such rigorous procedures. The author, an award-winning science journalist, spent a decade researching the book. Henrietta Lacks gave her cells and her name (*He* for Henrietta and *La* for Lacks) to medical science without her knowledge or consent. Skloot devotes chapters to the advances HeLa cells made possible, as the first immortal human cell

line, as well as the problems their aggressive growth caused for science. The history of human subject protection is also reviewed, from Nuremburg through the present trials regarding who may profit from patients’ tissue once it is removed from their bodies.

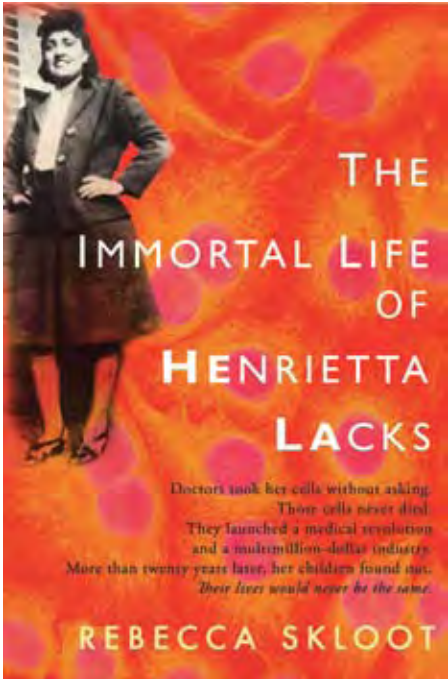
The most compelling, and time-consuming, research involves the Lacks family. Henrietta becomes more than a poor African American woman who died of aggressive cervical cancer; she emerges as a vibrant, beautiful person who loved to laugh and dance, cared generously for family and friends, and always kept her fingernails and toenails neatly polished in bright red.

The time spent gaining the trust of her widower, children, and other relatives drives home the rest of the book. While they are ultimately proud of what Henrietta’s cells accomplished, they are left with a mistrust

of doctors and medical research. Henrietta was never asked to donate her cells, nor was anyone in 1950. The Lacks family had no idea that any of this happened until the mid-1970s. Even subsequent genetic tests of the family were not clearly explained to the family members, who were lucky if they graduated from high school. Poverty and racism are major issues in their lives, and their story brings life to these concerns in a way statistics and studies cannot.

The Immortal Life of Henrietta Lacks tells a tale we, in biomedical science, have needed to hear for a long time. The book is available through most commercial retailers and at <http://rebeccaskloot.com>.

Reviewed by Pascale Lane, editor in chief, ASN Kidney News



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Index to Advertisers

Amgen	Back Cover
Genzyme	2-3
Yale-New Haven Hospital	6



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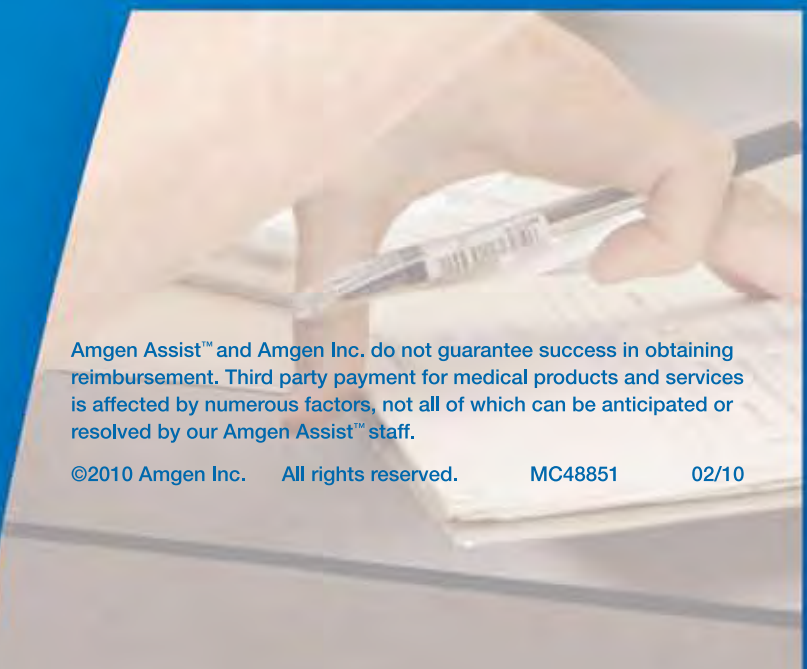
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