

## It Takes a Spark to Light a Fire: Kindling Interest in Nephrology Careers

Mark Rosenberg

Division of Renal Diseases and Hypertension, University of Minnesota Medical School, Minneapolis, Minnesota

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Recruiting the future nephrology workforce is a major responsibility and key priority for our specialty. There has been increasing concern regarding an impending shortage of nephrologists despite continued growth in the number of nephrology training programs and fellows during the past decade (Figure 1). This expansion has occurred despite the Balanced Budget Act of 1997 cap on the number of Medicare-funded graduate medical education positions.<sup>1</sup> Much of this increase has been composed of international medical graduates, with the percentage of these fellows increasing from 38.1% in 2002 to 65.8% in 2012. There has been a parallel increase in the number of practicing nephrologists in the United States. Between 2000 and 2010, the number of nephrologists has increased by 43.1%, making nephrology the fourth-fastest-growing specialty, exceeded only by combined internal medicine-pediatrics, geriatric medicine, and emergency medicine.<sup>2</sup>

The reason for concern about the future workforce is the declining interest in nephrology, as reflected in results from the National Resident Matching Program Specialties Matching Service (“the match”). In the December 2013 match for fellows starting July 1, 2014, 306 of 403 positions filled (76%), 81 of the 145 programs filled (56%), and the number of applicants per position was 0.8.<sup>3</sup> Of all matched positions, only 29.4% were with graduates from United States allopathic medical schools, the lowest of all specialties of medicine (gastroenterology was the highest at 66%). The specialty closest to nephrology was rheumatology at 35%. For the 2014 pediatric nephrology match, 18 of 42 programs filled (43%), 33 of 61 positions filled (54%), and the number of applicants per position was 0.6. Reasons for the declining

interest in nephrology have been discussed in many excellent reviews.<sup>4–7</sup> These reasons include dissatisfaction with early nephrology experiences in medical school, limited clinical exposure to the breadth of patients with nephrologic disease, the increased educational role of hospitalists at the expense of nephrologists, lack of new therapeutics, the perception that the job market is soft, lifestyle issues, negative role modeling, complexity of the specialty, the Medicare ESRD program, and changes in nephrology reimbursement.

This declining interest in nephrology careers coincides with the growing recognition of the public health challenges of CKD. More than 20 million Americans are living with kidney disease, with a disproportionate burden on minority populations.<sup>8</sup> CKD is the eighth leading cause of death in the United States; it accounts for 7% of Medicare expenditures but less than 1% of the Medicare patient population.<sup>9</sup> This burden has led to recommendations to screen high-risk populations.<sup>10</sup> The value of screening has come under scrutiny following issuance of the American College of Physicians’ guidelines on screening, monitoring, and treatment of CKD stages 1–3. These guidelines recommend “against screening for chronic kidney disease in asymptomatic adults without risk factors for chronic kidney disease.”<sup>11</sup> However, there is consensus in the nephrology community regarding the value of screening given the burden of kidney disease (especially in underserved populations); the fact that CKD is frequently clinically silent, especially at early stages; and the general lack of awareness of CKD in the population.<sup>10,12</sup> Screening is recommended for those with diabetes, hypertension, family history of CKD, history of AKI, cardiovascular disease, structural urinary tract disease, and multisystem diseases with potential kidney involvement.<sup>12</sup>

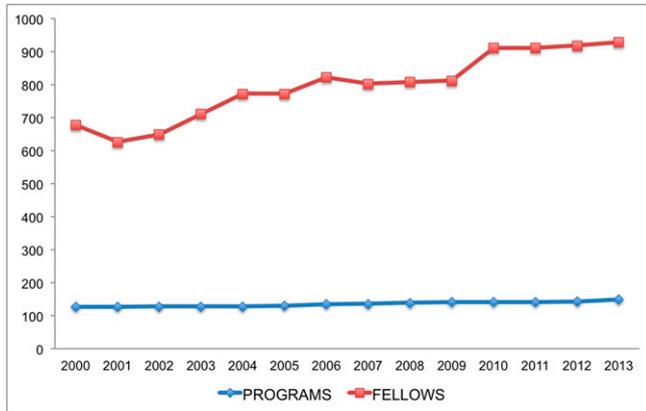
In this issue of *JASN*, Hsiao and colleagues present a pioneering model for addressing both of these critical nephrology issues: increasing interest in nephrology careers and screening for CKD.<sup>13</sup> The Kidney Disease Screening and Awareness Program (KDSAP) is a student-governed program created at Harvard College in 2008. Targeting primarily college students, KDSAP has enrolled 200 students ranging from high school to graduate school. Students work in community clinics screening for CKD in high-risk underserved populations. KDSAP incorporates the important components of physician mentoring, cultural competence, and direct interactions with patients. KDSAP also presents opportunities for students to participate in kidney research.

Outcomes of KDSAP were evaluated in a survey of participating college students ( $n=56$ ). The program was successful in raising awareness about CKD and nephrology careers and had a “strongly positive” impact on students in multiple domains, including attitudes toward working with underserved communities, participation in public health projects, interest in nephrology, knowledge in nephrology, interest in

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**Correspondence:** Dr. Mark Rosenberg, Division of Renal Diseases and Hypertension, University of Minnesota Medical School, B665 Mayo Memorial Building, 420 Delaware Street SE, MMC 293, Minneapolis, MN 55455. Email: [rosen001@umn.edu](mailto:rosen001@umn.edu)

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**Figure 1.** Increased numbers of nephrology fellows and programs. Trends in adult nephrology fellowship training in the United States, 2000–2013. The total number of programs and fellows are displayed.

medical research, and interest in a medical career. The career paths of 51 KDSAP alumni were tracked: 26 KDSAP students enrolled in medical school and 10 in other health disciplines or health research. So far, 3 of the KDSAP alumni plan to enter nephrology fellowships and 13 students have engaged in kidney-related research. The program has fostered many academic products, including grants, meeting presentations, and publications. The article did not discuss the effect of KDSAP on detecting clinically silent CKD or raising public awareness of CKD.

KDSAP represents a positive approach to increasing interest in nephrology careers. Although the article did not evaluate the reasons students chose to participate in KDSAP, many likely had a predetermined interest in medicine. KDSAP provided them an opportunity to explore this interest further and to demonstrate a commitment to human service. Channeling this student commitment into pathways that benefit nephrology is astute. KDSAP introduced students to public health issues related to kidney disease and to the social determinants of health, undoubtedly benefiting both the students and the communities. The University of Toronto and the Rutgers Robert Wood Johnson Medical School have established KDSAP chapters, while the program has inspired other kidney disease awareness initiatives.

A survey of practicing nephrologists showed that the decision to choose nephrology as a career most often occurred during residency, although initial interest began before or during medical school in 44% of respondents.<sup>14</sup> Reasons for choosing nephrology included intellectual aspects of the specialty, early mentoring, and participation in nephrology electives. KDSAP targets students at an early and impressionable stage in their educational pathway, harnessing their enthusiasm for volunteerism and their commitment to the human condition. This early experience and engagement and mentoring by nephrology role models are likely key factors in KDSAP's initial positive outcomes.

Many opportunities exist to positively affect the workforce challenges of nephrology. The kidney community is beginning to pursue these opportunities at a local level, such as through

KDSAP, and a national level, such as by the American Society of Nephrology and other organizations.<sup>4</sup> There is enormous potential to leverage the skill and commitment of nephrologists to spark interest in nephrology careers among the talented students and residents entering our medical schools and training programs. As Hsiao and colleagues have demonstrated, there are even opportunities to engage students farther upstream along the educational continuum.<sup>13</sup> Recruiting, training, and mentoring our future workforce remains one of the most important responsibilities in nephrology and needs to be approached with creativity and innovation.

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See related article, “The Kidney Disease Screening and Awareness Program (KDSAP): A Novel Translatable Model for Increasing Interest in Nephrology Careers,” on pages 1909–1915.

## When Erythropoietin Meddles in Immune Affairs

Frank Martinez<sup>\*†</sup> and Nicolas Pallet<sup>†‡§||</sup>

<sup>\*</sup>Department of Intensive Care and Renal Transplantation, Necker Hospital, Paris’ Public Assistance Hospital, Paris, France; <sup>†</sup>Paris Descartes University and Sorbonne Paris City, Paris, France;

<sup>‡</sup>Department of Nephrology, and <sup>§</sup>Department of Biochemistry, Georges Pompidou European Hospital, Paris’ Public Assistance Hospital, France, Paris, France; and <sup>||</sup>Institute of Health and Medical Research U1147, University Centre of the Holy Fathers, Paris, France

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A century ago, two French investigators reported that when injected into normal animals, small amounts of plasma from anemic rabbits caused an increase in red blood cell production.<sup>1</sup> They referred to this activity as *hemopoietine*. Over time, erythropoietin (Epo) was identified as the erythropoietic factor, which was then purified, and the molecular cloning of the *Epo* gene led to high-level production of recombinant human erythropoietin (rhEpo) in sufficient purity and quantity for the development of therapy.<sup>2,3</sup> In 1987, clinical trials were conducted to test the safety and effectiveness of rhEpo for treating anemia in patients with kidney failure. The results were dramatic,<sup>4</sup> and since this time, millions of patients worldwide have benefited from Epo therapy.

In response to decreased systemic and local oxygen tension, Epo is produced by a subset of peritubular fibroblasts in the cortex close to the boundary with the kidney medulla as well as by interstitial cells and hepatocytes in the liver. The transcription of the gene encoding Epo is under the control of the transcription factor hypoxia-inducible factor-2 $\alpha$  and, during hypoxia, its hydroxylation by prolyl hydroxylase domain hydroxylases, ubiquitination, and degradation by the proteasome are reduced.

Epo is a heavily glycosylated cytokine, and its concentration in the blood is low in the absence of anemia; however, hypoxic stress can enhance the concentration of Epo by a factor of 1000.

Importantly, glycosylation is of paramount importance for controlling its naturally short (5–8 hours) half-life. Epo circulates in the plasma and binds to receptors abundantly expressed on erythroid progenitor cells, thereby promoting the viability, proliferation, and terminal differentiation of erythroid precursors and causing an increase in red blood cell mass. The oxygen-carrying capacity of the blood is thereby enhanced, increasing tissue oxygen tension and thus completing the feedback loop and suppressing further expression of Epo.

Epo signaling occurs through the activation of its membrane receptor, EpoR, which is expressed at high levels on the surface of erythroid progenitors as a homodimer. Upon binding to Epo, the receptor undergoes a conformational change that brings its intracellular domains into close apposition. As a result, Janus kinase 2 and several subsequent signal transduction pathways are activated, including the phosphatidylinositol-3 kinase/Akt axis, signal transducer and activator of transcription 5, and extracellular signal-related kinases, which are implicated in cell proliferation and survival.<sup>5</sup> This signaling subsequently leads to the activation of cell survival factors, such as the B-cell lymphoma 2 family members, resulting in protection against programmed cell death.

In addition to the hematopoietic properties of rhEpo, EpoR-mediated signaling activates antiapoptotic and proliferative pathways and confers clinically relevant tissue-protective effects to rhEpo in cases of nonhematologic experimental disorders, such as stroke, AKI and CKD, retinal degeneration, and ischemia-reperfusion injuries (e.g., cardiac, liver, kidney).<sup>6,7</sup> Unexpectedly, several clinical trials failed to confirm in clinical settings the encouraging preclinical findings, particularly in the prevention of acute ischemic injury.<sup>8–10</sup>

In contrast to erythroid precursor cells, the expression of EpoR on nonerythroid cells is low and is unlikely to be sufficient for EpoR activation to occur. In addition, the protective activity of Epo may be due to the presence of a low-affinity heterodimeric receptor made with another partner, perhaps CD131, the cytokine receptor common  $\beta$  subunit.<sup>11–13</sup> Consequently, the tissue-protective properties of rhEpo are reached at higher doses of rhEpo, which may promote an increase in cardiovascular and thromboembolic events.<sup>14,15</sup> Nonerythropoietic erythropoietin derivatives have been developed by chemically modifying or mutating Epo. As an example, carbamylated Epo and ARA290 lack erythropoietic activity but maintain the tissue-protective effect of Epo and protect the kidneys from ischemic injury.<sup>16,17</sup>

The nonhematopoietic functions of rhEpo constitute an exciting research avenue, and numerous questions remain to be answered, one of the most important being the discrepancies between the encouraging results of preclinical studies and the lack of efficacy observed in clinical trials. In this context, a new study from a team led by Peter Heeger addressed the intriguing question of the immunomodulatory properties of Epo.<sup>18</sup> On the basis of the observations that rhEpo protects against chronic allograft injury in a rat kidney transplant model

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**Correspondence:** Dr. Nicolas Pallet, Department of Biochemistry, Georges Pompidou European Hospital, 20 rue Leblanc, 75015 Paris, France. Email: npallet@yahoo.fr

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