

World Kidney Day 2011

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World Kidney Day (WKD), established by the International Society of Nephrology and the International Society of Kidney Foundations in 2006, is a global effort to “raise awareness of the importance of our kidneys to our overall health and to reduce the frequency and impact of kidney disease and its associated health problems worldwide.” In 2010, more than 60 countries participated by organizing health screening events, public lectures, press conferences, political activities, and other efforts.

Chronic kidney disease (CKD) affects more than 20 million Americans. The link between CKD and cardiovascular disease is well established, and the number of people with both kidney disease and cardiovascular disease continues to climb at an alarming rate. On March 10, 2011, WKD highlights this association with the theme “Protect Your Kidneys and Save Your Heart.”

CKD accelerates the progression of heart disease and increases the likelihood of major cardiovascular events and related

deaths. Cardiovascular disease now accounts for more than half of all deaths among people with kidney failure. As noted by American Society of Nephrology (ASN) Public Policy Board Chair Tom Hostetter, MD, “It is of vital importance that the advocacy efforts of researchers, physicians, and advocacy groups to combat kidney disease work in conjunction with efforts to decrease cardiovascular disease. You cannot significantly reduce the prevalence of kidney disease unless its connections to other disease processes are recognized and addressed.”

On WKD 2011, the ASN and other organizations will bring the growing public health threat posed by both kidney and cardiovascular diseases to the attention of the worldwide community. ASN leaders will meet with members of Congress to discuss with them the important link between kidney disease and cardiovascular disease. ASN will also convene meetings with leaders at the Department of Health and Human Services including the Centers for Medicare and Medicaid Services. As the Department of Health and Human Services implements the Patient Protection and Affordable Care Act, ASN will continue to urge thought leaders within the government to consider the critical link between kidney disease and cardiovascular disease in policy formulation. A reception on Capitol Hill hosted by a number of kidney-focused organizations, including the National Kidney Foundation, will underscore efforts to increase awareness of CKD and cardiovascular disease.

ASN leaders and staff will emphasize robust funding for kidney and cardiovascular diseases in their WKD efforts. It is essential that lawmakers understand how much research is needed to understand the epidemiologic and biologic factors contributing to the associations between kidney and cardiovascular diseases so that providers will have the tools they need to improve the health of millions of patients.

Although the National Institute of Diabetes and Digestive and Kidney Diseases is a leader in this field of research, ASN will advocate for increased funding from other National Institutes of Health entities that conduct research crucial to heart and kidney health, including the National Heart, Lung, and Blood Institute and the National Institute on Aging.

This year ASN will place particular emphasis on the profound disparities that exist in the diagnosis, evaluation, and treatment of these diseases. Minority populations are particularly at risk for both progressive CKD and certain forms of heart disease. Early renal impairment is more likely to progress toward ESRD in black and Hispanic patients than in white patients. Recent studies have shed light on some of the basic reasons for ethnic disparities in kidney disease, but much more research has still to be done to understand these disparities better and help create effective treatment therapies.

WKD is an opportunity for kidney professionals worldwide to call attention to the growing public health threats of kidney and heart diseases at the local level. Recognizing

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WKD by speaking to colleagues and community members about the relationship between kidney disease and heart disease could be the first step in preventing ESRD or a cardiovascular event and saving a life. More information about preventing, recognizing, and managing kidney disease is available on the WKD web site (www.worldkidneyday.org/) and from the National Institutes of Health's National Kidney Disease Education Program. ASN encourages you to join in leading the fight against kidney disease this March 10, 2011.

Constructing an Immune System for Glomerulonephritis Studies

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Th17 cells mediate various immune-mediated diseases and have recently been proposed to contribute also to GN. A paper in this issue of the *Journal of the American Society of Nephrology* provides further evidence for this notion and identifies the transcription factor ROR γ T as an important regulatory element.¹ Because this transcription factor is also active in several innate lymphocyte populations, the authors had to exclude alternative interpretations by generating an animal model in which only T cells were ROR γ T deficient. To this end, they constructed an immune system in mice by adoptive transfer of defined components. This approach is faster than cell-specific genetic targeting and may turn out useful also for studying other forms of nephritis.

Scientific theories contrary to established dogma usually take long to become textbook knowledge. This certainly applies to the notion that T cells directly cause renal injury.^{2,3} It required three decades to gather sufficient mechanistic evidence in murine models of GN. Many of these studies originated from the laboratories of Holdsworth, Tipping, and Kitching in Melbourne, Australia, who showed in elaborate studies that T helper (Th) cells drive intrarenal delayed-type hypersensitivity reactions and thereby promote certain rapid-progressive forms of glomerular disease, such as pauci-immune or crescentic GN.⁴ This concept is widely accepted today, and the attention of scientists has turned toward clarifying the underlying molecular mechanisms, such as identifying the T cell subtypes, the antigen-presenting cells, and

the molecular mediators involved.⁵ Detailed mechanistic information is essential not only for understanding immunopathophysiology, but also for designing novel therapeutic approaches.

The Th subset causing crescentic GN are the Th type 1 (Th1) cells, which produce mediators like IFN γ to stimulate macrophages that cause renal injury.⁴ Normally, this is important for anti-viral and anti-bacterial defense. By contrast, Th2 cells activate eosinophils that mediate anti-parasite immunity. However, if dysregulated or autoreactive, both Th cell types may cause disease, such as Th1 cell-dependent contact dermatitis or Th2 cell-dependent asthma. An important extension of the Th1/Th2 dichotomy was the discovery of Th17 cells as a third differentiation type of Th cell.^{6,7} Th17 cells have been implicated primarily in immune-mediated diseases, especially in multiple sclerosis and rheumatoid arthritis, whereas their anti-infectious role remains unclear. While this unresolved question continues to puzzle basic scientists, clinical immunologists have realized that a T cell subset mainly involved in disease offers therapeutic opportunities: selective inhibition of Th17 cells should not result in serious immunosuppressive side effects if Th1 and Th2 cells remain functional. However, developing such approaches requires exact mechanistic knowledge on Th cell subsets and their regulation in immune-mediated diseases.

From this perspective, the simultaneous discovery from Ulf Panzer's group in Hamburg, Germany, and Richard Kitching's group in Melbourne, Australia, that Th17 cells can mediate kidney disease^{8–10} represents a major step forward in nephroimmunology. These two groups have joined forces and present in this issue of the *JASN* further evidence for an involvement of these cells in nephritis¹: Oliver Steinmetz from Hamburg discovered during a postdoctoral sojourn to Melbourne that the transcription factor ROR γ T, which is important in Th17 cell differentiation,¹² regulates nephritogenic Th17 cell responses. These authors induced accelerated crescentic GN in mice deficient for ROR γ T and found that clinical symptoms and renal infiltration with immune cells were much attenuated. Systemic IgG titers and macrophage responses were unaffected in these mice, confirming that Th1-dependent immunity was preserved. Until here, the study might be considered straightforward or even simple. However, ROR γ T knockout mice feature several other alterations, so that an observed phenotypic difference cannot be automatically attributed to the lack of Th17 cells. Most importantly, these mice lack lymph nodes,¹² because lymphoid tissue-inducer-like (LTi) cells, which mediate fetal lymphoid tissue organogenesis, depend on this transcription factor and are therefore absent in ROR γ T knockout mice.¹³ Furthermore, LTi cells can produce IL-17, and so does another recently discovered ROR γ T-dependent population of natural killer (NK)-like cells that occur in the intestine.^{14,15} Therefore, it remained to be investigated that the attenuation of disease in ROR γ T knockout mice was caused by the absence of lymph nodes or of IL-17-producing LTi and/or NK cells.

To rule out these alternative explanations, Steinmetz *et al.*¹¹ took advantage of an elegant immune system construction kit approach,

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