

## Kidney in Cardiovascular Disease

## From the Chair

Frank (Chip) Brosius, MD, FAHA



Frank Brosius at ASN Reception

This fall has been a quite active time for the Kidney Council. Together with the American Society of Nephrology, we sponsored the Young Investigator Award recognizing Dr. Thomas Benzing of the University of Freiburg at this year's ASN meeting in November in San Diego. His work in disease-relevant genes and their role in signal transduction in hereditary kidney diseases and podocyte biology is paving a way for a better understanding of many of the most critical chronic kidney diseases.

The Council also sponsored a Scientific Advisory for the "Detection of Chronic Kidney Disease in Patients With or at Increased Risk of Cardiovascular Disease" which was published in *Circulation* and *Hypertension* in November. This important advisory was intended to provide cardiologists and other care givers with up-to-date information on how to detect chronic kidney disease in their patients in order to aggressively diagnose and treat cardiovascular disease in these high risk individuals. Our advisory was co-sponsored by the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group and was developed in collaboration with the National Kidney Foundation. As the next critical installment in this series, Dr. Sharon Moe has spearheaded a Scientific Statement on the "Prevention and Treatment of Cardiovascular Disease in Patients with

Chronic Kidney Disease," which is in the final stages of review and should be coming out in the next several months. Again, we have garnered co-sponsorship from 4 other AHA councils or working groups and the National Kidney Foundation is also collaborating with Dr. Moe and her colleagues on this statement. Two other statements, Cardiovascular Pharmacology in Patients with Kidney Disease; and Renal Considerations in ACE Inhibitor and Angiotensin Receptor Blocker Therapy, are in early stages of preparation but should be finalized by the end of 2007.

Dr. Eric Simon and myself, as the Kidney Council representatives, have worked with the leadership of the other major nephrology professional groups (American Society of Nephrology, Renal Physicians Association, National Kidney Foundation) to develop a consensus to emphasize appropriate care for patients with chronic kidney disease. Initial efforts will focus on multiorganizational support of programs for World Kidney Day on March 8, 2007. Remember the date!

Through the efforts of Drs. Arlene Chapman and Lee Hamm, **Dr. Richard Lifton** of Yale University School of Medicine presented the **Donald Seldin Lecture** at the American Heart Association's Scientific Sessions 2006 in November. In addition, Kidney Council Leadership Committee

member, **Dr. Chris Baylis**, presented the **Lewis K. Dahl Memorial Lecture**, so we were very well represented at that meeting. Dr. Moshe Levi has led our council's efforts to propose a number of co-sponsored symposia and GME courses for the 2007 American Society of Nephrology Meetings. While these have yet to be decided upon, we are hopeful that the AHA Kidney Council will be on the podium at ASN next year.

While there have been a number of other important initiatives of the Kidney Council, I will not bore you with further details. Let me close by exhorting each of you to participate in Kidney Council activities, to send us any thoughts or suggestions about our participation in any relevant efforts, and importantly to recruit your colleagues to join the Kidney Council at the full professional membership level. The future success of the Council's efforts to help guide attention to the scientific understanding and management of patients with chronic kidney disease and other kidney disorders depends on an active and growing membership. We need you!



ASN Reception

## American Society of Nephrology

The Council on the Kidney in Cardiovascular Disease was a "house divided" this year when the American Society of Nephrology and the American Heart Association met simultaneously in different locations.

The highlight of activities at the ASN in San Diego was the presentation of the **Young Investigator Award to Thomas Benzing, MD, FASN**. His research focuses on signal transduction and protein interactions in hereditary renal disorders. Particular interests include roles of cilia in renal cells and podocyte signaling.

Dr. Benzing is a Professor of Medicine at the University of Freiburg. He is also Co-director of the Center for Systems Biology and Vice Chair of the Renal Division. This award is the latest in a number of research tributes. We look forward to a summary of his address in a future newsletter.

# AHA Scientific Sessions Highlights

## Donald Seldin Lecture

### Molecular Genetics of Cardiovascular Risks: The Kidney as the Cause of Hypertension

Richard P. Lifton, MD, PhD

Departments of Genetics and Internal Medicine  
Howard Hughes Medical Institute  
Yale School of Medicine



L-R: Lee Hamm, Richard Lifton, and Donald Seldin

Hypertension affects 1 billion people world-wide and is a major contributor to death from MI, stroke, CHF and kidney failure. Its pathogenesis has been unknown owing to the complexity of blood pressure regulation and only a minority of patients is adequately treated. To identify key pathways involved in long-term determination of blood pressure we have investigated rare families from around the world in which hypertension or hypotension show evidence of transmission via effects of a single gene. Using molecular genetic analysis we have identified the specific genes and mutations that cause these disorders and have determined their biochemical mechanisms of action. These include mutations in 9 genes that cause hypertension and 8 that cause hypotension. These genes converge on a final common pathway that regulates renal salt homeostasis; mutations that cause increased renal salt reabsorption raise blood pressure, while those that reduce salt reabsorption lower blood pressure. Mutated genes include those encoding ion channels and transporters that mediate or regulate salt reabsorption, enzymes and receptors that regulate production of aldosterone and transduction of its signal, and a novel family of serine-threonine kinases that regulate diverse flux pathways to coordinate the balance between renal salt reabsorption and K<sup>+</sup> secretion. These studies demonstrate the key role of renal salt handling in determination of blood pressure and identify promising new targets for therapeutic intervention. Moreover, they underscore the importance of reduction of salt balance in the treatment of hypertension in the general population while revealing limitations of single agent diuretic therapies.

## Louis K. Dahl Memorial Lecture

### Nitric Oxide Deficiency in Renal Disease

Christine Baylis, PhD

University of Florida, College of Medicine



L-R: Robert Carey and Christine Baylis

Nitric oxide (NO) production is reduced in renal disease, in part due to decreased endothelial production. Evidence indicates that NO deficiency contributes to cardiovascular events and progression of kidney damage. Two possible causes of NO deficiency are substrate (L-arginine) limitation and increased levels of circulating endogenous inhibitors of nitric oxide synthase (particularly asymmetric dimethylarginine [ADMA]). Decreased L-arginine availability in chronic kidney disease (CKD) is due to perturbed renal biosynthesis of this amino acid. In addition, inhibition of transport of L-arginine into endothelial cells and shunting of L-arginine into other metabolic pathways (e.g. involving arginase) might also decrease availability. Elevated plasma and tissue levels of ADMA in CKD are functions of both reduced renal excretion and reduced catabolism by dimethylarginine dimethylamino-hydrolase (DDAH). The latter might be associated with loss-of-function polymorphisms of a DDAH gene and/or functional inhibition of the enzyme by oxidative stress in CKD and end-stage renal disease. An increase in ADMA has emerged as a major independent risk factor in end-stage renal disease (and probably CKD). Raising endogenous L-Arginine and /or lowering ADMA concentration is a major therapeutic goal to reduce endothelial dysfunction, cardiovascular risk and possibly progression in renal disease.