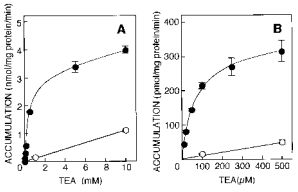
This Month's Highlights

Cell And Transport Physiology

cDNA Cloning, Functional Characterization, and Tissue Distribution of an Alternatively Spliced Variant of Organic Cation Transporter hOCT2 Predominantly Expressed in the Human Kidney

New Renal Organic Cation Transporter

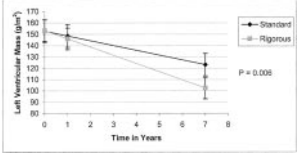


Endogenous organic cations and drugs, such as cimetidine and procainamide, are cleared from the blood by tubular secretion in the renal proximal tubule. Secretion is a two-step process that involves diffusion across the basolateral membrane by potential-sensitive transporters and secretion across the apical membrane by proton/cation exchange. Three members of the organic cation transporter gene family, OCT1, OCT2, and OCT3, have been identified in the kidney. In this issue, Urakami *et al.* describe a new renal organic cation transporter that is produced by alternative splicing of the OCT2 gene. Interestingly, the new protein, which is named hOCT2-A, is predicted to contain only 9 transmembrane segments compared with 12 in hOCT2, yet it still transports organic cations. Some differences in kinetic properties were identified. The subcellular localization of hOCT2-A remains to be determined, but the protein will likely represent a new transporter involved in clearing organic cations in the kidney.

Hormones, Growth Factors, Cell Signaling, Cell Biology and Structure

Cardiac and Renal Effects of Standard Versus Rigorous Blood Pressure Control in Autosomal-Dominant Polycystic Kidney Disease: Results of a Seven-Year Prospective Randomized Study

Better BP Control in ADPKD Reduced Risk of CVD but Not Progression of CKD

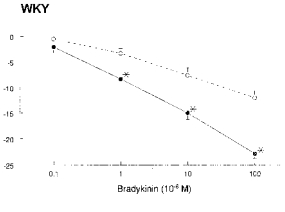


The rate of progression of renal insufficiency among individuals with autosomal dominant polycystic kidney disease (ADPKD) is highly variable. One risk factor associated with the rate of progression in ADPKD patients is elevated BP. This clinical trial by Schrier *et al.* tested the hypothesis that the degree of BP control over seven years of treatment would influence the progression of renal insufficiency. Patients were randomly assigned to either an intervention group with a BP goal of <120/80 mmHg or a standard care group with BP goal of 135–140/85–90 mmHg. Despite clinically important differences in BPe between the two groups, no difference was found in the rate of GFR decline in the two groups. In contrast to these findings, the authors also report on the influence of BP control on the progression of left ventricular hypertrophy. Regression of left ventricular hypertrophy was observed for both intervention and standard BP control groups, but the degree of decline in left ventricular mass index (LVMI) was substantially greater in the intervention group. What are the implications of these findings? First, they emphasize the need to identify suitable therapeutic targets to delay or prevent the progression of renal insufficiency among patients with ADPKD. Second, although no additional renoprotective benefit can be expected with reduction of BP below the level of 120/80 mmHg, unequivocal cardiac benefit was noted at this treatment goal. Left ventricular hypertrophy is an independent risk factor for morbidity and mortality among patients with chronic kidney disease, which suggests that strict reduction of BP to levels attained in this study may be clinically desirable. Subsequent trials among patients with ADPKD are, however, needed to determine if reductions in LVMI are indeed beneficial. The study of Schrier *et al.* clearly provides the foundation for such an effort. Further evidence is, however, necessary to support strong recommendations that stricter BP targets are a means of reducing cardiovascular morbidity and mortality among ADPKD patients.

Hemodynamics, Hypertension and Vascular Regulation

Impaired Regulation of Renal Oxygen Consumption in Spontaneously Hypertensive Rats

Nitric Oxide and Oxidants—New Mediators of Hypertension

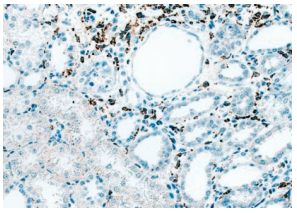


Although both oxidants and vasodilators are known to be abnormal in the spontaneously hypertensive rat, the role of these ubiquitous molecules in the pathogenesis of hypertension has not been defined. In this study, Adler *et al.* use the spontaneous hypertensive rat to document that nitric oxide availability in these animals is diminished as a result of apparent inactivation by oxidants, resulting in reduced vasodilatation and intrarenal hypoxia. With the advent of newer techniques to document tissue hypoxia and the recognition that genes such as hypoxia-inducible factor (HIF) are upregulated in hypoxic tissues associated with fibrosis, there has been a resurgence of interest in hypoxia as a mediator of renal events, including hypertension and progression. This topic is approached from a different perspective in the article by Rosenberger *et al.* in this issue, and it is the subject of "The Breathing Kidney," an editorial by Fine and Norman that nicely summarizes recent developments in this important area.

Immunology and Pathology

Peritubular Capillary Regression during the Progression of Experimental Obstructive Nephropathy

Is Progression VEGF-Dependent?

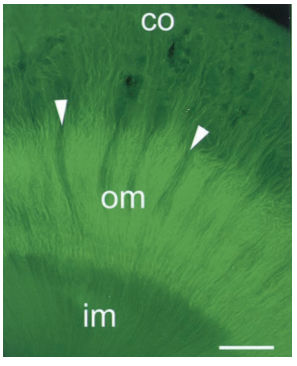


In keeping with the theme of several articles and an editorial in this month's issue, this article on peritubular capillary regression (presumably with consequent interstitial hypoxia) further expands our understanding of the process of progressive interstitial disease. Previously viewed as simply a consequence of impaired proximal glomerular capillary flow, we are now rapidly developing new insights into the physiology and cell biology of the peritubular capillary network as it relates to progression and fibrosis. In this article by Ohashi *et al.*, a non-glomerular insult (unilateral ureteral obstruction) was used to demonstrate that the subsequent development of interstitial fibrosis is preceded by a decrease in peritubular capillary lumina accompanied by diminished expression of VEGF and its receptor. Data from other studies suggest that VEGF itself may reverse this process and reduce progression. These observations, which involve molecules that can potentially be modified by therapeutic agents, are central to the quest to better understand the mechanisms of progressive renal disease and to design ways to block them.

Molecular Medicine, Genetics And Development

A Minimal Ksp-Cadherin Promoter Linked to a Green Fluorescent Protein Reporter Gene Exhibits Tissue-Specific Expression in the Developing Kidney and Genitourinary Tract

Specific Genes in Renal Tubules Can Be Selectively Manipulated

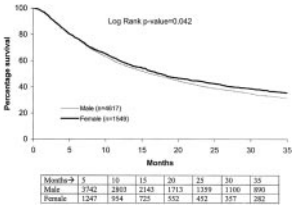


In this issue, Shao *et al.* describe two new reagents that will be of interest to researchers in the field of kidney development. The first is a fragment of a kidney-specific promoter from the Ksp-cadherin gene. Transgenic mice carrying the promoter linked to a GFP reporter gene produced green glowing renal tubules (see cover). The green fluorescence should facilitate identification of tubule cells during development and isolation by flow cytometry. Moreover, the same promoter fragment could be used to direct tissue-specific expression of any gene of interest in the developing kidney and genitourinary tract. One example of this type of experiment is shown in a companion article in which transgenic mice carrying the promoter linked to the Cre recombinase gene were produced. Expression of Cre recombinase was restricted to epithelial cells in the developing kidney and GU tract. This strain of mice should be useful for producing tissue-specific gene knockouts using the Cre/lox system.

Clinical Nephrology

Changing Trends in the Survival of Dialysis Patients with Human Immunodeficiency Virus in the United States

AIDS and ESRD—Better Results, but Not for Everyone Yet

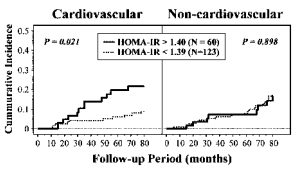


Months→	5	10	15	20	25	30	35
Male	3742	2803	2143	1713	1359	1100	890
Female	1247	954	725	552	452	357	282

Between 1995 and 1999, 1.1% of incident ESRD patients were diagnosed with AIDS nephropathy. This compares to a rate of 1.2% for lupus nephropathy and 2.4% for adult polycystic kidney disease. This report by Ahuja *et al.* examines the changes in survival among this important ESRD patient population. They report that survival for HIV patients has improved considerably during the last decade, from one- and two-year rates of 56% and 38% in 1990 to 68% and 54% in 1997/98. Furthermore, the one-year survival rate for HIV patients who started dialysis during 1999/2000 was 74%. These remarkable observations raise the question of which factors may have been associated with this improvement in survival. The authors speculate that availability and use of highly active antiretroviral therapy (HAART) might have contributed to better survival. It is important to note that the preferential survival generally noted among black ESRD patients was not found for the HIV patient population, and the authors raise the possibility that this might reflect differential access to HAART. If subsequent studies confirm these possibilities, it will then be important to ensure that HIV-infected ESRD patients have access to this life-extending therapy. Additional information about the appropriate management of this growing population of ESRD patients is clearly needed.

Insulin Resistance as an Independent Predictor of Cardiovascular Mortality in Patients with End-Stage Renal Disease

Insulin Resistance Is Bad in ESRD, but Is Obesity Good?

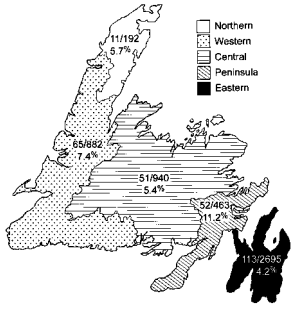


The insulin resistance syndrome (IRS) includes impaired glucose metabolism, insulin resistance, hypertriglyceridemia, low HDL cholesterol, and high BP. It is a risk factor for cardiovascular disease in non-ESRD populations, and the report by Shinohara *et al.* demonstrates for the first time a similar association between IRS and risk of cardiovascular disease among nondiabetic ESRD patients. They report, after controlling for other risk factors, an association between a standard index of insulin resistance, the ratio of fasting glucose and insulin levels, and increased risk of death due to cardiovascular disease (HR = 4.6; 95% CI, 1.8 to 11.6) when comparing the low and high tertiles of IRS. Central adiposity and obesity are strong mediators of IRS among patients without renal failure. In contrast, increased body weight reduces risk of all-cause mortality in the ESRD population. On average, the patients in this report were not overweight, and increasing body weight reduced risk of all-cause and CVD mortality. The IRS demonstrated in ESRD patients may reflect special factors associated with ESRD and renal replacement therapy. Understanding these relationships may identify potentially modifiable CVD risk factors among ESRD patients.

Epidemiology and Outcomes

Familial Risk of Preeclampsia in Newfoundland: A Population-Based Study

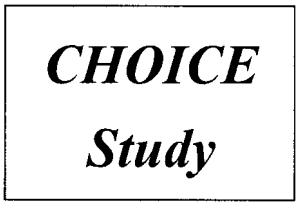
Preeclampsia Has a Genetic Basis



Preeclampsia complicates 5% of pregnancies and is one of the most common causes of maternal and perinatal morbidity and mortality. Preeclampsia usually occurs after the 20th week of pregnancy and may be due to placental dysfunction that causes systemic and placental vasospasm and thrombosis. Risk factors for preeclampsia include older maternal age, primiparity, multiple gestations, pregestational hypertension and diabetes mellitus, and preexisting renal disease. A family history is also a risk factor for preeclampsia. The study by Dawson *et al.* examines the aggregation of risk of preeclampsia among mothers and sisters in Newfoundland, a population characterized by a high degree of genetic isolation and kinship. They found striking aggregation of preeclampsia within families and important geographic variations in risk within the province. Severe preeclampsia characterized by high-grade proteinuria and the HELLP syndrome was furthermore associated with higher risk among sisters of probands. These findings suggest that clinicians should include a careful family history in their assessment of women at high risk for preeclampsia. As noted by the authors, identification of high-risk families living in isolated communities like those found in Newfoundland offer opportunities to search for candidate susceptibility genes and to explore gene-environment interactions.

Traditional Cardiovascular Disease Risk Factors in Dialysis Patients Compared with the General Population: The CHOICE Study

Cardiovascular Disease in ESRD Patients: More Complicated Than We Thought



In this issue, Longenecker *et al.* examine the association between traditional Framingham risk factors and increased risk of atherosclerotic cardiovascular disease. They compared risk factor prevalence among incident ESRD patients with that among participants from NHANES III. Adjusted for age, race, and gender, ESRD patients were more likely to have diabetes mellitus, hypertension, and LVH. In contrast, current smoking history and lipid-related ASCVD risk factors other than HDL levels were less prevalent among the ESRD patients. They used the Framingham risk logistic to estimate 1- and 5-year cardiovascular disease risk among ESRD patients and NHANES III participants. Although ESRD patients had 1.5 to 3 times the risk of cardiovascular disease compared with NHANES III participants, this increase is considerably less than previously reported. The discrepancy between observed and predicted risk again raises the question of the degree to which other nontraditional and potentially modifiable risk factors, such as homocysteine, ADMA, and inflammation, increase the risk of atherosclerotic cardiovascular disease among ESRD patients. Answers to this question await appropriately designed prospective studies and clinical trials.