

Important New Developments in Kidney Research in the last 10 Years

- 1. Identification of monogenetic disease genes:** Although these diseases constitute a small fraction of total kidney disease, the insights that have been obtained into the basic biology of renal development and tubule formation, maturation, and function are relevant for all of kidney disease. An example of this is the identification of nephrin and related molecules as components of the glomerular filter and their disruption as specific causes of congenital nephritic syndrome and focal and segmental glomerulosclerosis. We recommend classifying the identification of monogenetic disease genes as one of the key new developments in the last 10 years in conjunction with the American Society of Pediatric Nephrology (ASPN).
- 2. Finding that cilia likely play a primary role in PKD:** This finding has led to a better understanding of the basic defect in PKD, which was followed by the development of rational therapies that have resulted in the initiation of clinical trials. This recommendation is also being made in conjunction with ASPN.
- 3. Developing a number of good animal models:** Included are both naturally occurring and genetically designed models, and the extension of the concept of non-human models to zebrafish and *C. elegans*. These 'simpler' physiological systems have allowed elucidation of key molecules involved in normal renal physiology and mediating renal pathological processes.
- 4. Treatment of progressive kidney disease:** Several key advances have been made in this area, particularly in the treatment of diabetic kidney disease, including targeting of the renin angiotensin system as a key player, identifying the TGF β system as a major mediator of renal fibrosis, and demonstrating that in patients with advanced diabetic kidney disease who receive a pancreatic transplant, the diabetic nephropathy may be reversible.
- 5. Identification of the reactive oxygen species:** Understanding the physiological function of these oxidant molecules led to the characterization of their role in the genesis of hypertension, kidney disease (particularly in diabetic nephropathy and the progression of ESRD), and transplant rejection. These findings have identified a potential role for anti-oxidants in the treatment of the above conditions.
- 6. EPO and Ca⁺²-receptor agonists:** The concept that these molecules would be beneficial in the treatment of the anemia and hyperparathyroidism of ESRD came from renal-related basic science research, and lead to drugs that are now part of the main-stay of treating ESRD.

7. Initiation of nocturnal dialysis as a dialysis therapy: When the ESRD dialysis program was initiated, one of the 'promises' to the government was that with therapy patients with ESRD would be able to return to the work force. For numerous reasons, this has not happened to a large extent. One of the reasons is the large blocks of time required for dialysis therapy. With the initiation of nocturnal dialysis, patients with few co-morbidities are now dialyzed during the night, and thus, free and able to hold a daytime job.

8. Use of CVVHD and other treatment modalities in the treatment of acute renal failure: Slow continuous renal replacement therapies have made it possible to perform dialysis in patients that were previously too sick to tolerate the traditional more rapid hemodialysis procedure. Recently, the use of hybrid filters, comprised of an artificial membrane supporting cultured, confluent renal tubular cells, has shown promise in extending survival in patients with multi-organ failure. These treatment options were not readily available 10+ years ago, but are currently being employed in hospitals around the U.S. and in the treatment of our injured troops in such places as Iraq.

Related to the treatment of acute renal failure, but not limited to the treatment of acute renal failure, are the advances being made in the search for biomarkers for renal diseases using genomic approaches? While this is still an emerging field, the advent of global gene profiling is an important first step in defining subclasses of patients, and designing treatment to fit the patient.

9. Improvement of allograft survival: Renal basic science is responsible for identifying the molecules that can improve kidney allograft survival, which has led to the development of the immunosuppressive drugs that are now the main-stay of post-kidney transplant therapy. Related to this is the use of 'extended' donors and the establishment of eligibility criteria for qualifying as an extended donor. Refinement of these criteria has resulted in decreasing the inflammatory response during the harvesting procedure, and thus, improvement of allograft function post-transplant.

10. Finding that VEGF plays a major role in the development of eclampsia.

11. Initiation of longitudinal renal cohort studies: Examples of these are the CKD and CRIC studies, focusing on defining the natural history of chronic renal failure in children and adults, respectively. In particular, attention is now being focused on the cardiovascular and neurocognitive aspects of the physiology in uremia, in addition to the long-standing areas of concern, e.g. bone metabolism, endocrine function and immunity. This idea is being recommended in conjunction with ASPN.

12. Last, but NOT least, is the recognition that pre- and perinatal events contribute to adult diseases and that childhood obesity leads to early onset of diabetes and the metabolic syndrome: While we realize that there is plenty of clinical data supporting the above statements, not much success yet in dealing with the problem, but funding now becoming available, we feel that the recognition of these 'preventable' situations,

is in itself a major new development. Without this first step, programs designed to decrease or eliminate these preventable diseases would not be forthcoming. Again, this idea is being recommended in conjunction with ASPN.