

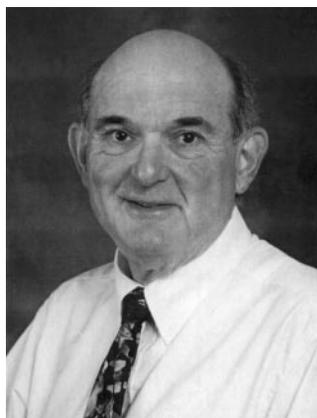
Acute Renal Failure: Directions for the Next Decade

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In their landmark paper published in 1941, Bywaters and Beall described the causative association between crush injury and an abrupt decline in renal function (acute renal failure). Subsequently, acute renal failure (ARF) has been documented in more diverse clinical settings and currently represents one of the most common entities that nephrologists are asked to diagnose and treat. The availability of dialysis reduced the mortality rate for patients with ARF from about 90% to 50%. However, despite advances in renal replacement therapy and nutritional support for patients with ARF, there has been little improvement in this unacceptably high mortality rate. This high mortality rate is undoubtedly related to several factors, including more elderly patients, multi-organ system failure, and the complex nature of contemporary medicine. In patients with a mild renal insult, usually contrast media–associated, data are conflicting on prevention or treatment. However, in patients with more substantial forms of ARF, clinical trials have been based on compelling animal data but have had no evident success. Consequently, there is currently no single or sequence of clinical interventions that will significantly improve renal function once a patient has acute tubular necrosis. The failure of these clinical trials has often been attributed to the fact that animal models of ARF do not unequivocally reproduce the clinical circumstances encountered by patients. Additionally, interventions that have been found to be effective in animal models may not be pertinent or relevant in the clinical circumstance in which the nephrologist encounters the patient with acute renal failure, often after a multifactorial insult has occurred. However, a careful scrutiny of previous clinical trials combined with knowledge of the appropriate design of clinical studies would suggest that our basic understanding of the clinical circumstances of ARF requires a very careful, scientifically based rediscovery and return to basic principles. The articles included in this installment of *Frontiers in Nephrology* have been selected to initiate such a discussion and stimulate basic and clinical studies in ARF.

The starting point for a renewed and rediscovered understanding of ARF must be based on an in-depth scientific



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understanding of the pathogenic mechanisms and the intrinsic processes that result in renal cell injury, including vascular and tubule components. To this end, Drs. Bonventre and Weinberg provide a contemporary update of our knowledge of the multiple factors that lead to ARF and the issues involved in the interpretation of experimental manipulations that may modify the course of disease.

In the clinical setting, the definition of ARF is highly variable and may vary greatly from one study to another and from one medical center to another. Consequently, the detection of early ARF does not commonly occur, and it is well known that the timing of interventions is critical to the potential success and outcome of a trial. It could be easily argued that in the current circumstances the disease process has progressed beyond a point at which therapeutic interventions are likely to be effective. This problem could be addressed, partially, by the identification of biomarkers that could reliably and sensitively predict the development of a significant renal insult. Such markers would aid not only in the early detection of ARF, but they would also serve to substantiate the diagnosis and provide an assessment of the severity of injury. Drs. Molitoris and Dagher provide an elegant overview of two-photo admission microscopy, which can be used to quantify cellular damage and irreversible cell injury. Drs. Herget-Rosenthal and Ruehm describe state-of-art magnetic res-

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onance imaging techniques that can interrogate and explore circulatory and regional perfusion abnormalities. In addition, Drs. Jo and Star describe the development of new imaging techniques that would allow the examination and detection of tubule injuries early in the clinical sequence of events. Finally, the article by Dr. Agarwal on the use of rapid HPLC techniques to measure GFR on multiple occasions provides new insight into ways in which early and even possibly subtle changes in GFR could be documented.

Another problem of significant proportions that limits the current feasibility of clinical trials is the heterogeneity of the clinical circumstances in which patients develop an ARF. In clinical trials, heterogeneity of the patient population can often be addressed by the stratification of patients based on the presentation of disease, underlying biologic factors and risk factors known to predict the severity of disease or ultimate outcome. Unfortunately, despite the common occurrence of ARF, appropriate biologic markers, prognostic indicators and rigorous criteria for the evaluation of the severity of the insult do not currently exist. To begin to address these issues, Drs. Mehta and Chertow, on behalf of the Program to Improve Care in Acute Renal Disease (PICARD), propose a new classification using a multidimensional diagnosis of ARF to capture the full context and complexity of the clinical circumstances. This provocative approach has the potential to provide new insight concerning the natural history of ARF, vulnerability of specific groups of patients, and prognostic factors that relate to the outcome of patients with ARF as well as enhance the design of future clinical studies and therapeutic interventions in ARF.

Finally, advances in reducing the current unacceptably high mortality rate for patients with ARF and the successful implementation of new therapeutic interventions will require a dedicated group of physicians who are committed to developing and implementing studies in the clinical setting. Undoubtedly, this effort

will need to include our colleagues who have the primary responsibility for this patient population and must include experienced clinical investigators who will devote the time and effort required to carry out these intensive and critical investigations. This effort would be greatly aided by the establishment of a clinical trials network devoted to studies in patients with ARF. An appropriately designed research consortium could provide the infrastructure support needed to sustain multiple clinical studies including longitudinal observation and cohort studies as well as therapeutic interventions. Moreover, the effective storage of data and biologic samples from enrolled patients with rigorously documented findings would assure newly discovered putative biomarkers or early indicators of renal injury could be rapidly tested, validated, and implemented. Moreover, pilot programs carried out by a clinical trials consortium would allow the rapid screening of new dynamic classifications of ARF and therapeutic interventions in appropriate subgroups of scientifically defined patients while expediting our progress toward understanding and treating this devastating disorder. The articles assembled in this installment of *Frontiers in Nephrology* should set us on the path to rediscovering the basic information needed to allow progress and even more importantly make the transition from the bench to the bedside an effective and rewarding experience for the treatment of ARF. To sustain the momentum of basic investigation in ARF and to stimulate clinical studies in this critically important aspect of nephrology, the American Society of Nephrology has formed an Acute Renal Failure Advisory Group (please access ASN web site for more information).

Our need for rediscovery to make progress with therapeutic interventions in ARF is described, best not by a scientist, but by the poet T.S. Elliot:

The end of all our explorations will be to come back to where we began and discover the place for the first time.