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Diabetic Nephropathy: Introduction

Diabetes mellitus has afflicted humankind for time immemorial, with its earliest medical documentation recorded over 3,000 years ago. However, it is only in the past century that the treatment and course of diabetes mellitus has undergone a sea change. With the introduction of insulin therapy in 1921, diabetic disease was transformed from an imminently lethal disease to a chronic disease. Before the advent of insulin therapy, diabetic nephropathy was essentially an unknown entity, but as World War II loomed on the horizon, so did the beginnings of the equally devastating epidemic of diabetic end-stage kidney disease, which we now face. The major etiology of diabetes has also seen a dramatic shift from type 1 diabetes, due to β-cell destruction, to type-2 diabetes, associated with an insulin-resistance syndrome. Irrespective of the etiology of diabetic hyperglycemia, both diseases are associated with a high incidence of end-stage renal disease. As emphasized by reviews in this issue, diabetic nephropathy is the single major cause of the emerging epidemic of end-stage renal disease in the United States and is expected to incur yearly costs of 18 to 30 billion dollars over the next decade. The identification and implementation of new approaches to mitigate both the human and monetary costs of this disease are imperative.

In a susceptible patient, hyperglycemia appears to initiate nephropathy through the generation of reactive oxygen species (ROS) and formation of advanced glycation end products (AGEs) as reviewed by Drs. Tan et al. Both ROS and AGEs contribute to glomerular cell injury and the development of microalbuminuria, which may signify systemic alterations in endothelial function not only in systemic capillary beds but also in large vessels. Drs. Zent and Pozzi review how the endothelium may provide a novel target for therapy of diabetic nephropathy. Additional preclinical research into the mechanisms contributing to diabetic nephropathy has pointed to an important role for the transforming growth factor (TGF) β pathway as well as other autocrine systems such as vascular endothelial growth factor and connective tissue growth factor. Dr. Zhu's review of the TGFβ pathway exemplifies a pathway yet to be tapped for clinical therapy. New understanding of the complexities of the renin angiotensin system may also provide additional opportunities for slowing the onset of kidney failure as overviewed by Drs. Gurley and Coffman.

Angiotensin-converting enzyme inhibition and/or angiotensin type 1 receptor antagonism has become a mainstay of clinical treatment of diabetic nephropathy as overviewed by Dr. Lewis. Treatment of hypertension in the diabetic patient has proven to be a key to slowing the pace of diabetic kidney failure. In those patients showing microalbuminuria, the risk of progression to cardiovascular death and overt nephropathy is pronounced and clinical approaches to preventing albuminuria are reviewed by Dr. DeZeeuw. The diversity of the histopathologic picture of diabetic nephropathy, as reviewed by Drs. Fioretto and Mauer, hints at diversity in the underlying factors contributing to diabetic nephropathy.

Importantly, only the minority of diabetic patients (10%-40%) are prone to nephropathy, and there is growing evidence that genetic predisposition to nephropathy plays a key role in the risk of diabetes mellitus contributing to renal failure. Thus, although the severity of impaired glucose control appears to enhance the risk of nephropathy, it may do so only in a susceptible genetic context. Three articles in this issue review new approaches to identify the genetic causes that predispose to diabetic nephropathy in both human beings and mice. It is hoped that by focusing on this important clinical problem, this issue will stimulate and facilitate further thought and progress that will allow us to once more alter the destiny of those with diabetes mellitus and remove renal failure from the list of its devastating complications.

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