Chapter 7

STRATEGIES FOR SLOWING PROGRESSION OF DIABETIC NEPHROPATHY

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THE SCOPE OF THE PROBLEM

Over the past 15 years renal disease attributed to diabetes mellitus has emerged as the leading cause of end-stage renal disease (ESRD) in the United States (Figure 1) (1). ESRD is also the leading cause of death in patients with insulin-dependent diabetes mellitus (IDDM) (2); ESRD registries and death certificates, however, may incorrectly presume that all "insulin-treated" diabetics have IDDM, hence deaths in patients with non-insulin dependent diabetes (NIDDM) may also contribute to this statistic. Indeed, most diabetics in ESRD programs have NIDDM, because of the much higher prevalence of NIDDM over IDDM (1). The health care costs per year incurred by diabetics with ESRD in the United States are 20% greater than non-diabetic ESRD patients (3), and the overall expense of medical care for diabetic ESRD patients exceeds $1 billion per year (4). Data from around the world confirm the dominant importance of diabetes to ESRD programs: The European Dialysis and Transplant Association (EDTA) reports that, in 1972, 0.5% of patients treated for ESRD were diabetics, while, in 1985, the figure had risen to 10.5% (5). In Australia and New Zealand, the annual increase in new diabetic ESRD patients has been less marked: 8% in 1985 versus 14% in 1990 (6); while in Japan, in 1990, diabetes accounted for 26.2% of 16,543 new patients begun on maintenance hemodialysis (7).

Evidence to be reviewed herein suggests that in many diabetic persons, it may be possible to prevent or retard the progression of clinical nephropathy. Knowledge of the pathogenesis of diabetic nephropathy permits the design of strategies to block its development. Major tasks include identification of the large minority of diabetics at risk for nephropathy, determining which prophylactic or therapeutic strategies to employ, and how early during the course of illness to intervene. A discussion of the clinical stages and
pathogenesis of nephropathy in IDDM and NIDDM will be followed by a discourse on the current state of knowledge regarding prevention and treatment of diabetic nephropathy.

Figure 1. Percent increase in the prevalence of end stage renal disease due to diabetes mellitus and other common renal diseases in the United States between 1985 and 1989.

NEPHROPATHY IN INSULIN-DEPENDENT DIABETES MELLITUS

Since symptoms herald the onset of IDDM within days or weeks, the profile of preclinical and clinical nephropathy in the disease has been well mapped. Five stages have been identified (8):

Stage 1: Glomerular hyperfiltration and renomegaly

Markedly increased inulin clearance in recently diagnosed patients with IDDM was first recognized in the 1930’s and 40’s (9, 10) and glomerular hyperfiltration was later confirmed by many workers (11-18). Glomerular filtration rates (GFRs) of up to 40% of normal values are seen (15), and, in some studies, the elevation in GFR is positively correlated with serum glucose concentration (19). The precise proportion of newly diagnosed diabetics who have hyperfiltration is not known but it appears to occur in the large majority of patients (20). Both functional and structural abnormalities probably