INTRODUCTION

Diabetic nephropathy is the most prevalent cause of end-stage renal disease (ESRD) in the United States. According to the 1994 United States Renal Data System (USRDS) report, diabetes accounted for 17,882 of 49,909 (35.8%) incident cases (Figure 1) and 48,274 of 186,261 (24.9%) prevalent cases of ESRD in the US in 1991 (1). The lower prevalence than incidence of diabetic ESRD patients in the US is a consequence of their higher mortality during uremia therapy. This point is illustrated in Figure 2 which plots relative survival for diabetic versus the entire population of hemodialysis and peritoneal dialysis patients.

Prior to the 1980s, diabetics were nearly uniformly excluded from ESRD programs because of their excessive mortality and morbidity attributed to blindness, coronary, cerebrovascular and peripheral artery vasculopathy. Illustrating this reality, Avram reported in 1966, in Brooklyn, that no diabetic on maintenance hemodialysis lived for longer than six months (2). A subsequent early series of 32 diabetics started on hemodialysis had only 8 survive as long as 3 months (3). Most pioneer reports of dialysis in diabetics (mainly insulin dependent patients) from the United States, recounted a two year survival ranging from 25–40% (4–6). In Europe, only 34% of diabetics survived after 3 years of dialysis (7).

Continuous growth in the number of diabetics treated for ESRD over the past 20 years is illustrated by their increased prevalence from 6,362 in 1981 (10% of the ESRD population) to 41,034 in 1990 (24.5% of the ESRD population). Registry statistics similarly document diabetes as the leading cause of treated renal failure in Canada (8). Throughout Europe, Japan, and Australia/New Zealand, diabetes ranks first among causes of ESRD. At least three interrelated reasons explain the dominance of diabetes as the preeminent cause of ESRD in the industrialized world: 1) Extended life expectancy results in an older population bearing a greater risk of non-insulin dependent diabetes (NIDDM). 2) After World War II, better access to food – associated with a greater prevalence of obesity – heightened expression of clinical diabetes in those carrying a genetic predisposition to NIDDM. 3) Realization that onset of uremia in diabetic patients need not end useful life promotes their increased acceptance into renal replacement programs. Establishment in the US of Medicare reimbursement for ESRD therapy
in 1972, stimulated expansion of long-term ESRD care including diabetics.

Medical-surgical team collaboration at the University of Minnesota initiated trials of dialytic therapy and kidney (and later, pancreas-kidney) transplants encouraging dialytic therapy of diabetics. By the early 1980s, improved survival of diabetics was achieved in the US and Europe in renal replacement programs. By the mid-1990s, mortality in hemodialyzed diabetics though greater than in non-diabetics (9), decreased to a one year death rate ranging between 11–30% (10–13). Diabetic cadaver donor renal transplant recipients may attain first year survival equivalent to that of non-diabetic age matched recipients (14).

**DIABETIC RENAL DISEASE**

Consensus thinking by nephrologists – inferred by the authors – holds that both renal disease and ESRD are more prevalent in patients with insulin-dependent diabetes mellitus (IDDM) than in NIDDM. Due to the greater than 10 to 1 higher prevalence of NIDDM over IDDM, however, the majority of diabetics in US hemodialysis programs have NIDDM. Before life extension for diabetic patients was the rule, there was a misperception that only 3–10% of patients with NIDDM developed ESRD (15), compared to 30–45% of those with IDDM (16). Contemporary reports (17, 18) indicate that the rate of renal disease is similar in NIDDM and IDDM. Humphrey et al.’s longitudinal study in Rochester, Minnesota (17) found that in 1,832 individuals with NIDDM and 136 with IDDM, followed for 30 years, there were equivalent rates of renal failure (133 per 100,000 person years in NIDDM, and 170 per 100,000 person years in IDDM). This finding was echoed in Heidelberg, Germany, in patient cohorts with IDDM and NIDDM followed for 20 years who developed nearly identical rates of renal impairment (serum creatinine level < 1.4 mg/dl) of 59% in IDDM, and 63% in NIDDM (18).

As a generalization from surveys of NIDDM in diverse ethnic groups (American Pima Indians (19), Blacks, and Hispanics (20)), NIDDM and ESRD are more prevalent than has been previously appreciated.

Mainly due to selective attack rates – by gender and race – in NIDDM, diabetic nephropathy afflicts 20% more women than men (21), and is three to seven times more prevalent in Blacks (22); Mexican Americans and Native Americans (23, 24) compared to other racial subgroups. Black women between 55–74 years of age have the highest attack rate of NIDDM explaining their disproportionate number of new cases of diabetic ESRD in the US.

In IDDM, nephropathy progresses through stages described by Mogensen (25); typically, in those destined to develop renal complications, ESRD occurs within 15–30 years of the initial diagnosis of diabetes, usually about three years after the onset of a nephrotic syndrome. Recent epidemiologic familial studies indicate that only a distinct subset – probably genetically predetermined – of those with IDDM are at risk for nephropathy (26). Less precision surrounds efforts to detail the natural history of NIDDM, mainly because of ambiguity in defining a specific date of onset which as extrapolated from retinal photographs is usually 7–9 years earlier than thought based on first recognition of hyperglycemia (27). Door to door surveys of random glucose levels from Alaska to Hawaii show that about one-half of those with NIDDM in the US are undiagnosed (28). The older the age at onset of NIDDM the more rapid the development of ESRD (29).

Renal failure has been most frequently reported (48–59%)