Figure 1-16
Diabetic nodules. Diabetic nodules are characterized by clear centers with cells along the periphery of the nodule, as shown here in a kidney biopsy specimen from a 44-year-old man with type II diabetes (hematoxylin and eosin stain).

Figure 1-17
Nodular size variability. Great variability in nodular size in diabetic nodular glomerulosclerosis is usual, as illustrated in this totally obliterated glomerulus obtained by biopsy from a 65-year-old woman with type II diabetes (periodic acid-Schiff stain).

Figure 1-18
A and B, Progression of nephropathy. Microalbuminuria, the excretion of minute quantities of albumin in the urine (more than 20 mg/day), is a marker of subsequent renal deterioration in diabetic nephropathy. Typically, proteinuria increases to the nephrotic range, leading to edema of the extremities and subsequent anasarca, which are often the presenting complaints in diabetic nephropathy.
FIGURE 1-19
Hyperfiltration. Almost immediately after the onset of hyperglycemia (signaling the onset of diabetes), glomerular filtration rate (GFR) increases to the limit of renal reserve function (hyperfiltration). Over subsequent years of hyperglycemia, a steady decline in glomerular filtration rate ensues in the 20% to 40% of diabetic individuals destined to manifest diabetic nephropathy. There is great variability in the rate of decline of GFR, from as rapid as 20 mL/min/year to 1 to 2 mL/min/year (usually seen in aging). Projection of future loss of GFR on the basis of the slope of the curve of prior decline in function contains errors as high as 37%. The importance of an inconstant and thus unpredictable decline in GFR lies in interpretation of interventional studies designed to protect kidney function. Careful attention to both selection of sufficient untreated controls and a “run-in” period is vital.

FIGURE 1-20
Renal failure cumulative incidence. Before careful studies of the natural history of type II diabetes were reported, it was not appreciated that diabetic nephropathy was a real endpoint risk. Older diabetic individuals with a “touch of sugar” are now known to be subject to the same microvascular and macrovascular complications that afflict individuals with type I disease. Population studies indicate that the rate of loss of glomerular filtration is superimposable in type I and type II diabetes. Humphrey and colleagues [21] documented the development of end-stage renal disease in diabetic subjects in Rochester, Minnesota. They showed that chronic renal failure was as likely to develop at a superimposable rate in both diabetic subsets. Numbers in parentheses indicate number of patients for each line. (From Humphrey and coworkers [21]; with permission.)

FIGURE 1-21
Creatinine clearance. Further evidence of the similarity in course of diabetic nephropathy in type I (A) and type II (B) diabetes was presented in Ritz and Stefansky’s study [22] of equivalent deterioration in creatinine clearance over the course of a decade in subjects with either type of diabetes in Heidelberg, Germany. (From Ritz and Stefansky [22]; with permission.)
Diabetic Nephropathy: Impact of Comorbidity

**FIGURE 1-22**
Diabetic nephropathy in types I and II. Whereas microalbuminuria and glomerular hyperfiltration are subtle pathophysiologic manifestations of early diabetic nephropathy, transformation to overt clinical diabetic nephropathy takes place over months to many years. In this figure, the curve for loss of glomerular filtration rate is plotted together with the curve for transition from microalbuminuria to gross proteinuria, affording a perspective of the course of diabetic nephropathy in both types of diabetes. While not all microalbuminuric individuals progress to proteinuria and azotemia, the majority are at risk for end-stage renal disease due to diabetic nephropathy. GFR—glomerular filtration rate.

**FIGURE 1-23**
Clinical recognition of diabetic nephropathy. The timing of renoprotective therapy in diabetes is a subject of current inquiry. Certainly, hypertension, poor metabolic regulation, and hyperlipidemia should be addressed in every diabetic individual at discovery. Discovery of microalbuminuria is by consensus reason to start treatment with an angiotensin-converting enzyme inhibitor in either type of diabetes, regardless of blood pressure elevation. As is true for other kidney disorders, however, nearly the entire course of renal injury in diabetes is clinically silent. Medical intervention during this “silent phase,” however (comprising blood pressure regulation, metabolic control, dietary protein restriction, and administration of angiotensin-converting enzyme inhibitors), is renoprotective, as judged by slowed loss of glomerular filtration.

**FIGURE 1-24**
Renoprotection with enzyme inhibitors. Streptozotocin-induced diabetic rats manifest slower progression to proteinuria and azotemia when treated with angiotensin-converting enzyme inhibitors than with other antihypertensive drugs. The consensus supports the view that angiotensin-converting enzyme inhibitors afford a greater level of renoprotection in diabetes than do other classes of antihypertensive drugs. Large long-term direct comparisons of antihypertensive drug regimens in type II diabetes are now in progress. In the study shown here by Lewis and colleagues [23], treatment with captopril delayed the doubling of serum creatinine concentration in proteinuric type I diabetic patients. Trials of different angiotensin-converting enzyme inhibitors in both types of diabetes confirm their effectiveness but not their unique renoprotective properties in humans. For patients who cannot tolerate angiotensin-converting enzyme inhibitors because of cough, hyperkalemia, azotemia, or other side effects, substitution of an angiotensin-converting enzyme receptor blocker (losartan) may be renoprotective, although clinical trials of its use in diabetes are uncompleted. (From Lewis and coworkers [23]; with permission.)