second messenger diacyl glycerol (DAG) is an important signal transduction pathway. Intracellular hyperglycemia stimulates the *de novo* synthesis of DAG from glycolytic intermediates, and hence causes excessive PKC activation. The downstream effects of PKC activation are numerous, including production of VEGF, TGF-β, and the procoagulant protein plasminogen activator inhibitor-1 (PAI-1) (Chapter 4) by the vascular endothelium.

It should be evident that some effects of AGEs and activated PKC are overlapping, and both likely contribute to diabetic microangiopathy.

Oxidative Stress and Disturbances in Polyol Pathways. Even in some tissues that do not require insulin for glucose transport (e.g., nerves, lenses, kidneys, blood vessels), persistent hyperglycemia in the extracellular milieu leads to an increase in intracellular glucose. This excess glucose is metabolized by the enzyme *aldose reductase* to sorbitol, a polyol, and eventually to fructose, in a reaction that uses NADPH (the reduced form of nicotinamide dinucleotide phosphate) as a cofactor. NADPH is also required by the enzyme glutathione reductase in a reaction that regenerates reduced glutathione (GSH). GSH is one of the important antioxidant mechanisms in the cell (Chapter 2), and any reduction in GSH increases cellular susceptibility to ROS ("oxidative stress"). In the face of sustained hyperglycemia, progressive depletion of intracellular NADPH by aldol reductase compromises GSH regeneration, increasing cellular susceptibility to oxidative stress. Sorbitol accumulation in the lens contributes to cataract formation.

Hexosamine Pathways and Generation of Fructose-6-Phosphate. Finally, it is postulated that hyperglycemia-induced flux through the hexosamine pathway increases intracellular levels of *fructose-6-phosphate*, which is a substrate for glycosylation of proteins, leading to generation of excess proteoglycans. These glycosylation changes are accompanied by abnormal expression of TGFβ or PAI-1, which further exacerbate the end-organ damage.

Morphology and Clinical Features of Chronic Complications of Diabetes

The important morphologic changes are related to the many late systemic complications of diabetes. As previously discussed, these changes are seen in both type 1 and type 2 diabetes (Fig. 24-34). We will first discuss the morphologic changes and then describe the clinical manifestations resulting from the altered morphology.

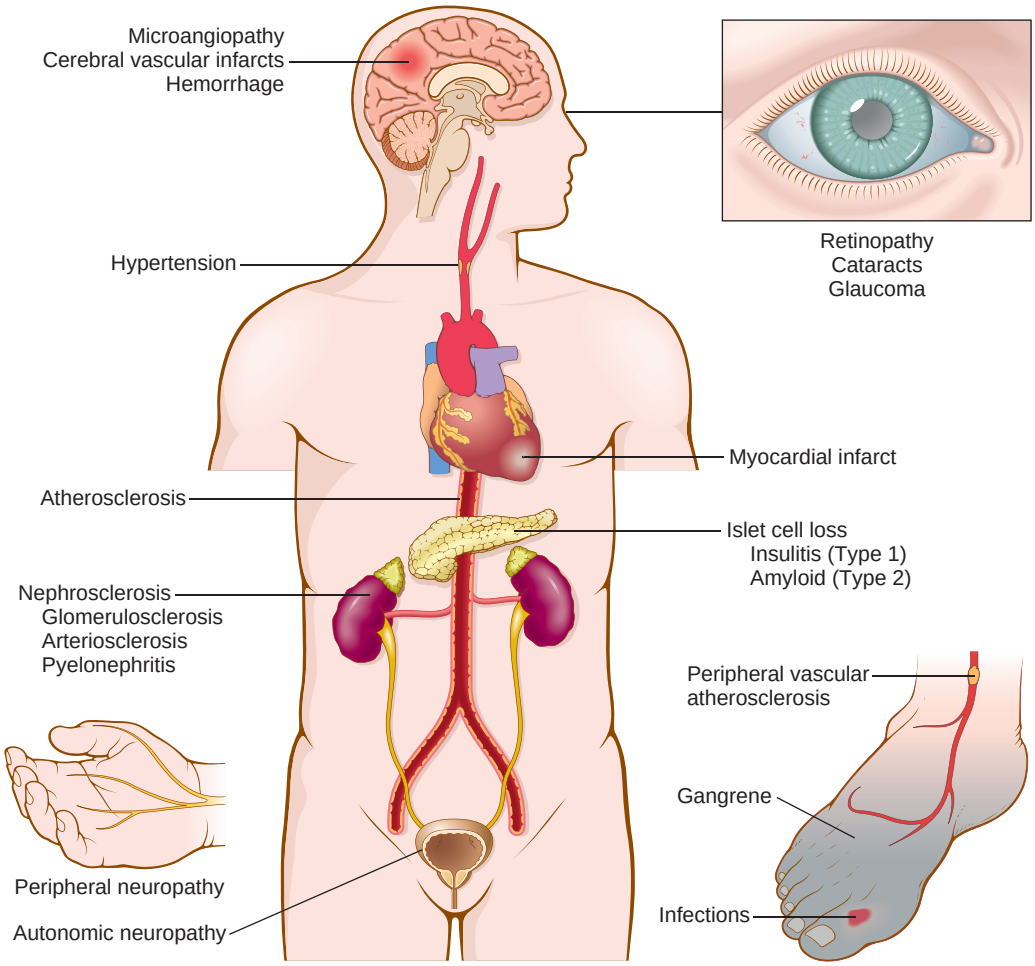

Figure 24-34 Long-term complications of diabetes.