administration of insulin, correction of metabolic acidosis, and treatment of the underlying precipitating factors such as infection.

In contrast to type 1 diabetes, the frequency of ketoacidosis is significantly lower in type 2 diabetes, presumably because of higher portal vein insulin levels in these patients, which prevents unrestricted hepatic fatty acid oxidation and keeps the formation of ketone bodies in check. Instead, **type 2 diabetics may develop a condition known as hyperosmolar hyperosmotic syndrome** (HHS) due to severe dehydration resulting from sustained osmotic diuresis (particularly in patients who do not drink enough water to compensate for urinary losses from chronic hyperglycemia). Typically, the patient is an older diabetic who is disabled by a stroke or an infection and is unable to maintain adequate water intake. Furthermore, the absence of ketoacidosis and its symptoms (nausea, vomiting, Kussmaul breathing) delays the seeking of medical attention until severe dehydration and impairment of mental status occur. The hyperglycemia is usually more severe than in diabetic ketoacidosis, in the range of 600 to 1200 mg/dL.

Ironically, the most common acute metabolic complication in either type of diabetes is *hypoglycemia*, usually as a result of having missed a meal, excessive physical exertion, an excess insulin administration, or during the phase of dose finding for antidiabetic agents. The signs and symptoms of hypoglycemia include dizziness, confusion, sweating, palpitations, and tachycardia; if hypoglycemia persists, loss of consciousness may occur. Reversal of hypoglycemia through oral or intravenous glucose intake prevents the onset of permanent neurological damage.

Chronic Complications of Diabetes

The morbidity associated with longstanding diabetes of either type is due to damage induced in large- and medium-sized muscular arteries (*diabetic macrovascular disease*) and in small vessels (*diabetic macrovascular disease*) by chronic hyperglycemia. Macrovascular disease causes accelerated atherosclerosis among diabetics, resulting in increased risk of myocardial infarction, stroke, and lower extremity ischemia. The effects of microvascular disease are most profound in the retina, kidneys, and peripheral nerves, resulting in *diabetic retinopathy, nephropathy, and neuropathy,* respectively (see later).

Pathogenesis of Chronic Complications. **Persistent hyperglycemia ("glucotoxicity") seems to be responsible for the long term complications of diabetes**. Much of the evidence supporting a role for glycemic control in ameliorating the long-term complications of diabetes has come from large randomized trials. The assessment of glycemic control in these trials has been based on the percentage of *glycated hemoglobin*, also known as Hb_{A1C}, which is formed by nonenzymatic covalent addition of glucose moieties to hemoglobin in red cells. Unlike blood glucose levels, Hb_{A1C} provides a measure of glycemic control over the lifespan of a red cell (120 days) and is affected little by day-to-day variations. *It is recommended that Hb_{A1C} be maintained below 7% in diabetic patients.* It is important to stress that hyperglycemia is not the only factor responsible for the long-term complications of diabetes, and that other underlying abnormalities, such as insulin resistance, and co-morbidities like obesity, also play an important role.

At least four distinct mechanisms have been implicated in the deleterious effects of persistent hyperglycemia on peripheral tissues, although the primacy of any one over the others is unclear. **In each of the proposed mechanisms, increased glucose flux through various intracellular metabolic pathways is thought to generate harmful precursors that contribute to end organ damage**.

Formation of Advanced Glycation End Products. *Advanced glycation end products* (AGEs) are formed as a result of nonenzymatic reactions between intracellular glucose-derived dicarbonyl precursors (glyoxal, methylglyoxal, and 3-deoxyglucosone) with the amino groups of both intracellular and extracellular proteins. The natural rate of AGE formation is greatly accelerated in the presence of hyperglycemia. AGEs bind to a specific receptor (RAGE) that is expressed on inflammatory cells (macrophages and T cells), endothelium, and vascular smooth muscle. The detrimental effects of the AGE-RAGE signaling axis within the vascular compartment include:

- Release of *cytokines and growth factors*, including *transforming growth factor β* (TGFβ), which leads to deposition of excess basement membrane material, and *vascular endothelial growth factor* (VEGF), implicated in diabetic retinopathy (see later)
- Generation of *reactive oxygen species* (ROS) in endothelial cells
- Increased *procoagulant activity* on endothelial cells and macrophages
- Enhanced *proliferation of vascular smooth muscle cells* and *synthesis of extracellular matrix*

Not surprisingly, endothelium specific overexpression of RAGE in diabetic mice accelerates large vessel injury and microangiopathy, while RAGE-null mice show attenuation of these features. Antagonists of RAGE have emerged as a therapeutic strategy in diabetes and are being tested in clinical trials.

In addition to receptor-mediated effects, AGEs can directly cross-link extracellular matrix proteins. Cross-linking of collagen type I molecules in large vessels decreases their elasticity, which may predispose these vessels to shear stress and endothelial injury (Chapter 11). Similarly, AGE-induced cross-linking of type IV collagen in basement membrane decreases endothelial cell adhesion and increases extravasation of fluid. Proteins cross-linked by AGEs are resistant to proteolytic digestion. Thus, cross-linking decreases protein removal while enhancing protein deposition. AGE-modified matrix components also trap nonglycated plasma or interstitial proteins. In large vessels, trapping of LDL, for example, retards its efflux from the vessel wall and enhances the deposition of cholesterol in the intima, thus accelerating atherogenesis (Chapter 11). In capillaries, including those of renal glomeruli, plasma proteins such as albumin bind to the glycated basement membrane, accounting in part for the basement membrane thickening that is characteristic of diabetic microangiopathy.

Activation of Protein Kinase C. Calcium-dependent activation of intracellular protein kinase C (PKC) and the