commonly, usually manifesting as a bilaterally symmetrical, distal, primarily sensory polyneuropathy (with or without motor involvement) in a *glove-and-stocking* distribution. Pain, numbness, hyperesthesias, and paresthesias progress to sensory loss. This condition, together with loss of proprioception, can lead to an abnormal gait with repeated trauma and potential for fractures of the tarsal bones, sometimes resulting in the development of Charcot joints. These changes lead to abnormal pressures in the feet that, together with the soft tissue atrophy related to peripheral arterial insufficiency, result in foot ulcers that may progress to osteomyelitis and gangrene. Detailed, regular neurologic examination of all patients is essential to elicit the early loss of light touch (using a size 5.07/10-g monofilament), reflexes, and vibratory sensation.

A second common form of diabetic neuropathy is autonomic neuropathy, which may develop in concert with or separate from distal polyneuropathy. Resulting symptoms can be debilitating, including postural hypotension leading to falls or syncope, gastroparesis, enteropathy with constipation or diarrhea, and bladder outflow obstruction with urinary retention. Diabetic autonomic neuropathy together with vascular disease is a contributor to erectile dysfunction in males. Gastrointestinal dysfunction with autonomic neuropathy can complicate efforts to achieve blood glucose control by causing variable absorption of food. A suspected diagnosis of autonomic neuropathy can be strengthened by demonstrating loss of normal variability in heart rate with deep respirations or the Valsalva maneuver.

Other, less common manifestations of diabetic neuropathy include thoracic and lumbar nerve root *polyradiculopathies*, individual peripheral and cranial nerve *mononeuropathies*, and asymmetrical neuropathies of multiple peripheral nerves (mononeuropathy multiplex). Diabetic amyotrophy causing muscle atrophy and weakness most often involving the anterior thigh muscles and pelvic girdle is an uncommon form of diabetic neuropathy that often resolves after several months.

The primary approach to all diabetic neuropathies consists of efforts to improve blood glucose control. Clinical trials have shown decreased development of distal polyneuropathy with improved glycemia in T1DM. It also is particularly important for patients with neuropathies to receive regular foot care, including daily self-inspection of the feet, regular physician examinations, and early interventions for developing callouses, infections, or other foot lesions. Painful polyneuropathies cause substantial morbidity and are difficult to treat. First-line drugs include amitriptyline, venlafaxine, duloxetine, and pregabalin. For patients who do not respond adequately to one drug, combination therapy with two drugs of different classes can be tested. Alternative treatments that may be effective in some patients include topical capsaicin cream, lidocaine patch, α-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation (TENS). *Gastroparesis* secondary to autonomic neuropathy may improve symptomatically with metoclopramide or domperidone (dopamine D2 antagonists), erythromycin (motilin agonist) for bacterial overgrowth, cisapride (cholinergic agonist), or mosapride (selective serotonin 5-HT4 receptor agonist). Diarrhea may respond to loperamide or diphenoxylate and atropine. Orthostatic hypotension can be treated by attention to mechanical factors such as elevation of the head of the bed, gradual rising from a lying to standing position, use of support stockings, and sometimes use of the mineralocorticoid fludrocortisone.

Macrovascular Complications

The risk of macrovascular disease including cardiovascular disease, transient ischemic attacks and strokes, and peripheral vascular disease is increased twofold to fourfold and accounts for 70% to 80% of deaths in patients with diabetes. This increased risk is believed to result from the altered metabolism in diabetes and also from the frequent occurrence of associated risk factors in diabetic patients, including hypertension and dyslipidemia. Screening for macrovascular disease and predisposing factors were discussed earlier. Approaches to decreasing the risk of macrovascular disease should include optimization of blood glucose control, weight loss for overweight and obese patients, smoking cessation, control of blood pressure, and treatment of dyslipidemia. (See Chapter 69 for details on the management of dyslipidemia.)

HYPOGLYCEMIA

Definition

Hypoglycemia most often occurs in patients with T1DM or T2DM under circumstances in which insulin or other antidiabetic therapies result in blood glucose levels' decreasing below the lower limit of normal (<50 to 60 mg/dL for most laboratories). This may be caused by overtreatment with glucose-lowering agents, failure to take in anticipated calories, or the combination of increased glucose utilization and increased insulin sensitivity induced by exercise.

Hypoglycemia much less commonly occurs as a primary disorder in patients who do not have drug-treated diabetes. Under these circumstances, clinically significant hypoglycemia can be difficult to identify based on blood glucose measurements alone, because the normal lower limit of blood glucose varies in individuals and is influenced by duration of fasting and gender. Plasma glucose levels during a fast in men decrease to approximately 55 mg/dL at 24 hours and 50 mg/dL at 48 and 72 hours, whereas in premenopausal women they may be as low as 35 mg/dL at 24 hours without symptoms of hypoglycemia. In evaluating glucose determinations, it is important to recognize that plasma levels are approximately 15% higher than glucose levels in whole blood. Clinically significant hypoglycemia can be most readily established if patients manifest *Whipple's triad*, which refers to the combination of: (1) symptoms suggestive of hypoglycemia, (2) documented low plasma glucose levels (<50 to 60 mg/dL), and (3) prompt resolution of symptoms when the low blood glucose is corrected.

Signs and Symptoms

Typical signs and symptoms of hypoglycemia are listed in Table 66-8. *Autonomic* symptoms result from sympathetic neural outflow that occurs as part of the counter-regulatory response to hypoglycemia. Although most patients appear to fully recover CNS function after a neuroglycopenic episode, there is a risk of irreversible brain damage or death with sustained or repeated episodes of severe neuroglycopenia.