times more often than men, and most develop the syndrome between the ages of 15 and 50. Presyncopal symptoms (lightheadedness, weakness, blurred vision) combined with symptoms of autonomic overactivity (palpitations, tremulousness, nausea) are common. Recurrent unexplained episodes of dysautonomia and fatigue also occur. The pathogenesis is unclear, but there is increasing evidence for sympathetic denervation distally in the legs with preserved cardiovascular function. Hypovolemia, venous pooling, impaired brainstem regulation, or increased sympathetic activity may play a role. Optimal treatment is uncertain, but expansion of fluid volume with water, salt, and fludrocortisone can be helpful as initial interventions. If this approach is inadequate, then midodrine, pyridostigmine, phenobarbital, beta blockers, or clonidine can be tried. Reconditioning and a sustained exercise program are important adjuncts to treatment.

INHERITED DISORDERS

There are five known hereditary sensory and autonomic neuropathies (HSAN I–V). The most important autonomic variants are HSAN I and HSAN III. HSAN I is dominantly inherited and often presents as a distal small-fiber neuropathy (burning feet syndrome) associated with sensory loss and foot ulcers. The most common responsible gene, on chromosome 9q, is *SPTLC1*. SPTLC is an important enzyme in the regulation of ceramide. Cells from HSAN I patients with the mutation produce higher-than-normal levels of glucosyl ceramide, perhaps triggering apoptosis. HSAN III (Riley-Day syndrome; familial dysautonomia) is an autosomal recessive disorder of Ashkenazi Jewish children and adults and is much less prevalent than HSAN I. Decreased tearing, hyperhidrosis, reduced sensitivity to pain, areflexia, absent fungiform papillae on the tongue, and labile BP may be present. Episodic abdominal crises and fever are common. Pathologic examination of nerves reveals a loss of sympathetic, parasympathetic, and sensory neurons. The defective gene, *IKBKAP*, may prevent normal transcription of important molecules in neural development.

PRIMARY HYPERHIDROSIS

This syndrome presents with excess sweating of the palms of the hands and soles of the feet beginning in childhood or early adulthood. The condition tends to improve with age. The disorder affects 0.6–1.0% of the population. The etiology is unclear, but there may be a genetic component because 25% of patients have a positive family history. The condition can be socially embarrassing (e.g., shaking hands) or even disabling (e.g., inability to write without soiling the paper). Topical antiperspirants are occasionally helpful. More useful are potent anticholinergic drugs such as glycopyrrolate (1–2 mg PO tid). T2 ganglionectomy or sympathectomy is successful in >90% of patients with palmar hyperhidrosis. The advent of endoscopic transaxillary T2 sympathectomy has lowered the complication rate of the procedure. The most common postoperative complication is compensatory hyperhidrosis, which improves spontaneously over months. Other potential complications include recurrent hyperhidrosis (16%), Horner's syndrome (<2%), gustatory sweating, wound infection, hemothorax, and intercostal neuralgia. Local injection of botulinum toxin has also been used to block cholinergic, postganglionic sympathetic fibers to sweat glands in patients with palmar hyperhidrosis. This approach is limited by the need for repetitive injections (the effect usually lasts 4 months before waning).

ACUTE SYMPATHETIC OVERACTIVITY SYNDROMES

The physician may be confronted occasionally with an acute state of sympathetic overactivity.

An *autonomic storm* is an acute state of sustained sympathetic surge that results in variable combinations of alterations in BP and heart rate, body temperature, respiration, and sweating. Causes of autonomic storm include brain and spinal cord injury, toxins and drugs, autonomic neuropathy, and chemodectomas (e.g., pheochromocytoma). Brain injury is the most common cause of autonomic storm and typically follows severe head trauma and postresuscitation encephalopathy anoxic-ischemic brain injury. Autonomic storm can also occur with other acute intracranial lesions such as hemorrhage, cerebral infarction, rapidly expanding tumors, subarachnoid hemorrhage, hydrocephalus, or (less commonly) an acute spinal cord lesion. The most consistent setting is that of an acute intracranial catastrophe of sufficient size and rapidity to produce a massive catecholaminergic surge. The surge can cause seizures, neurogenic pulmonary edema, and myocardial injury. Manifestations include fever, tachycardia, hypertension, tachypnea, hyperhidrosis, pupillary dilatation, and flushing. Lesions of the afferent limb of the baroreflex can result in milder recurrent autonomic storms; many of these follow neck irradiation.

Drugs and toxins may also be responsible, including sympathomimetics such as phenylpropanolamine, cocaine, amphetamines, and tricyclic antidepressants; tetanus; and, less often, botulinum toxin. Cocaine, including "crack," can cause a hypertensive state with CNS hyperstimulation. Tricyclic overdose, such as from amitriptyline, can cause flushing, hypertension, tachycardia, fever, mydriasis, anhidrosis, and a toxic psychosis. The hyperadrenergic state associated with Guillain-Barré syndrome can produce a moderate autonomic storm. Pheochromocytoma presents with a paroxysmal or sustained hyperadrenergic state, headache, hyperhidrosis, palpitations, anxiety, tremulousness, and hypertension. *Neuroleptic malignant syndrome* refers to a syndrome of muscle rigidity, hyperthermia, and hypertension in psychotic patients treated with phenothiazines (Chap. 449). Management of autonomic storm includes ruling out other causes of autonomic instability, including malignant hyperthermia, porphyria, and seizures. Sepsis and encephalitis need to be excluded with appropriate studies. An electroencephalogram (EEG) should be done to search for seizure activity; MRI of the brain and spine is often necessary. The patient should be managed in an intensive care unit. Management with morphine sulphate (10 mg every 4 h) and labetalol (100–200 mg twice daily) may be helpful. Supportive treatment may need to be maintained for several weeks. For chronic and milder autonomic storm, propranolol and/or clonidine can be effective.

MISCELLANEOUS

Other conditions associated with autonomic failure include infections, malignancy, poisoning (organophosphates), and aging. Disorders of the hypothalamus can affect autonomic function and produce abnormalities in temperature control, satiety, sexual function, and circadian rhythms (Chap. 403).

REFLEX SYMPATHETIC DYSTROPHY AND CAUSALGIA

The failure to identify a primary role of the ANS in the pathogenesis of these disorders has resulted in a change of nomenclature. The terms complex regional pain syndrome (CRPS) types I and II are now used in place of reflex sympathetic dystrophy (RSD) and causalgia.

CRPS type I is a regional pain syndrome that often develops after tissue injury and most commonly affects one limb. Examples of associated injury include minor shoulder or limb trauma, fractures, myocardial infarction, or stroke. *Allodynia* (the perception of a nonpainful stimulus as painful), *hyperpathia* (an exaggerated pain response to a painful stimulus), and spontaneous pain occur. The symptoms are unrelated to the severity of the initial trauma and are not confined to the distribution of a single peripheral nerve. CRPS type II is a regional pain syndrome that develops after injury to a specific peripheral nerve, often a major nerve trunk. Spontaneous pain initially develops within the territory of the affected nerve but eventually may spread outside the nerve distribution.

Pain (usually burning or electrical in quality) is the primary clinical feature of CRPS. Vasomotor dysfunction, sudomotor abnormalities, or focal edema may occur alone or in combination but must be present for diagnosis. Limb pain syndromes that do not meet these criteria are best classified as "limb pain—not otherwise specified." In CRPS, localized sweating (increased resting sweat output) and changes in blood flow may produce temperature differences between affected and unaffected limbs.

CRPS type I (RSD) has been classically divided into three clinical phases. Phase I consists of pain and swelling in the distal extremity occurring within weeks to 3 months after the precipitating event. The