Definition

While there are numerous historical clues in a variety of organ systems to suggest the presence or absence of autonomic dysfunction, bedside evaluation of the autonomic system is confined for the most part to careful study of the cardiovascular system. The most common and most prominent clinical feature of autonomic dysfunction is orthostatic hypotension. When severe, the fall in blood pressure with assumption of the upright posture is usually accompanied by dramatic symptoms of syncope or near syncope. Early in its course, however, the symptoms associated with orthostatic hypotension may be so vague as to be misleading. In these instances the postural hypotension associated with autonomic dysfunction would be overlooked unless the measurement of blood pressure in the supine and standing positions was recorded routinely in the course of the physical examination.

Normally, assumption of the upright posture is accompanied by a slight decrease in systolic pressure, usually 10 mm Hg or less, and a slight increase in diastolic blood pressure, usually less than 5 mm Hg. These changes in blood pressure may be accompanied by a physiologic increase in heart rate of 10 beats per minute or less. Under certain circumstances, normal blood pressure response to standing may include a decrease in the systolic blood pressure of up to 25 mm Hg and an increase in diastolic pressure of as much as 10 mm Hg. Although there is no uniform consensus, most authors define orthostatic hypotension as a sustained decrease in systolic pressure of 30 mm Hg or more and a decrease in diastolic pressure of 15 mm Hg or more upon standing. Orthostatic hypotension is not synonymous with autonomic dysfunction, but the association of symptomatic decrease in blood pressure of the above magnitude without an accompanying increase in heart rate must suggest a disordered autonomic response.

Technique

Bedside evaluation of the autonomic nervous system consists primarily of observations of: (1) cardiovascular reflexes, (2) pupillary changes, and (3) casual sweating patterns.

Cardiovascular Reflexes

The initial evaluation of normal autonomic control of the cardiovascular system is the postural response of the blood pressure and pulse rate. The patient should be supine for at least 2 minutes before blood pressure and pulse rate are recorded. Blood pressure should be recorded at 2-minute intervals upon standing for 8 to 10 minutes or until symptoms occur. Patients must be observed carefully during this exercise in order to prevent hypotension to the point of syncope. Assistance should be available to prevent injury to the patient from falling. Should syncope occur, the patient must immediately be placed in the head down, legs elevated position to restore cerebral perfusion.

Changes in heart rate can be recorded by a continuous rhythm strip on a conventional electrocardiogram obtained for 30 seconds prior to and 60 seconds after standing. In normal individuals, reflex acceleration of heart rate is maximal approximately 15 seconds after standing and slows to near-supine rate by approximately 30 seconds after standing. Failure of heart rate to increase with the development of symptomatic orthostatic hypotension is indicative of autonomic dysfunction.

The Valsalva maneuver is a commonly used method of assessing normal or disordered autonomic control of blood pressure and heart rate. The test requires the maintenance of forced expiration against resistance for at least 7 and, optimally, for 15 seconds. The physiologic response to the Valsalva maneuver has been divided into four phases. In the first phase, blood pressure increases slightly due to increased intrathoracic pressure. As forced expiration is continued, pulse pressure decreases. During the second phase, heart rate begins to increase. The third phase begins with release of the forced expiration and consists of a further drop in blood pressure due to a sudden drop in intrathoracic pressure, and the heart rate increase is sustained or may accelerate even more. The fourth phase is associated with increased cardiac output, "overshoot" hypertension, and finally a reflex bradycardia. In autonomic dysfunction, blood pressure declines progressively for as long as forced expiration can be maintained and heart rate does not increase. During the fourth phase, there is no blood pressure "overshoot" but only a gradual recovery of pre-Valsalva blood pressure, and no reflex bradycardia occurs.

The changes in blood pressure and pulse rate during the Valsalva maneuver occur over a matter of seconds and can be accurately recorded only with an intraarterial recording device. By repeating the maneuver several times after 3- to 5-minute rest intervals, however, it is usually possible to document the occurrence of the phase 4 blood pressure overshoot with a conventional sphygmomanometer. Similarly, a continuous electrocardiogram rhythm strip during several Valsalva maneuvers, interrupted by rest intervals, permits observable, measurable changes in heart rate that could not be appreciated by radial palpation or apical auscultation. Equally reliable results are obtainable with the patient in a sitting or supine position.

A subtle but important indication of autonomic dysfunction is the absence of respiration-associated sinus arrhythmia. A continuous conventional electrocardiogram rhythm strip is recorded while the patient is instructed to breathe slowly and deeply at a rate of 6 breaths per minute. Heart rate normally increases with inspiration and decreases with expiration, and at a respiratory rate of 6 per
minute the difference between fastest and slowest heart rate is usually more than 15 beats per minute. Differences of 10 beats per minute or less are observed in autonomic dysfunction.

Additional tests of cardiovascular response can be performed at the bedside to evaluate autonomic integrity. The induction of mental stress in the form of a mental arithmetic problem frequently produces a small (less than 10 mm Hg) rise in systolic blood pressure. Similarly, the immersion of an extremity (foot or hand) in ice water for 1 to 3 minutes results in an increase in systolic blood pressure in the non-immersed limb. The problem with both of these tests is that normal individuals may not respond with an increased systolic pressure, so absence of response does not necessarily imply autonomic dysfunction. Lastly, the integrity of the autonomic system can be assessed by means of a hand dynamometer, a device that measures the force of hand grip. The test requires the patient to maintain 30% of maximal hand grip strength for 3 to 4 minutes. The maneuver produces a rise in systolic blood pressure in normal individuals.

**Pupillary Changes**

A variety of pupillary abnormalities are observed in syndromes of autonomic dysfunction. They may be transient or permanent and may, therefore, be discovered only with repeated observation. Adie's pupil is larger than normal and responds poorly to light and slowly and incompletely to convergence. The pupillary abnormality results from interruption of parasympathetic innervation of the eye.

Horner's syndrome, consisting of a constricted pupil (miosis), drooping of the lid (ptosis), and lack of or diminished sweating (anhidrosis), is occasionally observed in autonomic dysfunction, as is the phenomenon of alternating anisocoria.

The instillation of various pharmacologic agents into the conjunctiva may help to determine the locus of autonomic abnormality in a patient with miotic pupils or abnormal pupillary responses to light. The normal pupil will dilate on installation of a 1% solution of hydroxyamphetamine or a 4% solution of cocaine. Neither agent will dilate the miotic pupil if the locus of autonomic dysfunction is preganglionic. If the pupil responds to hydroxyamphetamine, which stimulates the release of norepinephrine, but does not to cocaine, which inhibits norepinephrine reuptake, the defect in autonomic innervation of the pupil is preganglionic or central.

**Sweating Abnormalities**

While it is not possible to test systematically for disordered sweating at the bedside, casual observation of sweating patterns during the course of an examination may suggest autonomic abnormalities. Patients should be observed for total absence of sweating in an extremely warm environment, absence of sweating in isolated areas, or restriction of profuse sweating to the upper body while sweating in the lower body areas is absent. The casual observation of a patient suspected of autonomic dysfunction occasionally reveals the phenomenon of gustatory sweating, that is, profuse sweating associated with the ingestion of food. Such sweating abnormalities have been commonly associated with the autonomic neuropathy of diabetes mellitus.

**Basic Science**

Postural hypotension in autonomic dysfunction represents failure of autoregulation of peripheral vascular resistance that normally occurs upon standing. This problem is compounded by sympathetic denervation of the heart, which prevents a compensatory increase in heart rate. This interplay of perfusion pressure and heart rate is demonstrated by the physiology of the Valsalva maneuver in normal individuals. The declining mean arterial blood pressure during forced expiration is accompanied by an appropriate tachycardia during phases 2 and 3 of the maneuver. But in spite of diminishing venous return, blood pressure levels off due to intense peripheral vasoconstriction as a consequence of sympathetic outflow. The "overshoot" blood pressure observed during recovery, or stage 4, is a consequence of increased cardiac output associated with increased venous return pumped into a still vasoconstricted vascular bed. The overshoot hypertension results in reflex bradycardia and return of normal blood pressure, normal cardiac output, and reduced peripheral vascular resistance.

The compensatory vascular reflexes required for normal adaptation to restricted venous return associated with standing require the integrity of afferent, central, and efferent components of the autonomic reflex arc that may be disrupted at one or more loci in syndromes of autonomic dysfunction. Characterization of the nature of the lesion responsible for autonomic dysfunction is frequently helpful in narrowing the focus of etiologic possibilities. Diseases resulting in autonomic dysfunction are commonly categorized as preganglionic (presynaptic) or postganglionic (postsynaptic). Examples of the former include the central forms of autonomic dysfunction associated with movement disorders (Shy–Drager) or parkinsonian symptoms. In these syndromes, postganglionic neurons are intact, but the preganglionic neurons of the interomediolateral columns of the spinal cord undergo degeneration. The most common example of postganglionic autonomic dysfunction is the autonomic neuropathy associated with diabetes mellitus, which results from degeneration of peripheral autonomic fibers. Characteristically, the vasculature in syndromes of autonomic dysfunction associated with peripheral denervation is hyperresponsive to infused alpha-receptor stimulants. This feature is sometimes helpful in distinguishing preganglionic from postganglionic causes of autonomic dysfunction. Such tests are fraught with potentially serious complications and should be performed only by experienced individuals and under the most carefully monitored circumstances.

Preservation of a positive pressor response to ice water immersion of an extremity or to mental stress maneuvers implies an intact effenter autonomic pathway. Absence of a pressor response to these two tests, especially if associated with absent sweating, suggests an abnormality in the effenter limb of the reflex arc, but does not rule out abnormalities in other components of the autonomic system.

**Clinical Significance**

Autonomic insufficiency may result from any disease that affects the central or peripheral components of the autonomic nervous system. The diseases may involve primary (idiopathic) degeneration of autonomic postganglionic fibers without other neurologic abnormalities, as occurs in the syndrome of primary autonomic dysfunction. Alter-
natively, diseases may involve a central degenerative process in which orthostatic hypotension is associated with diffuse autonomic dysfunction and motor and cerebellar abnormalities, as described in the Shy–Drager syndrome. A related central degenerative process involving preganglionic neuronal degeneration and presenting with orthostatic hypotension and typical parkinsonian symptoms has been described.

More commonly, autonomic dysfunction occurs as a consequence of some other identifiable disease. The most frequently associated disease entity is diabetes mellitus and is usually accompanied by obvious peripheral polyneuropathy. Other nutritional or toxic/metabolic disorders that may result in autonomic dysfunction include porphyria, vitamin B₁₂ deficiency, Wernicke's encephalopathy, and alcoholism. Orthostatic hypotension due to autonomic dysfunction is a frequent presenting feature of the neuropathy of amyloidosis and may also occur in tabes dorsalis, usually in combination with other typical tabetic symptoms. The autonomic reflex arc may also be interrupted by a variety of central factors including tumors of the posterior fossa, cerebral vascular accidents, central hemorrhages, and syringomyelia. One must be cautious to distinguish poor postural adjustment of blood pressure in the elderly from autonomic dysfunction. The former generally occurs upon standing after prolonged recumbency and is accompanied by appropriate acceleration of heart rate. Orthostatic hypotension associated with episodes of hypertension must lead one to the consideration of pheochromocytoma.

The significance of autonomic dysfunction secondary to other diseases is related to the severity of orthostatic symptoms and its response to therapy and especially to the prognosis of the primary disease process. The primary forms of autonomic dysfunction, both peripheral and central, have a generally poor prognosis, especially those associated with movement disorders or parkinsonian symptoms. The mean age of onset of these primary syndromes is in the sixth decade, and survival 5 years after onset of neurologic symptoms is less than 50%.

References