Clinical Assessment of Autonomic Function

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A PROPERLY-FUNCTIONING autonomic nervous system permits man to adapt to most sudden changes in his environment. Abnormalities of the system may appear spontaneously or as a feature of other systemic or neurologic diseases. Drugs may interfere with autonomic function either as a desired effect, such as the action of some antihypertensive agents, or as a side effect, as with the phenothiazines, imipramine, and some antibiotics.

A proper assessment of the state of the autonomic nervous system is very important for determining what effects stressful procedures such as surgery will have on a patient, what drug regimen will be effective, and whether an existing course of treatment is fully effective. This paper reviews the structure and function of the autonomic nervous system and the means of judging the site and extent of abnormalities.

Structure and Function of the Autonomic Nervous System

The peripheral autonomic system comprises a two-neuron efferent pathway. Although not included in classic definitions of the autonomic nervous system, it is useful in the clinical setting to consider the somatic afferent pathway as an integral part of the system. The afferent fibers, coming from many of the visceral organs, the skin, and major vessels, enter the CNS and form reflex connections predominantly at the segmental level. The efferent sympathetic pathway is composed of nerve cells arising in the thoracic and lumbar segments of the spinal cord. The efferent neurons form a synaptic junction in prevertebral and trunk ganglia. The postsynaptic neurons pass to the effector organ where their terminal fibers, with few exceptions, liberate norepinephrine (fig. 1). The efferent parasympathetic pathway is composed of cells arising in the brain stem and in the sacral portion of the spinal cord. The cranial preganglionic fibers pass via the third, seventh, ninth, and tenth cranial nerves and the sacral fibers pass via the sacral nerves, with synapses in small ganglia in or adjacent to the effector organ. The postganglionic cells are short, and the terminal fibers liberate acetylcholine (fig. 2).

Usually the end-organ is innervated by both systems. Stimulation of both systems results in physiologic antagonism. Afferent impulses elicit constant efferent activity which usually requires only the participation of segmental reflex pathways, not the higher levels of the autonomic nervous system.

The central components of the autonomic nervous system include neural connections between afferent and efferent nerves as well as suprasegmental centers in the brain stem, hypothalamus, cerebellum, and perhaps the cerebral hemispheres.[1] The suprasegmental components are not essential to the function of lower reflexes, but appear to integrate and modify segmental reflexes.

Spatial and functional separation of the components of the autonomic nervous system as well as inherent biochemical differences between components make it possible for disease or drugs to produce isolated defects. The physician has an opportunity to use the patient's case history, physical findings, and results of physiologic and pharmacologic tests to localize defects in the autonomic nervous system. With such an approach, characteristic disease may be recognized, the extent of autonomic dysfunction assessed, and unusual responses to

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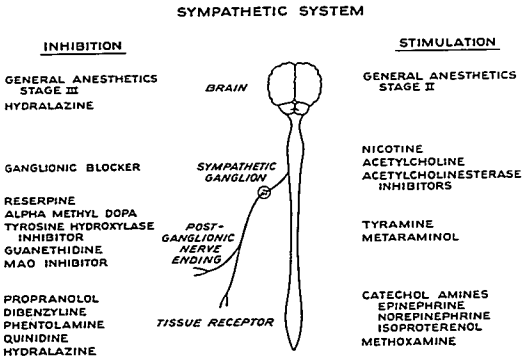

FIG. 1. Simplified schematic representation of anatomic levels at which a variety of drugs inhibit or stimulate sympathetic function. Some actions are more complex than figure would indicate, *i.e.*, cyclopropane, a general anesthetic, stimulates sympathetic activity during Stage III. Acetylcholine and acetylcholinesterase inhibitors may stimulate the sympathetic ganglion; then, if drug action persists, inhibit further activity.

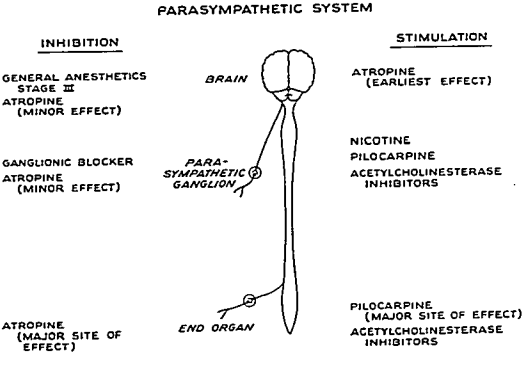

FIG. 2. Schematic representation of anatomic levels at which drugs inhibit or stimulate parasympathetic function.

drugs and anesthetics may be anticipated. This is particularly true of the patient taking antihypertensive drugs.

Assessment of Autonomic Nervous Function

SYMPATHETIC SYSTEM

Symptoms and signs of dysfunction. The most commonly recognized abnormality of the sympathetic system is orthostatic hypotension, marked by dizziness, fainting, and focal neurologic signs that resolve when the patient assumes a horizontal posture. More subtle evidence is a moderate fall in orthostatic mean blood pressure without the usual 10–20 beat/minute increase in heart rate. Failure of the pulse rate to increase when the patient stands and further failure to increase after exercise suggest dysfunction in the cardioaccelerator mechanism, which is controlled by the sympathetics.

Diminished sweating is a good indicator of sympathetic dysfunction. A too-youthful appearance, pallor, dry skin, muscle weakness, and fasciculations are also seen as part of the clinical syndrome of autonomic insufficiency.[2]

The pupillary responses provide an index of autonomic integrity. Small fixed pupils or pu-

TABLE 1. Disorders with Which Autonomic Insufficiency Occurs

Neurologic
Tabes dorsalis
Syringomyelia
Hematomyelia
Acute transection of spinal cord
Brain tumor in floor of fourth ventricle
Parkinsonism
Multiple sclerosis
Shy-Drager syndrome
Wernicke's disease
Familial dysautonomia
Systemic
Diabetes mellitus
Chronic renal disease
Malnutrition, with or without alcoholism
Combined system disease
Iatrogenic
Sympathectomy
Cordotomy
Drug induced

pils that do not dilate when the lower lateral aspect of the neck is sharply pinched (ciliospinal reflex) suggest impaired function.

Nocturnal polyuria is a frequent complaint. It is caused by a decrease in the glomerular filtration rate when the patient is erect, which becomes greater than normal when he is supine.[3] Weakness, hunger pangs, lethargy, yawning, and muscle fasciculations may be a sign of hypoglycemia due to impaired glucose mobilization.

A history of drug ingestion is of particular importance since many drugs interfere with the sympathetic system. Common offenders include the antihypertensive drugs (fig. 1). Other drugs that certainly influence the autonomic nervous system, but are not used for that purpose, include the phenothiazines, which have alpha-blocking activity; imipramine, which has anticholinergic and anti-adrenergic activity; amphetamines; and antibiotics such as isoniazid and furazolidone (monoamine oxidase inhibitors).

The symptoms of an underlying primary disease may dominate those of autonomic insufficiency. The recognition of any of the diseases listed in table 1 should direct attention to the need for further assessment of the autonomic nervous system.

Physiologic testing. Perhaps the most useful test for autonomic integrity is the Valsalva maneuver (fig. 3). The patient is instructed to exhale against a closed glottis or into a manometer for 20 to 30 seconds. This creates a positive intrathoracic pressure of about 40 mm. Hg, which markedly reduces venous return. In subjects with intact sympathetic pathways, there is a brief increase and then a precipitous fall in blood pressure and pulse pressure, accompanied by an increase in heart rate. When the systemic pressure falls, pressure receptors in the aorta and the carotid sinus initiate the increase in heart rate and peripheral vasoconstriction. After release of intrathoracic pressure, there is a bounding overshoot of systolic and diastolic blood and pulse pressures as venous return becomes supranormal and stroke volume suddenly increases. Parasympathetic influence then predominates and results in bradycardia. The normal response depends on an intact reflex arc, including baroreceptors, afferent pathways, vasomotor centers, sympa-

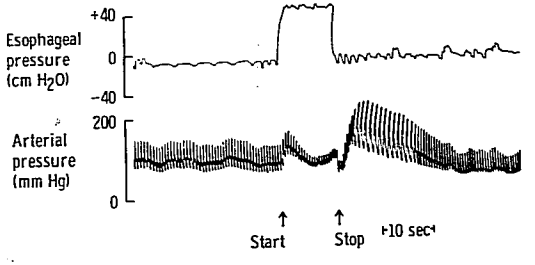

FIG. 3. Normal blood pressure and pulse response to the Valsalva maneuver in man. The esophageal pressure reflects positive intrathoracic pressure during straining. See text for discussion (courtesy of Dr. Malcolm B. McIlroy).

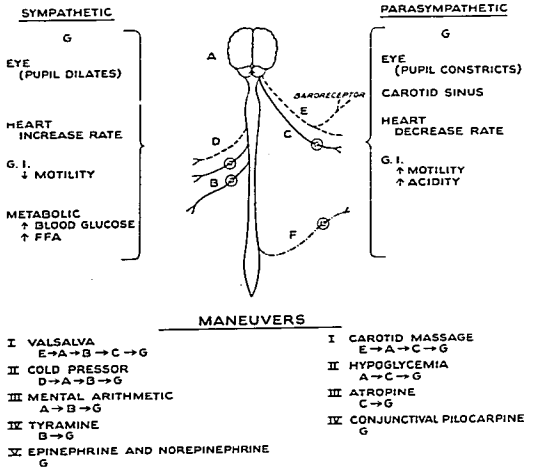

FIG. 4. Schematic representation of the autonomic nervous system that can be used to define where the defect lies. *A*, brain and spinal cord; *B*, efferent sympathetic pathway; *C*, efferent parasympathetic pathway via cranial nerves; *D*, afferent somatic pathway; *E*, afferent visceral pathway from baroreceptors; *F*, efferent parasympathetic pathway via sacral nerves; and *G*, end-organs and their response to sympathetic and parasympathetic influence. For detailed discussion see text.

thetic and parasympathetic outflow and responsive end-organs (arteriolar bed, venous capacitance bed, heart) (fig. 4). Autonomic dysfunction may be reflected by several abnormal response patterns. If impairment is due to disease of the sympathetics, the response is altered such that the heart rate fails to increase during the phase of positive intrathoracic pressure and overshoot of diastolic and systolic pressures is absent. (Blood pressure overshoot may also be absent in heart failure and hypovolemia.) Parasympathetic dysfunction may be manifest by failure of the heart rate to slow during the period of blood pressure overshoot.

The cold-pressor test may also be used to assess sympathetic function. When normal patients place their hands in ice water for 60 seconds, their blood pressure increases (16–20 mm. Hg systolic, 12–15 mm. Hg diastolic). If blood pressure does not increase, the reflex arc is probably incomplete. Such a breakdown can occur in the sensory nerves, spinothalamic tracts, suprapontine and infrathalamic relays, descending sympathetic pathways or peripheral sympathetic nerves, or at the end-organs (fig. 4). The combined use of the Valsalva maneuver and cold-pressor test helps to locate the lesion. If the response to the Valsalva maneuver is abnormal and the response to the cold-pressor test is normal, the lesion is probably in either the baroreceptor or the afferent baroreceptor nerve. Sharpey-Schafer found just such a defect in some diabetic and tabetic patients.[4, 5]

Manipulating the patient's blood volume is useful in assessing sympathetic function. In normal patients, inflation of cuffs on the thighs to within a few mm. Hg of diastolic pressures for ten minutes causes a fall in mean blood pressure no greater than 10 mm. Hg. During sympathetic autonomic impairment, such a bloodless "phlebotomy" is accompanied by an exaggerated and prolonged fall in blood pressure. Conversely, infusions of 3,000 ml. of 0.9 per cent sodium chloride in one hour will produce only minor changes in normal subjects, but a 20–35 mm. Hg increase in blood pressure in patients with sympathetic impairment. During such an infusion, normal subjects will produce an average of 6 ml. of urine per minute and 15 mEq. of sodium per hour, but patients with sympathetic impairment will excrete an average of 23 ml. per minute and 80 mEq. of sodium per hour.[3] Care must be taken not to use this test in patients with in-

cipient heart failure because of the risk of producing pulmonary edema.

In healthy people the stress of mental arithmetic usually will cause increases in blood pressure and pulse rate because it causes stimulation of efferent sympathetics but does not depend on the afferent limb (fig. 4). The results of this stimulation and the Valsalva maneuver give further information about the sympathetic reflex arc. An abnormal response to the Valsalva maneuver plus stable blood pressure and pulse rate during mental arithmetic suggest a lesion in the vasomotor center, efferent pathway, or end-organ.

Thus careful integration of the patient's history and physical findings during certain maneuvers can yield information about the integrity of the afferent, central, and segmental portions of the sympathetic system. Pharmacologic tests and biochemical determinations can give more information about the efferent side.

Pharmacologic tests. Several tests may be used to distinguish sympathetic denervation from end-organ insensitivity to catecholamines. Conjunctival instillation of 1–2 drops of 1:1,000 solution of epinephrine into a normally-innervated eye will produce minor changes in the size of the pupil. If the postganglionic sympathetic pathway is denervated, then denervation hypersensitivity occurs and the pupil will dilate widely. In normal subjects, infusion of norepinephrine (0.05 μg./kg./min.) will increase the systolic pressure less than 23 mm. Hg and the diastolic pressure less than 19 mm. Hg (average, 8–9 mm. Hg), but in patients with denervation hypersensitivity, such an infusion will produce a marked pressor response. When the response is less than expected, the end-organ may be insensitive, as is seen in amyloidosis. However, ingestion or administration of drugs that produce alpha blockade must be excluded. Such compounds include dibenzyline, phenothiazine, quinidine, and a variety of psychoactive agents. Before the patient undergoes surgery, it is particularly important to ascertain whether alpha blockade is present, because if it is, the patient will tend to be refractory to the usual doses of commonly-used pressor agents (levarterenol, metaraminol). In this setting, drugs such as angiotensin that do not act on the alpha receptors are more effective.

Exaggerated responses to a variety of vasoactive drugs occur during autonomic insufficiency. Sublingual nitroglycerin ordinarily produces a small decrease in blood pressure. With dysfunction of afferent pathways, the vasomotor center, sympathetic outflow, or end-organs, the blood pressure decreases more than 15 mm. Hg systolic and 5 mm. Hg diastolic.[6] Exaggerated hypotensive responses to tetraethylammonium chloride and oxytocin may be equally effective signs of defective sympathetic reflexes.[7]

The function of sweat glands other than those in the axilla depends on efferent sympathetic integrity from the hypothalamus to the skin. Normal subjects sweat when they are placed in a warm environment, such as under a leg cradle with a heat lamp so that rectal temperature rises 0.5–1° C. If this fails to produce sweating, the defect can be further defined by assessment of axon reflex sweating. When intradermal injections of 0.1 ml. of 1:10,000 acetylcholine (or 1:100,000 nicotine) result in sweating around the injection site, the local nerve supply to the sweat gland is intact. When acetylcholine has no effect, intradermal injection of 1:1,000 pilocarpine may produce a wheal and local sweating. Such a response is evidence that the sweat glands are intact and capable of responding to stimuli.

Recently, tests which are particularly helpful in evaluation of function and neurotransmitter stores of the postganglionic sympathetic nerve ending have been devised. These tests are most useful when the patient is taking anti-adrenergic agents (*e.g.*, reserpine, guanethidine, alpha-methyldopa, monoamine oxidase inhibitors) or adrenergic blocking agents (phentolamine, dibenzyline, propranolol). Such agents interfere with autonomic activity by interrupting the function in the postganglionic nerve or by blocking the reception of the neurotransmitter at the effector site.

Tyramine, a primary amine found frequently in naturally-fermented dairy and grape products, produces its primary pharmacologic effect by releasing amines stored in the sympathetic nerve endings. After injection or infusion of tyramine, neurotransmitter is released and characteristic alpha and beta stimulation oc-

curs. Normally the effects of tyramine are transient because it is so rapidly oxidized by monoamine oxidase in tissue and plasma. The dose of tyramine necessary to provoke a pressor or cardioaccelerator response depends in part on the size of readily-released catecholamine stores, the ease with which such amines are released from nerve endings, and the ability of tyramine to reach the nerve ending. The test may be conducted in the following manner: The patient should be supine in a quiet room. A slow intravenous infusion of 5 per cent dextrose in water is started, and when blood pressure and pulse are stable, a placebo is injected and cardiovascular measurements are made. Then doses of tyramine are administered starting at 250 μg., increasing to 500 μg., 1,000 μg., 1,500 μg., and 2,000 μg., with higher doses given in 1,000-μg. increments to a limit of 6,000 μg. Response is measured after each dose with a 10–15-minute interval between doses. A rise in systolic pressure greater than 20 mm. Hg after injection of 1,000 μg. is an exaggerated response.[8] Absence of blood pressure after 6,000 μg. may be considered a depressed response.

In patients with pheochromocytoma, tyramine injections result in transient but profound blood pressure increases due to release of greater-than-normal amounts of catecholamines from the expanded stores in the nerve endings.[8] When a patient's nerve endings are depleted of catecholamines by reserpine or guanethidine, the tyramine pressor response is diminished. The more tyramine necessary to provoke a standard pressor response, the greater is the sympathetic interference that can be attributed to these antihypertensive drugs. In addition, the more difficult it is to evoke a tyramine response, the more unlikely it will be that standard doses of pressor agents, which work primarily by release of endogenous catecholamines (metaraminal, mephentermine), will be effective for treatment of hypotension in medical or surgical settings.

The tyramine response is complex during administration of anti-adrenergic agents such as alpha-methyldopa. At least part of the anti-adrenergic action of alpha-methyldopa depends on (1) its uptake into sympathetic nerve endings, (2) its decarboxylation to alpha-methyl dopamine and (3) its later conversion by dopamine beta oxidase to the false neurotransmitter alpha-methyl norepinephrine.[9] A false neurotransmitter, a substance not normally found in the nerve ending, accumulates at the same site as norepinephrine and is responsive to the same physiologic and pharmacologic stimuli as norepinephrine. Alpha-methyl norepinephrine accumulates in place of norepinephrine and can be released by tyramine. However, alpha-methyl norepinephrine may be less potent than norepinephrine as a pressor or cardioaccelerator agent. The tyramine response is thus decreased during the early phase of treatment with alpha-methyldopa as nerve endings are depleted of norepinephrine but before alpha-methyl norepinephrine accumulates. During later stages of therapy, the tyramine response may return or even become exaggerated, presumably due to larger stores and release of greater amounts of transmitter now composed primarily of alpha-methyl norepinephrine but with small amounts of norepinephrine. "Denervation hypersensitivity" is another factor that may result in an augmented tyramine response after long-standing treatment with alpha-methyldopa. Hypersensitivity can be tested by determining whether there is increased responsiveness to direct-acting sympathomimetic drugs (*e.g.*, norepinephrine or phenylephrine).

When a patient is receiving monoamine oxidase inhibitors, another group of anti-adrenergic drugs, tyramine response may be increased as much as 1,000 per cent to 10,000 per cent. The principal reasons for such an exaggerated response are (1) a prolonged half-life of tyramine, which is normally metabolized by monoamine oxidase and (2) expansion of the stores of both native transmitter (norepinephrine) and false neurotransmitter (octopamine) in the sympathetic nerve.[10] Testing with tyramine must be approached with caution and started at low doses (*e.g.*, 2.5 μg.). With judicious use, however, the results of tyramine testing can yield information regarding the degree of MAO blockade.

Adrenergic blocking agents which inhibit alpha receptors will blunt the effects of tyramine, which releases endogenous catecholamines, as well as the effects of infused exogenous catecholamines. In low or commonly-used doses, the blockade is competitive and

can be overcome by increasing doses of catecholamines or tyramine. The tyramine or norepinephrine necessary for a standard pressor response relates directly to the degree of adrenergic blockade. When using beta blocking agents (*e.g.*, propranolol), the degree of blockade of the cardioaccelerator effects of isuprel or infused epinephrine can be used to determine the effectiveness of beta blockade.

Parasympathetic System

Symptoms and signs of dysfunction. Symptoms related to abnormal parasympathetic function are usually less conspicuous than those associated with sympathetic dysfunction. The most common symptoms include impotence and impaired libido. Anorexia, incontinence of urine and feces, urinary retention, and alternation of constipation and diarrhea are encountered. The iris may be atrophic and exhibit no pupillary response to light or accommodation; tearing is diminished after repeated corneal irritation, and the salivation response to the taste of lemon is diminished. Rapid resting heart rate becomes disproportionately increased during orthostatic change and may be evidence of less-than-normal parasympathetic function.[11] Each of the above functions depends upon an intact reflex arc that includes efferent parasympathetic fibers. Anal sphincter tone and the bulbocavernosus reflex also depend on sacral parasympathetic integrity.

The history of drug ingestion must be considered carefully. Drugs, rather than disease, frequently cause the autonomic dysfunction by their parasympatholytic action.

Physiologic tests. The results of the Valsalva maneuver are useful for determining parasympathetic insufficiency as well as sympathetic insufficiency. A slowing of the heart rate after the systolic and diastolic overshoot requires intact parasympathetic function (fig. 3).

Carotid sinus massage produces slowing of the heart rate in most normal patients. Failure to slow the heart may indicate interrupted parasympathetic pathways (fig. 4). Similar conclusions are warranted when cold (ice bag) applied to the face fails to produce bradycardia. Slowed gastrointestinal motility after a barium swallow may bear the same connotation.

Pharmacologic tests. Acetylcholine is the neurohumoral transmitter at all levels in the parasympathetic system (*i.e.*, synaptic junctions within the central nervous system, within peripheral ganglia, and at the nerve terminal and receptor organ junction). The pharmacologic tests aimed at assigning failure to transmit at any one of these sites are difficult to use because the pharmacologic agents (atropine, acetylcholinesterase inhibitors) act at each of the sites. Atropine, however, can give useful information because it affects the receptor more than it affects the other junctions.

Figure 4 attempts to outline a simplified scheme for locating a break in the parasympathetic reflex arc. If the heart slows with carotid massage, this suggests that the entire reflex arc is intact (pathway E-A-C-G). If there is no slowing of the heart, yet hypoglycemia produces an increase in gastric acidity, this may suggest dysfunction in the afferent nerves (E). If gastric acidity is not increased by hypoglycemia and atropine produces no change in heart rate and no pupillary dilatation, interruption between nerve terminal and effector organ is implied (C-G). The responsiveness of the pupillary end-organ can be tested by conjunctival instillation of pilocarpine (G).

Central Autonomic System

Malfunction of suprasegmental centers is the most difficult to diagnose. Dysfunction of central systems may be a feature of diffuse or focal central nervous system diseases, such as multiple sclerosis, Shy-Drager syndrome,[12] Parkinson's disease,[13] familial dysautonomia, syringomyelia,[13] hematomyelia,[13] tabes dorsalis,[5, 13] Wernicke's disease,[14] and tumors of the fourth ventricle.[7] Central dysfunction should be suspected when results of tests involving afferent–efferent reflexes (*e.g.*, Valsalva, carotid sinus massage) are normal, yet those involving reflexes independent of the afferent fibers (*e.g.*, mental arithmetic, hypoglycemia) are abnormal.

Summary

A conceptual framework of the anatomy and physiology of the autonomic nervous system, necessary for evaluation of the system in clinical settings, has been presented. The emphasis has been on the use of the patient's case

history, results of physical examination and selected physiologic and pharmacologic tests as means of assessing the extent of the abnormality of the autonomic nervous system. The importance of making a detailed assessment has been emphasized, particularly as it applies to understanding symptoms, predicting responses to vasoactive drugs and, in the case of antihypertensive drugs, assessing whether full therapeutic effect has been achieved.

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