HISTORY

76 Clinical Evidence of Dysautonomia

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Definition

Dysautonomia refers to an abnormality of function of the autonomic nervous system. There are two divisions of the autonomic nervous system: the sympathetic and the parasympathetic. Although the latter occasionally may be involved, abnormal function of the sympathetic division produces the most striking symptoms of dysautonomic syndromes. The term *orthostatic hypotension* is often used as a synonym for dysautonomia. It is the most dramatic of the symptoms and is the one that most often brings the patient to the physician, but it is not an adequate description of the full dysautonomic syndrome.

Dysautonomia is not a single disease process. The autonomic nervous system may undergo injury as part of several different degenerative neurologic diseases. These are the *primary dysautonomias*. There are also nonneurologic systemic illnesses of a variety of causes in which injury to the autonomic nervous system may occur and become a predominant component. These are the *secondary dysautonomias*. Finally, side effects of drugs are often manifested as abnormalities of function of the autonomic nervous system, producing an *iatrogenic* form of dysautonomia. The many causes of dysautonomia are listed in Table 76.1.

Technique

Dysautonomia does not produce unique symptoms. The patient's individual complaints can each be part of another disease process. It is the set of symptoms, taken together, that suggests that a dysautonomic state is present. In obtaining the history, therefore, three tasks must be accomplished. The physician must:

1. Develop a sufficient body of information to establish that a dysautonomic syndrome actually exists.
2. Distinguish the secondary dysautonomias, including drug side effects, many of which will improve or disappear when the causative problem is treated, from the primary dysautonomias for which there is only symptomatic relief.
3. Distinguish among the several forms of primary dysautonomia, since these have different natural histories and prognoses.

The symptoms of primary dysautonomia are listed in Table 76.2. Other than postural syncope, the symptoms are often mild or subtle and may become evident only after a careful and detailed review of systems.

Postural dizziness or syncope is the most striking symptom of dysautonomia. It is the most commonly reported, and is usually sufficiently disturbing to be a chief complaint or presenting problem. Note that the symptoms evident to the patient are postural dizziness, syncope, or one of the other manifestations of cerebrovascular ischemia noted in Table 76.2. These symptoms are due to orthostatic (postural) hypotension, but the latter is a sign to be elicited on physical examination and is not, strictly speaking, part of the historical database.

There are many causes in addition to primary dysautonomia for postural syncope due to orthostatic hypotension; these are listed in Table 76.3. The terms *sympathicotonic* and *asympathicotonic* have been coined to describe situations in which the autonomic nervous system is normal (the former) and those in which a dysautonomic state exists (the latter). An important point of differentiation between these two groups of problems is that when the autonomic response system is functioning normally (the sympathicotonic state), assumption of the upright posture is accompanied by an increase in heart rate. This may be perceived and reported as palpitation. In the asympathicotonic state, the heart rate response is usually impaired along with the other impairments of autonomic function.

Table 76.1
The Dysautonomias

Primary
Familial dysautonomia (Riley–Day syndrome)
Idiopathic orthostatic hypotension (progressive autonomic failure)
Multiple system atrophy with autonomic failure (Shy–Drager syndrome)
Parkinson's syndrome with autonomic failure
Secondary
Amyloidosis
Autoimmune neuropathies
Guillain–Barré syndrome
Myasthenia gravis
Rheumatoid arthritis
Carcinomatous autonomic neuropathy
Central nervous system diseases
Hypothalamic lesions
Posterior fossa tumors
Syringomyelia
Tertiary syphilis—tabes dorsalis
Wernicke's syndrome
Diabetes mellitus
Metabolic diseases
Fabry's disease
Pernicious anemia
Porphyria
Tangier disease
Drug Related (see Table 76.7 for more detailed list)
Alcohol
Antidepressants
Antihypertensives
Tranquilizers–antipsychotic agents

Modified from Bannister R. *Autonomic failure, a textbook of clinical disorders of the autonomic nervous system* (New York: Oxford University Press, 1983), p. 4.

Table 76.2
Symptoms of Dysautonomia

Symptom	Frequency
Postural hypotension Lightheadedness, fainting, dimness of vision, weakness, unsteady gait, slurred speech, exercise syncope	94%
Urinary dysfunction Frequency, nocturia, urgency, stress incontinence	65%
Sexual dysfunction Impotence, loss of libido, dry or retrograde ejaculation	51%
Bowel dysfunction Intermittent diarrhea, nocturnal diarrhea, rectal incontinence	30%
Decreased sweating	11%

Data derived from: Thomas JE, Schirger A. Idiopathic orthostatic hypotension. Arch Neurol 1970;22:289–93.

Table 76.3
Causes of Orthostatic Hypotension

Asympathicotonic—autonomic dysfunction; characterized by absent tachycardia
Primary dysautonomias
Secondary dysautonomias
Sympathetic inhibiting drugs (see Table 76.7)

Sympathicotonic—no autonomic dysfunction; characterized by tachycardia
Volume depletion
  Addison's disease
  Dehydration
  Hemorrhage
Vascular insufficiency
  Parade fainting
  Pregnancy
  Thermodilation
  Varicose veins
Deconditioning
  Loss of gravity forces
  Postinfectious
  Prolonged bed rest
Drug induced
  Alcohol vasodilation
  Diuretics
  Nitrates
Potassium depletion
Vasovagal reaction

The patient who experiences the postural symptoms associated with orthostatic hypotension describes a sensation of dizziness or transient weakness on arising from the supine position. This is especially obvious when the movement is sudden. The feeling is often described as though a "wave" of weakness had passed over the individual. The symptom is not accompanied by shortness of breath or chest pain. Palpitation will not occur in the dysautonomic patient. The postural syncope resolves quickly once the head is lowered, and the symptom can sometimes be prevented by having the patient stand slowly enough to allow the circulatory system to adjust. When the syndrome is fully developed, however, adjustment does not occur, and severe syncopal symptoms can be controlled only through use of support garments and therapy to expand the blood volume.

As noted, these symptoms are a manifestation of a sudden decrease of blood supply to the brain and can have any of the characteristics of transient cerebral ischemia. For example, some patients will experience slurring of speech or dimming of vision rather than the more commonly described dizziness. In other individuals, particularly with certain drug-related secondary dysautonomias, the symptoms present as postexercise syncope or weakness rather than just occurring with postural change.

At times, even a normal individual will experience postural dizziness (e.g., on a hot day, after a hot bath, or with social drinking). The historian must determine whether postural symptoms are a common occurrence, under what circumstances they occur, whether the events are increasing in severity or frequency, and what other symptoms occur in association in order effectively to sort among the many and varied causes.

Urinary tract dysfunction is described by almost two-thirds of the patients with primary dysautonomia. These symptoms also are common in individuals with secondary dysautonomia, particularly diabetics. The bladder symptoms are very nonspecific; for example, nocturnal frequency may be part of a symptom complex due to congestive heart failure, urinary tract infection, or bladder outlet obstruction, any of which are more frequent in occurrence than dysautonomia. It could also be due to the osmotic duresis that occurs in diabetics more commonly than severe dysautonomia. For these reasons, the historian must carefully evaluate each individual symptom within a complete context.

A point of differential value in the history pertaining to bladder function is that the dysautonomias, particularly the primary syndromes, may be accompanied by failure of bladder sensation as well as motor function abnormalities. Thus the dysautonomic patient may not be aware of a distended bladder.

This sensory abnormality can help differentiate among the causes of urinary frequency, since osmotic diuresis and the frequency of congestive failure are accompanied by an apparent sense of urgency. Similarly, the absence of cystic inflammation in the dysautonomic results in frequency without dysuria, allowing differentiation from urinary tract infection. The absence of sensation, along with the motor function abnormalities of the syndrome, also make dysautonomic individuals (particularly women) subject to stress or overflow incontinence.

Sexual dysfunction, a common occurrence in dysautonomia, may also be caused by a wide variety of other illnesses (Table 76.4). For many years, this problem had been written off as being almost always of psychogenic origin. More recently, however, an organic or pharmacologic cause has been established in 80% of impotent men, and more than 50 organic causes of impotence have been identified.

Iatrogenic sexual dysfunction caused by side effects of drugs on the autonomic nervous system is a problem of special concern. The drugs involved, particularly the antihypertensive agents, are needed for lifelong treatment of an important cardiovascular risk factor. The occurrence of side effects like sexual dysfunction often results in noncompliance with prescription and may seriously impair a treatment program. Therefore, whenever a patient is known to be taking a drug with the potential of producing this side effect, the possibility should be explored by careful and sensitive questioning for evidence of sexual performance

Table 76.4
Organic Causes of Impotence

Inflammatory:	Urethritis, prostatitis, seminal vesiculitis, cystitis, urethral stricture, gonorrhea, tuberculosis
Mechanical:	Congenital deformity, Peyronie's disease, marked obesity, hydrocele, phimosis
Postoperative:	Prostate biopsy, prostatectomy (simple or radical), abdominoperineal resection, sphincterotomy, vascular surgery
Occlusive–vascular:	Atherosclerosis, arteritis, priapism, thrombosis, embolism
Traumatic:	Penectomy, urethral rupture
Endurance:	Myocardial failure, angina pectoris, pulmonary insufficiency, anemia, leukemia, metabolic disease, other systemic illness
Neurologic:	Dysautonomia, peripheral neuropathy, tumor or transection of the spinal cord, amyotrophic lateral sclerosis, multiple sclerosis, spina bifida, syringomyelia
Chemical:	Drug abuse (alcohol, stimulants, narcotics), psychotropic agents (tranquilizers, antidepressants, antipsychotics), anticonvulsants, antiparkinsonian drugs, antihypertensives
Endocrine:	Pituitary disease, adrenal disease, thyroid disease, hypogonadism, diabetes mellitus, chromosomal abnormalities (Klinefelter's or Turner's syndrome)

Adapted from: Smith AD. Causes and classification of impotence. Urologic Clinics of North America 1981;8:79–89.

difficulties. If these are discovered, the drug regimen should be changed.

Specific historical points tend to suggest dysautonomia or some other organic cause for sexual dysfunction. When evaluating impotence, the special clue is the presence or absence of morning erection. The morning erection is a frequently experienced event in the male. It tends to decline in frequency with age, but still occurs even in the older man. It is a manifestation of sympathetic nervous system activity during the REM sleep cycle; as such, it is a true measure of the competence of the autonomic nervous system. The historian should determine whether the patient has morning erection, its frequency, and whether changes in its character (i.e., becoming less turgid) are occurring. Where the history is unclear, it is possible to test for this phenomenon using objective methods (nocturnal penile tumescence).

Another clue in the differentiation between organic and psychogenic sexual dysfunction is the relationship of arousal and potency to specific sexual partners. Psychogenic sexual dysfunction is often limited to a specific partner. It may be a manifestation of guilt because of extramarital sexual activity, anxiety over possible transmission of venereal disease, or may be due to performance anxiety. Organic problems are manifested with all partners.

Differentiating among the many causes of organic impotence is not easy. In inflammatory diseases the presence of pain may provide a clue. Most of the other causes must be differentiated by evaluation of this symptom within context of the entire history.

Bowel dysfunction seems to be less often a symptomatically disturbing problem in the dysautonomic patient. This may be because minor changes in stool consistency or frequency will not be considered abnormal or deserving of mention by most patients. Since the dysautonomias most often have the characteristics of sympathetic division dysfunction, the patient will experience increased frequency and less solid stool. As the situation becomes more severe, there may be explosive diarrhea. The patient may also have uncontrollable flatus. Since sphincter control is lost, the extremely embarrassing situation of sudden stool incontinence may occur.

Nocturnal diarrhea is often present. This provides a good historic differentiating point between organic and functional bowel syndromes (it does not occur with psychogenic or functional diarrhea). Nocturnal diarrhea is particularly common in diabetic dysautonomia, but is not unique to this syndrome.

Abnormalities of sweating are reported by only a small number of patients with dysautonomia. Most often, the loss of sweating involves the lower extremities to a greater extent than the trunk or arms. In diabetics the distribution of areas that do not sweat can be very irregular.

The failure to report this symptom does not mean that loss of sweating is an uncommon event in dysautonomia. It points out the fact that most of the functions of the autonomic nervous system are outside conscious perception. Failure of these functions, therefore, does not produce symptoms at the usual level of awareness. Only those aspects of activity in which dysfunction produces either very dramatic symptoms (postural blood pressure control) or where the dysfunction is very apparent (bowel, bladder, and sexual activity) are the symptoms disturbing enough to be reported.

The confirmation of the diagnosis rests with the physical findings, many of which will have no historic equivalents, and in the performance of certain objective tests of autonomic function. These are described in Chapter 79, Laboratory Evaluation of the Autonomic System.

Basic Science

The autonomic nervous system innervates every tissue and organ in the body. Most of the functions it subserves are outside of the normal realm of the conscious. It is the guardian of "le milieu interieur." In many of its activities a balanced interplay between the sympathetic and parasympathetic divisions is necessary. The system also functions through rapidly responsive reflexes that control a wide variety of physiologic functions. When dysautonomia exists, the system no longer functions in a balanced or sufficiently rapid manner. This combination of imbalance and loss of responsiveness results in emergence of the symptoms that characterize the dysautonomic syndromes. As noted, many of the activities of the autonomic system never produce symptoms because they never appear at the level of patient awareness even when functioning abnormally.

Blood Pressure Control, Orthostatic Hypotension, and Postural Syncope

Autonomic nervous system reflexes provide a rapidly responsive mechanism for moment-to-moment control of the blood pressure. These reflexes are critical for the maintenance of adequate blood supply to the brain when an individual stands. Although the vascular system of the brain is capable of autoregulation and will dilate if blood pressure falls, this capability is limited; if blood pressure falls suffi-

ciently, so does brain perfusion. Thus orthostatic hypotension, a drop in blood pressure on standing, will be accompanied by syncope or dizziness, the most striking of the symptoms of dysautonomia.

The baroreceptor/cardioaccelerator-pressor reflex is the autonomic mechanism responsible for this aspect of blood pressure control. The reflex arc consists of several components: sensory receptors, the site of integration, the efferent system, and the effector organ.

The sensory receptors. Arterial baroreceptors are specialized stretch receptors located in the walls of the highly elastic great vessels. The commonly described sites of these receptors are the carotid sinus and the aortic arch, although such sensory receptors are probably widely distributed in the walls of the major arteries of the head and neck. These sensory organs respond to the stretch exerted on the elastic vessel wall by the pulsatile column of blood and translate the distention created by the energy in the pulse wave into an analog signal. This travels to the brain in fibers of the sensory fibers of the vagus nerve.

The site of integration. The "vasomotor center" is located in the pontomedullary portion of the hindbrain in a region containing nuclei closely associated with the reticular activating system. This impulse-integrating area receives input from the arterial baroreceptors and stimuli arising from a wide variety of other sources. These sources include higher neurologic sites such as the thalamus, hypothalamus, and cortex, as well as additional peripheral sensory receptors located on the venous side of the circulation, in the heart itself, and in other organs and tissues. The signals from all these sources are constantly being received, provide an instantaneous description of the individual's physiologic status, are integrated in the "vasomotor center," and ultimately control the tonic level of impulse activity in the autonomic system. Since this system is constantly active, the continuous modulation of neural traffic allows for instantaneous response to the changing environment.

The input from the arterial baroreceptors has an inhibitory effect on the tonic level of autonomic cardiovascular activity. If blood pressure rises, the baroreceptors undergo increased stretch and an increased number of neural impulses are transmitted. The effect of this increased input to the vasomotor center is twofold: there is *increased* parasympathetic output to the heart—this slows the heart rate; there is *decreased* activity in the sympathetic nervous system—this also tends to slow the heart rate and, more important, it allows relaxation of the arteriolar resistance blood vessels and decreased intensity of contraction of the cardiac musculature. All these effects will result in a drop in blood pressure with restoration at the "set-point" of the baroreceptors.

Conversely, if the blood pressure falls, the baroreceptors send fewer signals. Parasympathetic activity *decreases*, allowing the heart rate to rise. More important, sympathetic neural impulse activity *increases* and there is resultant stimulation of the rate and contractility of the heart, and constriction of arteriolar and venous blood vessels. These effects all serve to reverse the drop of blood pressure.

The efferent system. The autonomic nervous system has been classically described as operating as a "two neuron" efferent system. Information from the integrating centers is transmitted within the central nervous system via a "first neuron" that exits the CNS to reach a ganglion in which a synaptic event occurs. Actually several neurons (intercalated neurons) are involved in the transmission process within the central nervous system. The cell bodies of some of these intercalated neurons are located in the intermediolateral columns of the spinal column and are the cells noted to degenerate in *multiple system atrophy with autonomic failure.*

Axons of the last of the intercalated cells of the sympathetic division travel to ganglia after exiting from the spinal cord. For this division, the exit points from the spinal cord are located in the thoracolumbar region, and the ganglia are located in a chain close to the spinal column. Ganglionic synaptic transmission is not on a one-neuron-to-one-neuron basis. It involves extensive reintegration of the neural impulses through multiple synaptic events in which individual presynaptic axons stimulate many postsynaptic cell bodies, and individual postsynaptic cells are stimulated by many presynaptic transmitter axons.

In the parasympathetic division the exit points from the central nervous system are divided into two units. The majority of divisional activity, particularly the controls for heart and splanchnic organs, travels with the cranial nerves, especially the vagus nerve (cranial nerve X). A second area for exit of impulses from the CNS is located in the sacral divisions of the spinal cord. This area handles the parasympathetic impulses controlling large bowel, bladder, and sexual function. In the parasympathetic division, the axonal fibers exiting from the CNS travel all the way to the effector organ before making synaptic contact with the "second neuron." The synaptic interactions take place in neural plexi, rather than in consolidated ganglia. Acetylcholine is the synaptic neurotransmitter in both the sympathetic ganglia and the parasympathetic plexi.

The effector organ. For autonomic cardiovascular reflexes, the effector organ is the entire cardiovascular system. The several different portions of the cardiovascular system each respond to sympathetic stimulation in a characteristic manner. The sum of these individual responses produces the complete response:

- *The venous circulation:* Sympathetic stimulation of veins causes constriction. This decreases the reservoir capacity for the blood volume and the immediate result is that an increased volume of blood returns to the heart. This increase in "preload" is translated into increased cardiac output (CO).
- *The arteriolar circulation:* Sympathetic stimulation of arterioles causes smooth muscle constriction and leads to an increase in peripheral vascular resistance (PVR). The most sensitive arteriolar beds are those in the splanchnic organs and skin. Constriction of these vascular beds results in a shift of perfusion toward the heart and brain, organs in which the vessels tend to respond less, or not at all, to the arteriolar constrictor stimuli. As a result of these effects, not only does blood pressure rise but blood volume is redistributed, preserving perfusion to the most vital organs. Arteriolar constriction is mediated by the alpha postsynaptic membrane receptor. This response predominates in the vessels of skin and viscera. In striated muscle, however, the arterioles have a relatively higher concentration of beta postsynaptic receptors. These mediate a vasodilator response when stimulated by norepinephrine, the "second neuron" neurotransmitter of the sympathetic division. Exercise also produces a direct vasodilator effect through the autoregulatory mechanism. If the balance between sympathetic vasoconstriction and combined neural and autoregulatory vasodilation is lost, as may occur in dysautonomia or as a side effect of some drugs, syncope with exertion

or with exercise may result. This symptom should be explored in the history, especially in individuals receiving guanethedine or alpha-receptor inhibiting drugs.

- *The heart:* Sympathetic stimulation of the heart causes an increase in both heart rate and in the force of ventricular contractility. Both of these effects are beta-receptor-mediated responses and will increase the cardiac output.

The effects of increased levels of sympathetic stimulation on the blood pressure are predictable based on the following equation:

$$\text{Blood pressure} = \text{Cardiac output} \times \text{Peripheral vascular resistance}$$

Reflex actions that increase either the cardiac output (CO) or the peripheral vascular resistance (PVR) will raise the blood pressure. When both CO and PVR are increased, there is a synergistic effect that produces an even greater effect on the blood pressure.

The effects of postural change (assumption of the standing posture) thus can be described as follows: When an individual stands, there is momentary pooling of blood in the legs and in the splanchnic venous bed as a result of the effects of gravity on the column of venous blood. There is a sudden drop in the volume of blood returning to the heart, and this sudden reduction of preload causes a momentary drop in cardiac output and blood pressure. All of this occurs in a single heartbeat of time and is immediately perceived by the baroreceptors. The integrated autonomic response results in venoconstriction, restoring the preload; increases the rate and contractility of the heart, increasing cardiac output; and constricts the arterioles, raising blood pressure and redistributing arterial blood flow to preserve perfusion of heart and brain.

If the reflex is functioning normally, the systolic blood pressure tends to remain slightly lowered after the compensatory events (because it is particularly sensitive to the effects of reduced preload), and the diastolic tends to rise (because it is reflective of the increase in PVR). There are no absolutely agreed upon "normal" limits to these changes. A 10 mm Hg drop of systolic pressure is frequently seen, and up to 25 mm Hg may be acceptable if no symptoms occur. Similarly, the diastolic pressure may rise 5 mm Hg, may not change or may even fall 5 to 10 mm Hg. The response will still be considered "normal" if the patient remains asymptomatic.

The reflex-mediated compensatory responses do not occur in the patient with dysautonomia. When the patient stands, the blood pressure falls beyond tolerable limits and redistribution of perfusion does not occur. Blood supply to the brain is reduced and postural syncope results.

Sympathetic Control of Genitourinary Function

Understanding the distribution and function of the sympathetic nervous innervation of the bladder also helps understand the symptoms of dysautonomia. Sympathetic motor fibers go to the bladder body where they relax the muscle (beta-receptor mediation), and to the bladder outlet sphincter where they stimulate constriction (alpha-receptor mediation). Failure of the entire system would, therefore, lead to spontaneous constriction of bladder wall musculature and to relaxation of the sphincter. The small bladder with poor sphincter tone will exhibit rapid filling and decreased reservoir capacity. Frequency and incontinence are the consequences of this set of events.

Sympathetic innervation is also important in sexual performance. There is a series of events in the sexual experience that all have some dependence on a normally functioning sympathetic nervous system.

- *Arousal:* Visual stimuli, fantasy, and other cortical events, integrated with thalamic and hypothalamic impulses, all appear to be important to sexual interest (libido) and arousal. The integrated outflow of these higher neurologic centers seems to involve the sympathetic system, since many drugs that inhibit aspects of CNS sympathetic function diminish the libido; and in experimental study a CNS sympathetic stimulator, yohimbine, appears to be aphrodisiac in rats.
- *Tumescence:* The actual engorgement of genital structures with blood is mediated by sympathetic outflow both from central nervous system centers and through spinal reflexes. In men this is potency—penile erection. In women, tumescence is manifested as clitoral erection and labial engorgement.
- *Recruitment:* Secretions from the testes, seminal vesicles, and prostate are mobilized by the smooth muscle motor-propulsive activity of ductile structures, all of which are richly innervated and respond to sympathetic stimuli. The lubrication process involving secretions from glandular structures of labia and vagina probably represents the analogous event in women.
- *Ejaculation:* This is a reflex event mediated in the sacral division of the spinal cord by a parasympathetic loop and is rarely if ever inhibited in dysautonomia or by drugs. Normal anterograde ejaculation, however, depends on adequate closure of the bladder sphincter. This is, as noted, a sympathetic motor function and will be impaired in some dysautonomic syndromes, particularly in diabetes, and by certain drugs.

  The consequence of failure of sympathetic stimulation to cause closure of the bladder sphincter during the parasympathetic reflex event of ejaculation is retrograde ejaculation. Even though the ejaculatory sensation is present, the failure to emit seminal fluid is a bothersome symptom. It can be sufficiently disquieting to the patient to compromise prescription compliance severely.

  The event in women corresponding to ejaculation is not known. The muscular contractions of vagina and uterus that occur at the time of climax may be mediated by the parasympathetic reflex system, but this has not been demonstrated.
- *Climax:* The autonomic events associated with the culmination of sexual stimulation have the characteristics of a generalized discharge of the sympathetic nervous system. Blood pressure rises, heart rate rises, piloerection occurs, etc. Some drugs that inhibit sympathetic outflow have been described by individual patients, both men and women, as delaying or diminishing the sensation of climax. These reports are apocryphal and have not been studied in a systematic or controlled manner.

Given this wide variety of effects of the sympathetic nervous system on sexual performance, and considering that dysautonomia is rarely complete, there are many different ways in which sexual function could be disrupted in the

dysautonomic syndromes. The literature does not usually differentiate among these effects. Most often, it describes only failure of potency or loss of libido. As illustrated in Table 76.5, which details the effects of some antihypertensive drugs on sexual performance, it is possible to differentiate among the various aspects of sexual failure as a function of the probable site of autonomic inhibition.

This approach to analysis of the effects of the antihypertensives makes it apparent that impairment at the central site of sympathetic integration leads to inhibition of potency and libido, with limited effect on ejaculation. Inhibition of neurotransmission at peripheral sites (ganglion or nerve terminal) causes impairment of potency and ejaculation but no effects on libido. Of note is the fact that the beta blockers, which have actions confined to the peripheral nervous system, have no reported sexual effects, while propranolol, the drug of this class that enters the CNS, has a pattern of effect on sexual performance similar to that of other centrally acting drugs.

Information on these effects is not complete for most drugs, even for antihypertensive agents, which probably have been be studied in the greatest detail, because these issues are not systematically examined in most drug evaluation protocols. Nonetheless, certain characteristic side effects are predictable based on the site of action of a drug. For example, it has been shown that the histamine receptor antagonist cimetidine has a central nervous system site of effect. The drug inhibits libido and potency; this pattern of side effects is exactly what would be predicted given the drug's receptor-blocking mechanism and central nervous system site of action.

The Primary Dysautonomias

The literature of the nineteenth century contains a number of case reports that describe patients with symptoms consistent with dysautonomia. They emphasize the postural hypotensive symptoms. Related basic research was focused on the factors responsible for blood pressure control. Clinical interest was stimulated by the report in 1925 of three patients with these characteristics:

Orthostatic hypotension

Syncope

Fixed heart rate

Nocturnal polyuria

Impotence

Loss of libido

Chronic diarrhea

Anhidrosis

Heat intolerance

Minimal signs of neurologic illness

Youthful appearance

Anemia/pallor

Low metabolic rate

Elevated blood urea nitrogen

This syndrome was called "idiopathic orthostatic hypotension" by its describers, Bradbury and Eggleston. The symptom complex suggests, however, that the patients had a form of dysautonomia. More recently, the term *progressive autonomic failure* has been proposed as a more appropriate name for the syndrome.

Despite the many abnormalities present in patients with this syndrome, interest was focused on the postural syncope and orthostatic hypotension. This interest culminated in

Table 76.5
Reported Effects of Some Antihypertensive Drugs on Sexual Performance

Agent	Decreased libido	Impaired potency	Impaired ejaculation	Delayed climax
Centrally acting				
Alpha-methyldopa	√√	√√	√	A
Clonidine	√√	√√	—	—
Guanabenz	√√	√√	—	—
Reserpine	√√	√√	√	—
Ganglionic blocker				
Trimethaphan	—	√√	√√	—
Nerve terminal active				
Guanethedine	—	√√	√√√[a]	—
Guanadryl	—	√√	√√[a]	—
Receptor antagonists				
Alpha				
Dibenzyline	—	—	√√	—
Phentolamine	—	—	√√	—
Prazocin	—	√	—	—
Beta				
Metoprolol	—	—	—	—
Propranolol	√√	√√	—	—

[a]Retrograde.
Key: √ infrequent (0–5% of patients)
√√ frequent (5–20% of patients)
√√√ very frequent (>20% of patients)
— not reported in the literature
A apocrypha only
Modified from: Reichgott MJ. Problems of sexual function in patients with hypertension. Cardiovasc Med 1979;4:149–56.

1959 with the publication by Wagner of a landmark review of the subject. Although the emphasis of this review was on the postural change in blood pressure, the list of causes he identified includes all of the more common dysautonomic illnesses, both primary and secondary.

One year later, Shy and Drager published the description of a syndrome that carries their name. It also is characterized by the presence of orthostatic hypotension, but additional aspects of neurologic dysfunction were very evident and received emphasis. The patients, men in the fifth to seventh decades, manifested the following symptoms and signs:

Orthostatic hypotension

Atonic bladder

Urinary incontinence

Impotence

Loss of rectal sphincter tone

Rectal incontinence

Loss of sweating

Iris atrophy

External ocular palsies

Rigidity

Tremor

Absent gait-associated movement

Fasciculations

Wasting of distal muscles

Abnormal EMG

Neuropathic muscle injury

The authors described pathologic changes in the intermediolateral columns of the spinal cord. Subsequent confirmation of these pathologic findings, and the association of the spinal cord pathology with the autonomic symptoms, have shifted the emphasis in evaluation and management away from just the blood pressure to the broader aspects of the entire disease process.

Familial dysautonomia (the Riley–Day syndrome), a totally different kind of primary dysautonomia, was initially described in 1949. This syndrome has been considered a pediatric problem, although with improved treatment there are now several patients who have survived to young adulthood. The disease is genetic, with transmission having an autosomal recessive characteristic. It is almost entirely limited in occurrence to Ashkenazi (Northern European) Jews.

A highly specific characteristic of this disease is the almost complete absence of somatosensory function in the affected individuals. Both the autonomic and sensory nervous systems have a diminished number of peripheral fibers, and it appears that this is a "peripheral" rather than "central" nervous system disease. The major characteristics of the syndrome are as follows:

Orthostatic hypotension

Lack of tears

Absent taste buds

Drooling

Vomiting

Abdominal distention

Constipation

Diarrhea

Enuresis

Overflow incontinence

Abnormal gait (wide based)

Depressed reflexes

Although this syndrome shares some of the characteristics of other dysautonomias, it is a very different disease by virtue of the extent and distribution of additional neurologic injury, the genetic nature of transmission, and the congenital presentation. Of interest is the fact that two of the female victims who have survived to child-bearing age have been fertile and have delivered normal children.

Clinical Significance

The Primary Dysautonomias

The syndromes of primary neurologic disease with autonomic insufficiency require very careful evaluation and differentiation.

In *progressive autonomic failure* (Bradbury–Eggleston syndrome or idiopathic orthostatic hypotension) the symptoms of autonomic failure are an early manifestation. The history at the time the patient first seeks care is of postural syncope. It may also include genitourinary or bowel symptoms, but these usually are revealed in the review of systems rather than offered spontaneously by the patient. This syndrome, although progressive, develops slowly. The patient can live for many years in relative comfort once effective blood pressure control is achieved.

Conversely, the *Shy–Drager* syndrome is a more rapidly progressive illness and is much more problematic in its management. The dysautonomic symptoms usually follow the appearance of signs of other aspects of neurologic degeneration. The Parkinson-like symptoms common in this syndrome are particularly difficult to manage and may actually make management of the postural dizziness more difficult. The drug L-dopa, for example, may be useful for the control of rigidity, but is one that can cause orthostatic hypotension.

In addition, there appears to be more than one form of neurologic degenerative illness present in the cluster of patients who have been diagnosed as having Shy–Drager syndrome. While they all ultimately develop dysautonomia, some have this only in conjunction with Parkinson-like abnormalities consistent with olivo-ponto-cerebellar degeneration. Others may have different distributions of neurologic abnormalities including both sensory system abnormalities and voluntary motor dysfunction. Because there can be degeneration of several different neurologic systems in this syndrome, the name *multiple system atrophy* has been proposed. These patients do not develop dementia.

Finally, to complicate the situation, autonomic dysfunction may occur in some patients with true Parkinson's syndrome. The righting reflex abnormalities commonly present in this illness make sudden standing difficult. They are often confused with true orthostatic blood pressure abnormalities and postural syncope. But some patients will actually develop signs of autonomic system degeneration and ortho-

Table 76.6
Differential Diagnosis of the Major Primary Dysautonomias

Progressive autonomic failure
Slowly progressive
Dysautonomic symptoms occur early and predominate
Symptom control is relatively easy
No dementia
Multiple system atrophy
More rapidly progressive
Parkinson's and dysautonomic symptoms both present early
Sensory or voluntary motor system symptoms may develop
Difficult to manage because of conflicting effects of drugs on different aspects of illness
No dementia
Parkinson's syndrome
Slowly progressive
Dysautonomic symptoms occur late (righting reflex problems may be confusing)
Dementia a common late manifestation

static hypotension late in the course of their illness. Dementia is a manifestation of Parkinson's syndrome that does not occur in the Shy–Drager syndrome or in progressive autonomic failure.

Because these primary syndromes have such different natural histories and because there are differences in their ease of treatment, it is important to try to differentiate among them. The differential points are summarized in Table 76.6.

The primary dysautonomic syndromes can be devastating illnesses causing severe disruption of a patient's life because of their pattern of symptoms: inability to rise, inability to control bowel and bladder, failure of normal sexual function. These symptoms may be accompanied by tremor, rigidity, and other Parkinson-like symptoms and signs when autonomic degeneration occurs in association with multiple system atrophy. Fortunately these are rare illnesses. No methods of treatment can arrest or cure them. It is possible to control some of the symptoms, however, particularly the postural syncope, but this is often made more difficult by the therapy required for control of the Parkinsonian syndrome. There are no really effective treatment modalities for the other aspects of primary dysautonomia.

Secondary and Iatrogenic Dysautonomias

Diabetes mellitus is probably the most important of the systemic illnesses in which dysautonomia is a manifestation. The diabetic may demonstrate the symptoms of autonomic nervous system dysfunction very early in the disease process, even before major changes in glucose tolerance have developed; and the dysautonomic process may be particularly difficult to diagnose in the diabetic because it often does not follow the classic pattern of presentation. For example, even though the pressor component of the baroreceptor reflex may be inhibited, the cardioaccelerator component often will remain intact. The asympathicotonic character of othostatic hypotension in the diabetic will not be evident because the heart rate response to postural change persists.

The diabetic may also demonstrate some of the effects of dysautonomia on visceral function before developing postural blood pressure control problems. Thus it is common for the diabetic to develop nocturnal diarrhea or diarrhea alternating with constipation as a manifestation of dysautonomic bowel function. Impotence and retrograde ejaculation are also frequently reported.

Table 76.7
Drugs Causing Dysautonomic Orthostatic Hypotension

Alcohol	MAO inhibitors
Alpha-methyldopa	Mecamylamine
Barbiturates	Phenothiazines
Bethanidine	Phentolamine
Clonidine	Prazocin
Dibenzyline	Pronestyl
Guanabenz	Quinidine
Guanadryl	Tricyclics
Guanethedine	Trimethaphan
Isoniazid	Reserpine
L-dopa	Vincristine

The occurrence of orthostatic hypotension and postural syncope is a major problem with some drugs (Table 76.7). This side effect will make it impossible to continue to use an agent in a therapeutic regimen even if it is producing the desired treatment effect because of the risks to the patient and the inability of a patient to tolerate this problem.

The list of drugs that can cause postural syncope is long and varied. Some produce this effect through actions in the autonomic nervous system. Others do not impair autonomic function, but result in diminution of the circulating blood volume. These drugs share the common characteristic, whether causing autonomic inhibition or producing postural symptoms through volume depletion, that they reduce cardiac output and preload. Drugs that only reduce peripheral vascular resistance (e.g., hydralazine, minoxidil) *do not cause* orthostatic hypotension. This is an important consideration when planning a change in therapy in an attempt to alleviate postural syncope as a side effect.

The most important consequence of these side effects is probably not the postural syncope or impairment of sexual performance per se, but the failure of the patient to remain compliant with the treatment regimen once a drug is identified as the cause of discomfort. The mistrust of drugs is often carried over to other agents, and even minor discomforts are blamed on a drug. Since drugs are needed for lifetime treatment in most of the patients, such compliance failure and the associated unwillingness to trust any agent become an extremely important clinical management problem.

Other secondary dysautonomias are relatively uncommon. In addition, the symptoms of failure of the autonomic system are only a part of the entire syndrome presented by the patient. Most often, the diagnosis of these illnesses will be suggested by these other symptoms. The full differential diagnosis must be reviewed, however, because the secondary dysautonomic syndromes are often part of correctable problems and will resolve with successful treatment or control of the underlying systemic illness.

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