AUTONOMIC INSUFFICIENCY

WILLIAM L. HENRICH, M.D.

MEDICAL GRAND ROUNDS

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL SCHOOL

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I. INTRODUCTION

The British physiologist Leonard Hill reported in 1895 on the blood pressure responses to alterations in posture of several species of quadriped and biped animals (1,2). He postulated that splanchnic vasoconstriction was involved in the hemodynamic response to the upright position, and believed that abnormalities related to low blood pressure could exist in man. The first clinical report of three patients with postural hypotension was by Bradbury and Eggleston in 1925; the

TABLE I

CLINICAL FEATURES DESCRIBED

By BRADBURY AND EGGLESTON

Orthostatic hypotension
Syncope
Fixed heart rate
Heat intolerance
Anhidrosis
Low basal metabolic rate
Slight and indefinite signs of neurological disease
Nocturnal polyuria
Impotence
Youthful appearance
Pallor
Anemia
Chronic diarrhea

description of the syndrome of orthostatic hypotension by these authors is remarkably complete in light of our present understanding of this illness.

It is now recognized that 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 neurological diseases. Table 2 is a partial list of several

TABLE 2

DISORDERS WITH WHICH AUTONOMIC INSUFFICIENCY OCCURS

A. 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

B. Systemic

- Diabetes mellitus
- Chronic renal disease
- Malnutrition, with or without alcoholism
- Combined system disease

C. Iatrogenic

- Sympathectomy
- Cordotomy
- Drug induced

D. Idiopathic Orthostatic Hypotension

conditions known to impair autonomic function. Each of the disorders listed in the table may disrupt the afferent, efferent, or central nervous system limbs of the autonomic nervous system pathways. Whether the condition is "idiopathic" or due to an identifiable neurologic disease, there is, characteristically, an associated loss of cholinergic as well as adrenergic function. Thus, many patients will be afflicted with constipation and anhidrosis in addition to postural hypotension. An exception exists in the use of a selective adrenergic blocker such as guanethidine, which leaves parasympathetic pathways intact. Interestingly, when cholinergic as well as adrenergic insufficiency is involved (which usually is the case), such usual cholinergic signs of impending syncope such as diaphoresis and bradycardia are absent. The faint develops suddenly upon standing without any warning signals.

This discussion will review the anatomy (briefly) and clinical tests useful in the assessment of autonomic function. Finally, three common clinical syndromes which involve autonomic system insufficiency (idiopathic orthosatic hypotension, diabetes, and dialysis-related hypotension) will be considered.

II. ANATOMY AND ORGANIZATION OF THE AUTONOMIC NERVOUS SYSTEM

The peripheral autonomic nervous system consists of a somatic afferent pathway, a central nervous system integrating complex (spinal cord and brain), and two distinct efferent systems (sympathetic and

parasympathetic outflow) (4).

The afferent fibers arise from the visceral organs, the skin, and the great vessels and enter the CNS and form reflex connections primarily at the segmental level. 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 cerebral hemispheres. The suprasegmental components are not essential to lower reflex function, but appear to modify and integrate segmental reflexes. The one anatomical feature which distinguishes the autonomic system from the peripheral motor system to voluntary muscle is that autonomic fibers which leave the central nervous system do not terminate on an end organ as do voluntary motor fibers; rather, these fibers terminate in autonomic ganglia (Figures 1, 2, and 3). The ganglionic cells

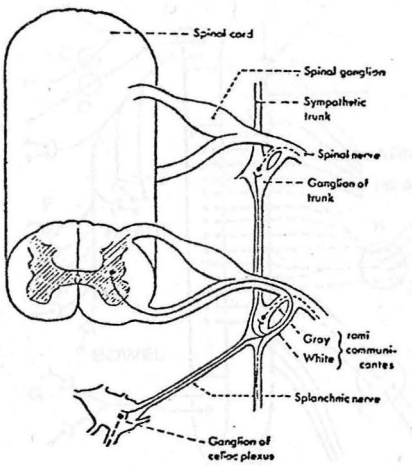


Figure 1. Spinal Cord Section and Ganglia of Sympathetic Nervous System

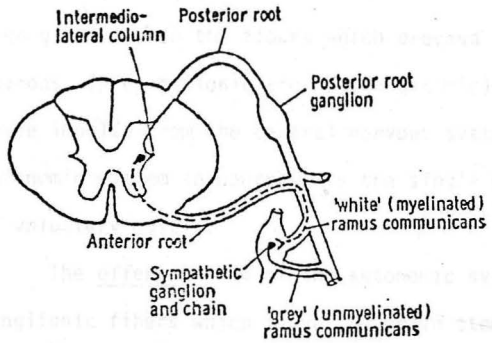


Figure 2. Preganglionic and Postganglionic Sympathetic Fibers

PREGANGLIONIC = DASHED LINE

POSTGANGLIONIC = SOLID LINE

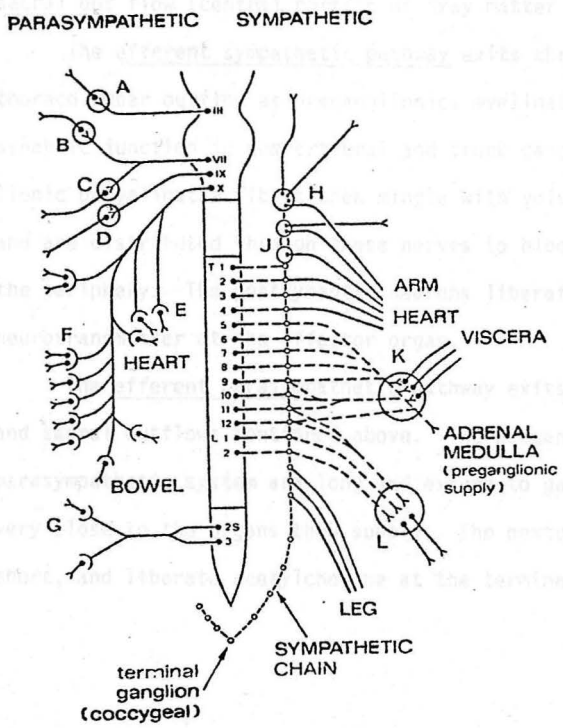


Figure 3. Peripheral Autonomic Nervous System

then give rise to the fibers which proceed to an end organ. Thus, two neurons, (preganglionic and postganglionic) are required to transmit a nerve impulse from the central nervous system to an end organ in the autonomic system in contrast to the single neuron employed in the case of voluntary muscle.

The efferent limb of the autonomic system arises therefore in preganglionic fibers which leave the brain stem and spinal cord in three locations: cranial outflow (axons of the accessory oculomotor, superior and inferior salivatory, and the dorsal motor nucleus); thoracolumbar outflow (from the intermediolateral gray column of the spinal cord in the twelve thoracic and the first or second lumbar segment); and the sacral out flow (central portion of gray matter in the spinal cord).

The efferent sympathetic pathway exits the spinal cord through the thoracolumbar outflow as preganglionic, myelinated fibers and form a synaptic junction in prevertebral and trunk ganglia. The post ganglionic unmyelinated fibers then mingle with voluntary motor nerve fibers and are distributed through these nerves to blood vessels and organs in the periphery. The postsynaptic neurons liberate nonepinephrine as a neurotransmitter at the effector organ.

The efferent parasympathetic pathway exits the CNS via the cranial and sacral outflows mentioned above. The preganglionic fibers of the parasympathetic system are long and extend to ganglia located within or very close to the organs they supply. The postganglionic fibers are thus short, and liberate acetylcholine at the terminal synapse site.

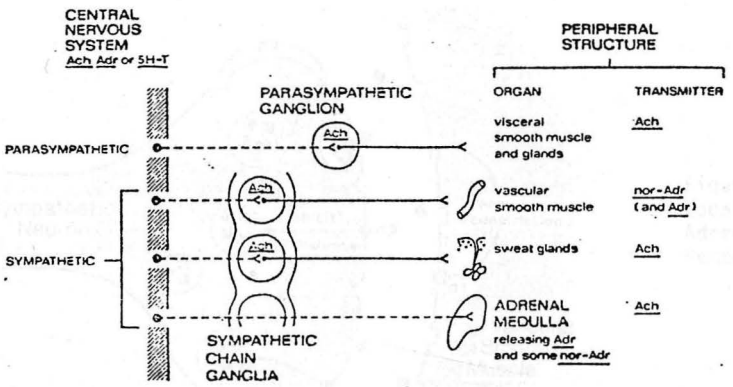


Figure 4. Chemical Transmitters of the Autonomic Nervous System

As depicted in Figure 4, the transmitter substance in the ganglia of both the sympathetic and parasympathetic systems is acetylcholine; however, these ganglionic synapses are not inhibited by the action of atropine. Atropine inhibits the distal postganglionic synapse involving acetylcholine of primarily the parasympathetic system. However, as noted in Figure 4, acetylcholine is the neurotransmitter in a few end organs of the sympathetic system, notably in the adrenal gland and some sweat glands. Thus, norepinephrine is the principal transmitter agent for postganglionic sympathetic nerves and is stored in the nerve terminal and is released by firing of the nerve and by drugs such as tyramine, amphetamine, and ephedrine. The physiologic actions of the sympathetic activity which results from norepinephrine and/or epinephrine release involve α - adrenergic effects (mediated primarily via α - 1 receptors located on the post-synaptic cleft, see Figure 5) and

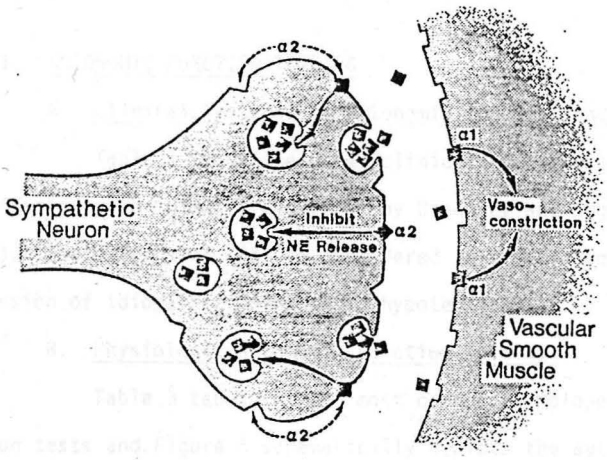


Figure 5.
Location of α - Adrenergic Receptors

FROM BERTHELSON AND PETTINGER, LIFE SCI 21:59, 1977.

β - adrenergic effects (via β - receptors) (5). Clinically important α - adrenergic effects include vasoconstriction, intestinal relaxation, and pupillary dilatation. β - adrenergic stimulation results in vasodilation in muscles, a marked increase in inotropic and chronotropic cardiac effects, and bronchial relaxation (6).

The anatomical and biochemical differences of the components of the autonomic nervous system allow diseases and drugs to produce isolated effects. The localization of a defect to one component of the reflex arc is therefore possible with a series of autonomic tests. These tests allow the physician to precisely assess the location and extent of any deficit (7,9).

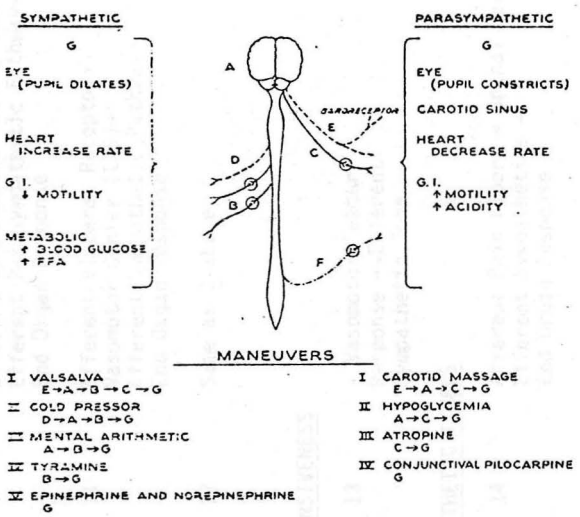
III. AUTONOMIC FUNCTION TESTING

A. Clinical Features of Autonomic Insufficiency

Table 1 lists the usual clinical features of autonomic insufficiency, originally described by Bradbury and Eggleston in 1925 (3). These features will be considered in greater detail in the discussion of idiopathic orthostatic hypotension.

B. Physiologic Autonomic Function Testing

Table 3 tabulates the most commonly employed autonomic function tests and Figure 6 schematically depicts the autonomic pathways



A = BRAIN, SPINAL CORD
B = EFFERENT SYMPATHETIC PATH
C = EFFERENT PARASYMPATHETIC PATH
D = AFFERENT SOMATIC PATH
E = AFFERENT VISCERAL PATH
F = EFFERENT PARASYMPATHETIC PATH
G = END ORGANS (SYMPATHETIC AND PARASYMPATHETIC)

Figure 6. Schematic Representation of Autonomic Pathways

TABLE 3

AUTONOMIC FUNCTION TESTS

	NAME OF TEST	REFERENCE	PATHWAY(S) TESTED	NORMAL RESPONSE
A.	**INTEGRITY OF BARORECEPTOR REFLEX**			
1.	Valsalva Maneuver	10	Afferent Visceral Receptors → Vasomotor Center (CNS)→ Efferent Sympathetic Pathway and Efferent Parasympathetic Pathway→ End Organ Response	4 Phase Response With Arterial Pressure Overshoot and Bradycardia. See text and Figure 7.
2.	Amyl Nitrate	11	Afferent Visceral Receptor→ Vasomotor Center (CNS)→ Efferent Sympathetic Pathway→ End Organ Response	Δ HR/Δ Art. Pressure = 1.0
3.	Tilt-Table (Head-Up 60°)	12	Same as 2 above	$\leq$ 10 mm Hg Decrease in Systolic and Diastolic B.P.; Hr. Increase = 10/min. See Figure 8.
B.	**VASOMOTOR CENTER RESPONSIVENESS**			
1.	Hyperventilation	13	↓ Vasomotor Center Response →↓Efferent Sympathetic Tone	Decrease in Arterial Pressure 10 - 20 mm Hg
C.	**TESTING EFFERENT SYMPATHETIC FIBERS**			
1.	Cold Pressor Test	14	Afferent Pain Fibers → Spinal Cord → Efferent Sympathetics → End Organ Response	$\geq$ 15 mm Hg Increase in Systolic and Diastolic B.P.

TABLE 3

(Continued p2)

	NAME OF TEST	REFERENCE	PATHWAY(S) TESTED	NORMAL RESPONSE
2.	Mental Arithmetic With Harrassment	15	Cortical Function → Vasomotor Center → ↑Efferent Sympathetic Tone → End Organ Response	> 10 mmHg in Systolic B.P.
3.	Reflex Sweat Test (↑ Core Temperature 1° C or ≈ 1.8° F)	16	Visceral Afferents → Vasomotor Center → Efferent Sympathetic Pathways	Quinizarin Powder on Skin Turns From Blue to Purple
4.	Direct Sweat Test With Pilocarpine (5-15 mg) or Electrical Stimulation	17 21	Absence or Disease of Sweat Glands	Same End Point as in 3 Above
D.	AFFERENT AUTONOMIC FIBERS AND HIGH PRESSURE BARORECEPTORS			
1.	Phenyl Ephrine (50 to 100 mg) or Angiotensin (0.25 to 2.0 ng/kg) Injection	18	Arterial Baroreceptors → Afferent Sympathetic Pathways (Via Cranial Nerve IX) → Vasomotor Center → Efferent Parasympathetics → End Organ Response	↑ Arterial Pressure and Bradycardia (↑ RR Interval/Systolic Pressure = Slope of 12.8) See Figure 13

TABLE 3

(Continued, p3)

E. EFFERENT VAGAL FIBERS

	NAME OF TEST	REFERENCE	PATHWAY(S) TESTED	NORMAL RESPONSE
1.	Atropine (0.02 mg/kg)	19	Efferent Parasympathetic Fibers → End Organ Response	↑ in Heart Rate ≥ 20% of Control

F. EXTRA ADRENAL STORES OF NOREPINEPHRINE

1.	Tyramine (250 ng, 500 ng, 1000 ns, 1500 ng....up to 6000 ng)	20 23	Efferent Sympathetic Pathway → End Organ Response	< 20 mmHg ↑ in B.P. With Each 1000 ng Bolus is Normal: No Response to 6000 ng is Abnormal
*2.	Norepinephrine (0.05 pg/kg/min)	7	End Organ Response	< 20 mmHg ↑ in Systolic B.P. and < 19 mmHg ↑ in Diastolic B.P.
*3.	Epinephrine 1:1000 (1-2 gtts) into Eye	22	End Organ Response	No Change in Pupil

*Tests of Denervation Hypersensitivity

involved in several of the reflex arcs. A combination of these tests is usually necessary to define the pathway responsible for autonomic nervous system malfunction.

Of the tests utilized to assess both low and high pressure baroreceptor integrity, the Valsalva maneuver is the most widely used. The test was first utilized in 1707 by an Italian surgeon (Antonio Maria Valsalva, 1660-1723) as a maneuver to inflate the middle ear via the Eustachean tubes.

The test is performed by having the subject exhale against a closed valve (producing a 40 mm Hg pressure gradient) for 10 seconds. Four distinct phases in the arterial pressure response are described with the maneuver (see Figure 7). In phase I, arterial pressure increases transiently as the increase in intrathoracic pressure compresses

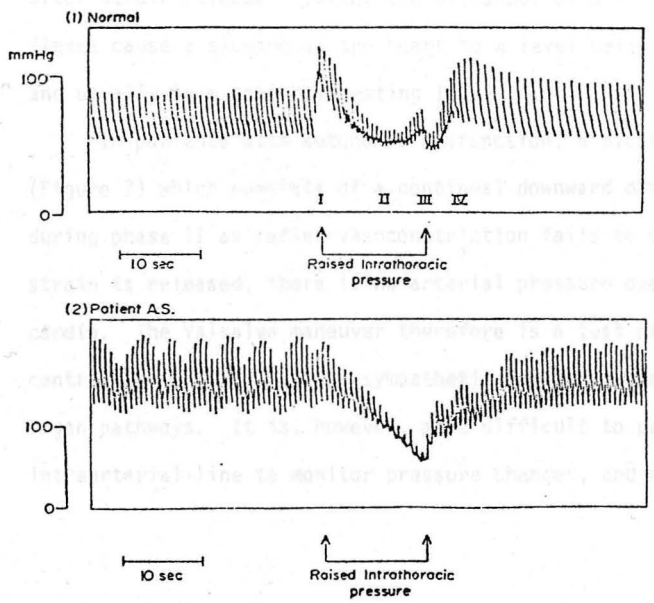


Figure 7. Normal (Top) and Abnormal (Bottom) Responses To Valvalva's Maneuver

the aorta. Phase II consists of a fall in systolic B.P., diastolic B.P., and pulse pressure due to a reduction in venous return and therefore of cardiac output. This fall in blood pressure is somewhat variable in normal subjects but is reproducible on repetitive testing in individual patients; it plateaus after 5 seconds due to reflex vasoconstriction, and the heart rate usually increases slightly. Phase III is the 1-2 seconds after release of the strain; a sharp, transient fall in mean blood pressure without a change in pulse pressure is observed presumably due to release of pressure compressing the aorta, the reverse of the phenomenon in phase I. In phase IV, systolic and mean B.P. rise above the resting level within 10 seconds of strain release and pulse pressure widens. The B.P. overshoot is due to the lingering effects of vasoconstriction induced by phase II and returns to resting values by 1.5 minutes after strain release. During the overshoot of B.P., baroreceptor reflexes cause a slowing of the heart to a level below that of phase II and usually less than the resting level.

In patients with autonomic dysfunction, a blocked response occurs (Figure 7) which consists of a continual downward drift of blood pressure during phase II as reflex vasoconstriction fails to occur. When the strain is released, there is no arterial pressure overshoot and no bradycardia. The Valsalva maneuver therefore is a test of afferent visceral, central vasomotor, efferent sympathetic and parasympathetic, and end organ pathways. It is, however, more difficult to perform without an intraarterial line to monitor pressure changes, and may therefore be

impractical in some patients. The amyl nitrate test is another test of baroreceptor response to low pressure and is performed by simply breaking an ampule of amyl nitrate under the subject's nose and having him inhale deeply 3 times. While this test does not assess efferent parasympathetic pathways, it has the advantage of ease of administration, standardization, and absence of any intraarterial line. Tilt-table testing is another useful and well defined test of afferent low pressure baroreceptors, central, and efferent reflexes, but is of less practical help in routine clinical testing (see Figure 8).

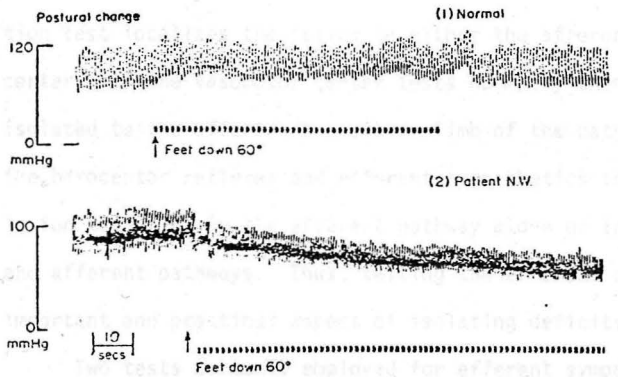


Figure 8. Normal (Top) and Abnormal (Bottom) Responses To Head-Up Tilt

Accurate testing of the CNS and vasomotor center is difficult. Hyperventilation and a fall in pCO_2 causes cerebral vasoconstriction. The vasoconstriction is believed to reduce efferent sympathetic tone acutely and result in a decrease in blood pressure of 10 - 20 mmHg. However, this test is less reliable than tests of the baroreceptor arc because of a more variable response among normal controls. A fall in blood pressure

is helpful, therefore, in excluding vasomotor center defects, but a negative test is difficult to interpret.

Selective testing of the efferent sympathetic system is possible with several tests and affords separation of abnormalities of the afferent and efferent limbs of the reflex arc. Studies of the baroreceptor reflexes discussed above test both afferent and efferent function. No clinically applicable examination which isolates the afferent pathway is available (especially in the presence of a deficit in the efferent system). However, the demonstration of a normal efferent pathway in a patient with an abnormal Valsalva or amyl nitrate inhalation test localizes the lesion to either the afferent limb or vasomotor center. If the vasomotor center tests normally then the lesion is isolated to the afferent/baroceptor limb of the pathway. When both the baroceptor reflexes and efferent sympathetics test abnormally, the lesion may exist in the efferent pathway alone or in both the efferent and afferent pathways. Thus, testing the efferent pathway only is an important and practical aspect of isolating deficits in autonomic function.

Two tests commonly employed for efferent sympathetic testing are the cold pressor test (14), and the mental arithmetic test(15). Painful cold stimuli are carried by the lateral spinothalamic tracts in the spinal cord while the motor impulses to the arterioles are in the efferent sympathetic fibers. The test is performed by placing the patient's hand in ice slush (4°C) for one minute; an increase in systolic BP of $\geq$ 15 mmHg is considered normal. Having the patient perform arithmetic

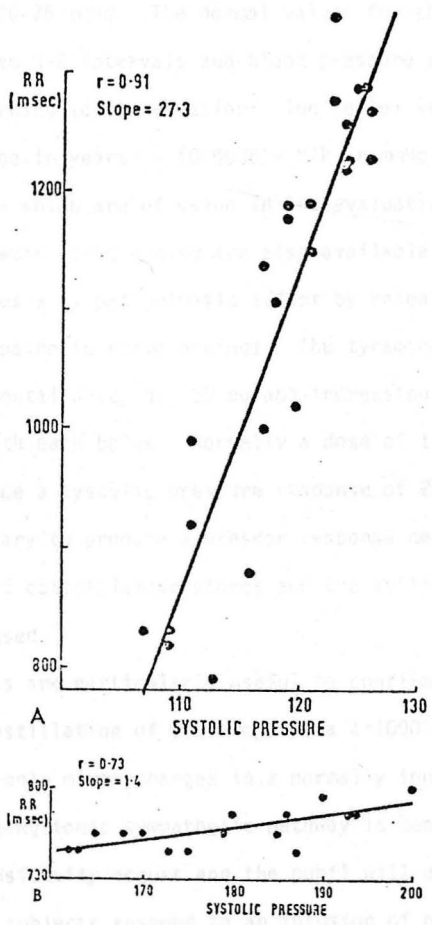
computation under harassment is also a test of the integrity primarily of efferent sympathetics. This test is more difficult to standardize and depends on complete patient cooperation. Other stimuli utilized for efferent function assessment include sudden loud noises, an ice pack to the forehead, and immersion of the face in ice water. These tests also have problems with standardization.

Motor impulses to the sweat glands other than those in the axilla are also carried by efferent sympathetic fibers. By placing the hand or arm under a heating lamp or in water with a temperature of 110°F, rectal temperature will increase 0.5 to 1.0°C. The increase in blood temperature will produce sweating if the efferent sympathetics are intact. When this test is negative, the intradermal injection of 1:1000 pilocarpine may be utilized to verify that there is no anatomical absence of the sweat glands. Electrical stimulation of the nerves is another way to directly test efferent sympathetics and sweat gland integrity.

The high pressure baroreflex arc may be tested in greater detail utilizing a sudden increase in arterial pressure as the stimulus, and the resultant normal increase in the R-R interval (or bradycardia) as the response. Bristow et al (18), Smyth et al (24) and Pickering et al (25) have demonstrated that by plotting the R-R interval (msec) vs. systolic pressure (mmHg) a line is generated which reflects high pressure baroreceptor sensitivity (see Figure 9). The steeper the line generated, the more responsive the baroreceptor reflex (18). This test does require

BARORECEPTOR SENSITIVITY TO A PRESSOR DOSE OF ANGIOTENSIN

NORMAL (TOP) AND ABNORMAL (BOTTOM) RESPONSES



FROM BRISTOW et al, CIRCULATION 39:49, 1969.

Figure 9.

intact efferent parasympathetic fibers for a normal result, and is performed by injecting phenylephrine 0.25 to 2.0 ug/Kg I.V. to raise arterial pressure 20-25 mmHg. The normal values for the slope of the relationship between R-R intervals and blood pressure decrease with advancing age according to the equation: log reflex sensitivity = 2.47 - (0.0164 x age in years) - (0.0086 x MAP in mmHg) (26).

Several tests which are of value in the evaluation of the postganglionic sympathetic nerve ending are also available. Tyramine is an amine which produces a sympathomimetic effect by releasing stored norepinephrine in sympathetic nerve endings. The tyramine test is performed by infusing incremental doses of 250 ug and increasing the dose by a factor of two with each bolus. Normally a dose of 1 to 6 mg (1000 to 6000 ug) will induce a systolic pressure response of 25 mmHg. The dose of tyramine necessary to produce a pressor response depends on the size of readily-released catecholamine stores and the ability of the amine stores to be released.

Several tests are particularly useful to confirm sympathetic denervation. The instillation of 1-2 drops of a 1:1000 epinephrine solution will produce only minor changes in a normally innervated eye. However, if the postganglionic sympathetic pathway is denervated, then denervation hypersensitivity occurs and the pupil will dilate widely. Similarly, normal subjects respond to an infusion of norepinephrine systemically (0.05 ug/Kg or 1 to 8 ug I.V.) with an increase in systolic pressure of 25 mmHg. Patients with denervation hypersensitivity have an exaggerated pressor response to the norepinephrine infusion.

IV. SPECIFIC DISEASES

A. Idiopathic Orthostatic Hypotension and the Shy-Drager Syndrome

Since the original report of autonomic insufficiency by Bradbury and Eggleston (3) as an isolated disease entity, a recognition that autonomic dysfunction may occur independently and as a feature of other systemic illnesses has become apparent.

A significant decrease in orthostatic blood pressure and a failure of increase in heart rate should alert the physician to the diagnostic possibility of autonomic dysfunction and suggest a series of possibilities.

Secondary causes of autonomic failure include identifiable diseases of the sympathetic outflow: eg., in the CNS, the Shy-Drager syndrome (discussed below), brain tumors, and cerebral infarction are possibilities. In the spinal cord, lesions such as tabes dorsalis, syringomyelia, and combined systems disease are common. Disorders of the peripheral nervous system like alcoholic and diabetic neuropathy, porphyria, and amyloidosis or the use of sympathetic blocking agents which act peripherally such as guanethidine may lead to autonomic failure. Similarly, several miscellaneous causes of this disorder exist including hypokalemia (34,35), anemia, extensive surgical sympathectomy, or the use of antidepressive medication. A partial list of psychotropic drugs which may impair autonomic function is provided in Table 4.

After the above illnesses associated with autonomic insufficiency have been excluded, there remains a group of disorders which are idiopathic, of which Bradbury and Eggleston (3) made the initial report. In

TABLE 4

PSYCHOTROPIC DRUGS WHICH MAY AFFECT AUTONOMIC ACTIVITY

Generic name	Pharmacopeial name	Trade name	Autonomic effects
Phenothiazines	Chlorpromazine Promazine Trifluoperazine Perphenazine	Largactil Sparine Stelazine Fentazin	Hypotension Hypothermia Impotence
Tricyclic (imipramine) group	Imipramine Desipramine Amitriptyline Nortriptyline	Tofranil Pertofran Tryptizol Allegron, Aventyl	Hypotension Hypothermia Dry mouth Urinary retention Glaucoma
Monoamine oxidase inhibitors	Phenelzine Mebanazine Phenoxypropazine Iproniazid Nialamide Pivhydrazine Tranylcypromine	Nardil Actomol Drazine Marsilid Niamid Tersarid Parnate	Hypertension, especially with tyramine-containing foods Hypotension Impotence

1960 Shy and Drager (36) described the disease with additional neurological features of multiple system atrophy; autonomic failure with apparently atypical parkinsonism was added in 1969 (37). It is this entity of combined peripheral and central nervous system defects which comprises the syndrome of idiopathic orthostatic hypotension (IOH).

IOH afflicts more men than women (3-4:1), and symptoms frequently develop insidiously over a period of years. Presenting complaints may localize to the peripheral nervous system (commonly) or central nervous

system (uncommonly) early in the course of the illness. Orthostatic symptoms, bowel-bladder dysfunction, impotence, anhidrosis, and profound weakness usually occur. Several years later, a neurological disorder that is characterized by hyperreflexia, and extrapyramidal signs with muscle rigidity, a shuffling gait, and a masked face may occur which provide evidence of widespread neurological involvement (38). In the advanced stages, the disorder is symmetrical and bilateral and affects the corticobulbar and corticospinal tracts, basal ganglia, and cerebellar pathways. The disorder appears to be relentless even if the original symptoms and signs of orthostatic hypotension are controlled with therapy (39).

Thus, IOH may be a manifestation of primary degenerative disease of the CNS, in which peripheral involvement and CNS involvement represent a continuum or spectrum of the original process. The neuropathological lesion common to all patients with autonomic failure is loss of up to 80% of intermediolateral column cells in necropsy cell counts (40). Degenerative changes in sympathetic ganglia and post-ganglionic sympathetic endings have also been demonstrated (41). Central lesions in IOH include degeneration of the substantia nigra, locus ceruleus, nucleus tractus solitarius, and the preganglionic vagal neurons (41). The hypothalamic and limbic system are depleted of norepinephrine and dopamine in autonomic failure with multiple system atrophy (41). This loss of catecholamines centrally may point to a common defect in susceptible neurons; however, despite several overlapping features, the cause of the illness remains

completely obscure.

The limb of the sympathetic system affected in IOH is usually the central and efferent pathways. As noted earlier, there is no simple way to detect an afferent limb block in the presence of an efferent lesion. Further evidence of the lack of efferent sympathetic activity has been provided by studies by Bannister (29) and Ziegler et al (33) (see below) which demonstrate that norepinephrine levels fail to increase upon standing in patients with IOH.

Variations in Plasma Hormones in Patients With IOH

1. Plasma Renin Activity (PRA)

A wide variation exists in the responsiveness of the renin-angiotensin system in patients with autonomic insufficiency. Clearly sympathetic nerves are an important efferent stimulus to renin release, probably through an intrarenal β receptor (27). However, other factors known to increase renin release (eg., a decrease in renal perfusion pressure or an increase in chloride delivery to the macula densa) should be normally operant in patients with autonomic dysfunction, and thus theoretically would be expected to be able to compensate for any decrement in efferent sympathetic activity. The possibility that any interpretation of PRA in patients with autonomic insufficiency may be spuriously low has been suggested by older studies which demonstrated a 10% decrease in plasma volumes in such patients (28). Nonetheless, the most comprehensive assessment of PRA in autonomic insufficiency was by Bannister et al (29) and demonstrated a wide variability in baseline PRA and a variable response to posture as well.

2. Plasma Aldosterone

Most investigators have observed a decrease in plasma aldosterone in patients with autonomic insufficiency (29,30). As Figure 10 demonstrates, supine plasma levels of aldosterone are low (111 ± 12 pmol/L vs a normal of 251 pmol/L $p<.01$) in patients with IOH, and, although the

ORTHOSTATIC CHANGES IN PLASMA ALDOSTERONE IN NORMALS (RIGHT) AND PATIENTS WITH IOH (LEFT)

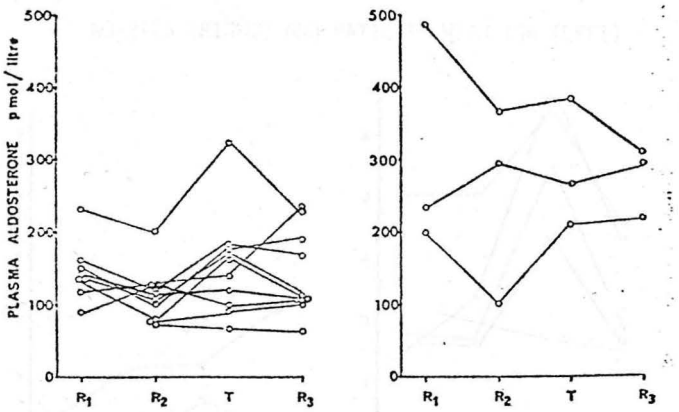


Figure 10.

FROM BANNISTER et al, BRAIN 100:327, 1977.

levels increase upon standing, the upright levels are still lower than normals (154 ± 23 pmol/L vs 289 ± 51 pmol/L, p<.0125). The importance of these observations in relation to the measured decrease in plasma volume (28) and the maintenence of upright blood pressure remains speculative.

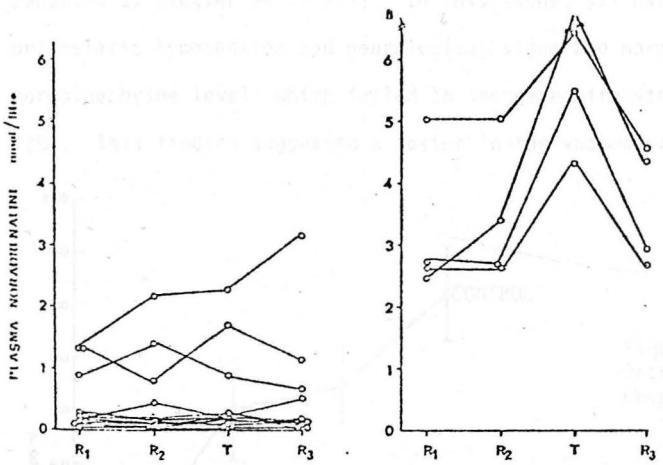
3. Plasma Catecholamines

The recent availability of a radioenzymatic assay for norepinephrine and epinephrine (31) has made possible the accurate measurement of plasma catecholamines. Furthermore, the measurement corelates well with the severity and location of the autonomic lesion.

The first comprehensive investigation of plasma norepinephrine was by Bannister et al (29) who demonstrated low plasma norepinephrine levels in patients with primarily an efferent sympathetic lesion (Figure 11A). Upright posture had no effect on these levels (0.54 ± 0.23 to 0.61 ± .25 nmol/L, NS) in marked contrast to normals (3.47 ± .58 to 5.99 ± .69 nmol/L p<.025).

ORTHOSTATIC CHANGES IN PLASMA NOREPINEPHRINE IN NORMALS (RIGHT) AND PATIENTS WITH IOH (LEFT)

Figure 11A.



FROM BANNISTER et al, BRAIN 100:327, 1977.

These observations were extended by Kontos et al (32) who demonstrated an efferent sympathetic block with an abnormal Valsalva and ice to forehead tests in five patients with idiopathic orthostatic hypotension. These authors also noted that these patients had no pressor response to I.V. tyramine, further suggesting depleted norephinephrine stores in postganglionic sympathetic nerves. An enhanced pressor response to norepinephrine infusion also suggested denervation hypersensitivity. These authors further demonstrated histochemically the absence of norepinephrine from nerve endings in sympathetic motor nerves in muscles.

A further clarification of these two observations was recently reported by Ziegler et al (33). In this study, six patients with orthostatic hypotension and neurological signs had normal plasma norepinephrine levels which failed to increase with standing (Figure 11B). This finding suggested a lesion in the vasomotor center and a

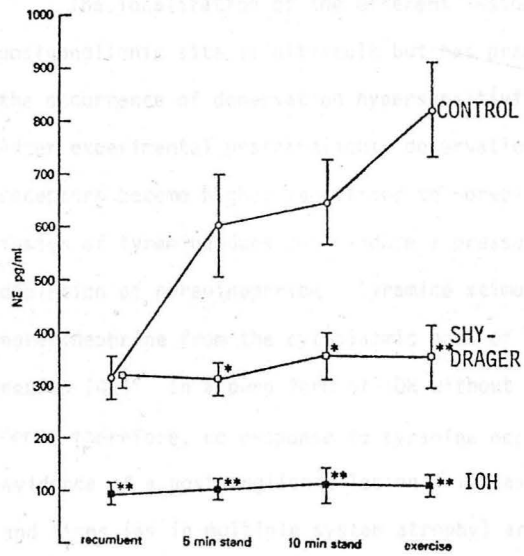


Figure 11B.
Orthostatic Plasma NE Levels

primary failure in activation of efferent sympathetics on standing. Four other patients without a neurological disorder but with orthostatic hypotension had low norepinephrine levels which also did not increase with standing (Figure 11B). Thus, these patients had an efferent sympathetic disruption similar to the patients reported by Bannister and Kontos, and could be distinguished on the basis of resting supine norepinephrine levels (normal in central lesions, low in peripheral lesions).

In summary, plasma norepinephrine levels correlate well with the clinical tests of autonomic function and the location of the lesion in the autonomic system. In contrast, the importance of the renin - angiotensin system is at present less clearly defined, and aldosterone levels are most often low in patients with this syndrome.

The localization of the efferent lesion to the preganglionic or postganglionic site is difficult but has practical importance because of the occurrence of denervation hypersensitivity to norepinephrine infusion. After experimental postganglionic denervation, adrenergic blood vessel receptors become highly sensitized to norepinephrine; however, the infusion of tyramine does not produce a pressor effect because of neuron depletion of norepinephrine. Tyramine stimulates the release of norepinephrine from the cytoplasmic pool of the terminal sympathetic neuron (41). In a pure form of IOH without central nervous system involvement, therefore, no response to tyramine occurs, providing compelling evidence of a postganglionic lesion. In cases in which CNS symptoms and signs (as in multiple system atrophy) are present, there is usually less hypersensitivity to norepinephrine and a weak but discernable response to tyramine, suggesting both preganglionic and postganglionic involvement.

The therapy of IOH is imprecise at best. Only in patients who are symptomatic (even with standing blood pressures of 70 mmHg) should attempts at therapy be made. If the standing pressure is increased with pressor drugs, for example, recumbent hypertension may develop (43).

Head up body-tilt at night often improves postural hypotension by reducing renal perfusion pressure and leading to higher circulating angiotensin levels. The volume of gravity - induced pooling of blood in the lower extremities may be treated by elastic stockings. This therapy is often unhelpful.

Fludrocortisone is utilized to increase plasma volume and thus repair any modest decrement present in these patients (28). It also may enhance sensitivity to circulating norepinephrine. Doses range from 0.1 to 1.0 mg/day. Indomethacin has also been utilized with success in one case of IOH, but the role of prostaglandins in this syndrome is totally speculative (44). Monoamine oxidase inhibitors and tyramine have been found to be useful occasionally, but supine hypertension may be therapeutically limiting.

Management of the extrapyramidal symptoms in patients with CNS involvement and IOH is also difficult. Patients respond less reliably to L-dopa than patients with Parkinsonism, although successes have been reported (45). Bromocriptine is also available for this purpose, but also lacks effectiveness.

B. Diabetic Autonomic Neuropathy

Peripheral motor and autonomic nerves are commonly involved in diabetics, although peripheral motor nerve disease has received the greatest attention until recently. While the pathophysiology of peripheral nerve degeneration in diabetics is not entirely clear, it is known that diabetic nerves lack myoinositol, a polyol that has an important role in lipid synthesis and is essential for the normal structure and integrity of peripheral nerve (46). Chronic depletion

of myoinositol may occur in some diabetics since urinary excretion is increased in uncontrolled diabetes. Abnormalities in myelin composition also occur in diabetic nerves (47). Specific studies of autonomic ganglia in diabetics have revealed the presence of large, foamy ganglion cells with vacuolization (48); inflamation of autonomic nerve bundles and ganglia has also been appreciated (48). A reduction of the total number of nerve cells in the intermediolateral cells of the spinal cord is another typical feature of the neuropathology.

Most diabetic patients with symptoms from autonomic neuropathy have evidence of other diabetic complications, particularly peripheral neuropathy (49). The location of lesions in the sympathetic pathways is generally in the efferent limb of the system, particularly in the post-ganglionic sympathetics (50). Sympathetic afferent function and more proximal efferent abnormalities are often detectable, however (51). The parasympathetic system is more frequently involved than the sympathetic system, with complaints referable to the gastrointestinal tract and sexual function dominant (51).

The clinical expression of diabetic autonomic dysfunction is often focussed on gastrointestinal complaints. Abnormalities in esophageal motility and reflux, gastric emptying with obstruction, and intestinal motility with diarrhea have all been frequently reported. These disorders represent independent therapeutic problems, but also contribute to the general difficulty in the delicate management of many "brittle" diabetics. The most disabling of these gastrointestinal conditions is probably the

profuse, watery, and often nocturnal diarrhea with or without sphincter incontinence (51). The roles of bacterial overgrowth and bile salts in this phenomenon remain unsettled (51). The transit time through the small intestine is usually prolonged (52), and it is generally accepted that the diarrhea is the result of damage to the innervation of the gut. In this regard, structural abnormalities in both the sympathetic and parasympathetic components of gut innervation have been demonstrated. Therapy is symptomatic with hypomotile agents, antibiotics, cholestyramine, and cholinergic agents (51).

Cardiovascular abnormalities in diabetic patients are similar in expression to those discussed in IOH but without the extrapyramidal symptoms. Recent studies by Watkins and Mackay (52) demonstrate that detectable cardiac denervation is often present in diabetics many years before clinical symptoms appear when using a technique of heart rate variation during deep breathing. These authors suggest that the high mortality rate in these patients due to sudden deaths may be in part attributable to autonomic dysfunction. This hypothesis is shared by Ewing et al (53,54) who have documented a markedly enhanced mortality rate in diabetic patients with autonomic dysfunction. Figure 12 displays this mortality curve comparing diabetics with cardiac autonomic dysfunction to diabetics not afflicted with cardiovascular autonomic dysfunction. An interesting observation made by these investigators is that patients with symptoms of parasympathetic dysfunction such as

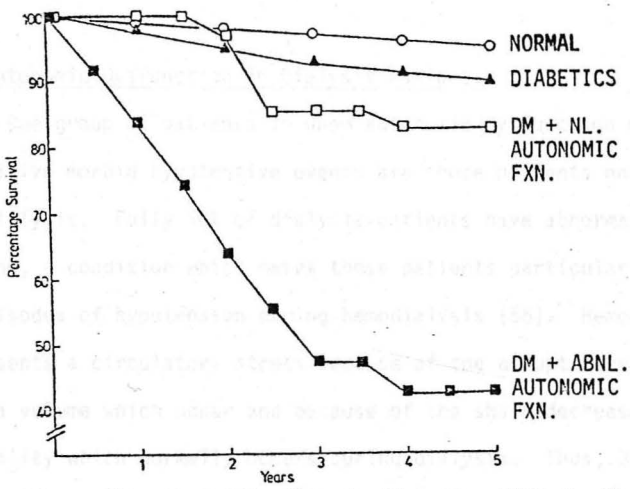


Figure 12. Mortality Rate in Diabetics With Cardiovascular Autonomic Dysfunction.
FROM AN INT MED 92(II):308, 1980.

impotence often have normal cardiovascular testing whereas abnormal cardiovascular testing is observed in symptomatic autonomic dysfunction other than impotence. Obviously, the recognition of this cardiovascular autonomic dysfunction has grave prognostic implications, and may in part reflect a selective and severe predilection of the disease for the autonomic nerves. Patients dying suddenly with autonomic dysfunction in diabetes had a surprising absence of ischemic heart disease at postmortem (53).

The symptoms, management, and consequences of urinary bladder and sexual dysfunction has been recently updated in a symposium on diabetic autonomic dysfunction (55).

C. Autonomic Dysfunction in Dialysis Patients

One group of patients in whom autonomic dysfunction may lead to repetitive morbid hypotensive events are those patients on maintenance hemodialysis. Fully 50% of dialysis patients have abnormal autonomic testing, a condition which makes these patients particularly vulnerable to episodes of hypotension during hemodialysis (56). Hemodialysis represents a circulatory stress because of the abrupt decrements in plasma volume which occur and because of the sharp decrease in plasma osmolality which normally occurs during dialysis. Thus, 30% of dialysis patients experience repetitive episodes of dialysis hypotension during some time in their history (57).

Three recent studies have clarified the pathogenetic mechanisms operant in dialysis hypotension. In the first of these studies, Kersh and co-workers investigated 6 patients who experienced repeated episodes of low blood pressure on dialysis (58). Two of the patients had normal autonomic testing (Valsalva and amyl nitrate inhalation), and reliably responded to infusions of saline to repair blood pressure. However, four of the patients had abnormal autonomic testing and were resistant to infusions of colloid and crystalloid to increase blood pressure. These patients did, however, respond to norepinephrine infusion. The authors concluded that a failure of afferent sympathetic function was likely, given the abnormal baroreceptor sensitivity alluded to earlier (18).

These studies were extended by the observations of Lilley et al (59) in which two groups of hemodialysis patients were investigated.

In one group of patients (Group I) hemodialysis hypotension was infrequent whereas in Group II patients hypotension (mean pressure <70 mmHg) occurred in 90% of dialyses. As noted in Figure 13, the group II patients had a

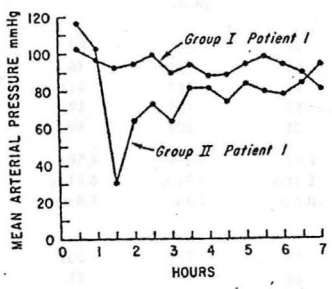


Figure 13. BP Changes During Dialysis in a Patient With (Group II) and Without (Group I) Autonomic Dysfunction

FROM LILLEY et al JCI 57:1190, 1976.

higher supine blood pressure than Group I patients prior to dialysis, and blood pressure fell dramatically once dialysis was begun. Further examination of the two groups of patients revealed an abnormal amyl nitrate test in Group II patients but a normal cold pressor test. Group I patients had normal responses to both maneuvers (Figure 14 and 15). Thus, the efferent sympathetic pathways appeared to be intact in Group II patients, and the afferent pathway was inferentially felt to be abnormal. Further evidence for this possibility was provided by the circulating dopamine-beta-hydroxylase (DBH) levels in the two groups of patients. DBH is the enzyme which converts precursors to norepinephrine in terminal sympathetic neurons, and

HEMODYNAMIC CHANGES WITH THE COLD PRESSOR TEST

TABLE II
Hemodynamic Changes with Cold Pressor Test

Patient number	MAP (semirecumbent)			R-R			$\frac{\Delta R\text{-}R}{\Delta MAP}$
	Control	Maximum	Δ	Control	Minimum	Δ	
	mm Hg			*ms*			*ms/mm Hg*
Group I							
1	80	91	11	700	660	40	3.63
2	81	117	36	600	540	60	1.67
3	114	140	26	620	600	20	0.77
4	93	107	14	800	720	80	5.71
5	96	106	10	700	660	40	4.0
Average	92.8	112.2	19.4	684	636	48	3.15
SD	±13.8	±18.1	±11.2	±79.3	±68.4	±22.8	±1.96
SEM	±6.2	±8.1	±5.0	±35.4	±30.6	±10.2	±0.9
Group II							
1	100	117	17	840	760	80	4.71
2	75	91	16	560	510	50	3.13
3	102	113	11	860	720	140	12.72
4	94	131	37	620	580	40	1.08
5	98	123	25	720	700	20	0.80
Average	93.8	115.0	21.2	720	654	66	4.49
SD	±10.9	±15.0	±10.2	±131.9	±104.8	±46.7	±4.9
SEM	±4.9	±6.7	±4.5	±59.0	±46.9	±20.9	±2.2
P	>0.90	>0.80	>0.70	>0.50	>0.70	>0.40	>0.60

(GR I = NORMALS, GR II = AUTONOMIC DYSFUNCTION)

FROM LILLEY et al JCI 57:1190, 1976.

Figure 14.

AMYL NITRATE INHALATION IN NORMAL (GR I) AND

AUTONOMIC DYSFUNCTION (GR II) PATIENTS

TABLE III

Hemodynamic Changes with Amyl Nitrite Inhalation

Patient number	Δ MAP	Δ R-R	ΔR-R / ΔMAP
	mm Hg	*ms*	*ms/mm Hg*
Group I			
1	13	60	4.62
2	30	130	4.33
3	44	220	5.0
4	30	233	7.76
5	33	120	3.63
Average	30	152.6	5.07
SD	±11.1	±72.7	±1.6
SEM	±5.0	±32.5	±0.7
Group II			
1	53	27	0.51
2	21	20	0.95
3	26	54	2.08
4	36	40	1.11
5	32	40	1.25
Average	33.6	36.2	1.18
SD	±12.2	±13.2	±0.58
SEM	±5.5	±5.9	±0.26
P	>0.30	<0.01	<0.001

Figure 15.

FROM LILLEY et al JCI 57:1190, 1976.

plasma levels are therefore an index of sympathetic activity. As shown in Figure 16, Group II patients had significantly greater DBH levels than the

DBH LEVELS IN NORMAL (GR I) AND

AUTONOMIC DYSFUNCTION (GR II) PATIENTS

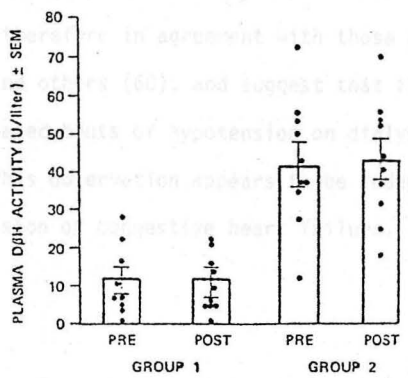


Figure 16.

FROM LILLEY et al JCI 57:1190, 1976.

non-hypotensive Group I patients. Taken together, these results point to a lesion in the baroreceptors, cardiopulmonary receptors, or visceral afferent nerves as the primary autonomic defect in patients with dialysis hypotension. These studies further suggest that this condition of "deafferentation" leads to a loss of negative feedback on sympathetic outflow and an increase in baseline (resting) DBH levels and supine hypertension. Moreover, these patients are often maximally vasoconstricted prior to dialysis, are unable to adequately sense low blood pressure, and therefore are especially prone to the effects of volume depletion to induce hypotension.

A final study by Nies et al (15) confirmed these earlier observations on the afferent limb of the reflex arc as being the primary deficit in dialysis patients who experience frequent bouts of hypotension. In this study, 5 patients with dialysis hypotension underwent a complete battery of autonomic function tests and the results were compared with 8 normotensive dialysis patients. As noted in Table 5, the patients with dialysis hypotension (Group A) were distinguishable from non-hypotensive patients (Group B) only by the results of the baroreceptor slope sensitivity. These results are therefore in agreement with those of Lilley et al (59), Kersh et al (58) and others (60), and suggest that the primary defect in patients with repeated bouts of hypotension on dialysis is baroreceptor dysfunction. This observation appears to be independent of any history of either hypertension or congestive heart failure.

TABLE 5

AUTONOMIC FUNCTION IN PATIENTS WITH (GROUP A) AND WITHOUT (GROUP B) DIALYSIS HYPOTENSION

	GROUP A (N = 5)	GROUP B (N = 8)
MAP DURING DIALYSIS (mmHg)	74.2*	96.4
PERCENT OF SYSTOLIC BPs < 100 mmHg DURING DIALYSIS	44.4†	3.0
INCREASE IN SYSTOLIC BP BY MENTAL ARITHMETIC (mmHg)	11.3	17.0
INCREASE IN SYSTOLIC BP BY COLD PRESSOR TEST (mmHg)	26.0	34.0
BARORECEPTOR SLOPE AFTER PHENYLEPHRINE (PREDICTED)	6.4* (14.9)	3.0 (4.3)

*$p < 0.001$.
†$p < 0.05$.

ADAPTED FROM NIES ET AL, J LAB CLIN MED 94:395, 1979

Summary and Conclusions

Patients with IOH usually have a defect in the efferent postganglionic sympathetic neuron, and plasma catecholamines are useful in the diagnosis and characterization of autonomic neuropathy in this group. Efferent parasympathetic dysfunction is also usually present. Patients with central nervous system involvement and symptoms and IOH (Shy-Drager syndrome) most often have a mixture of efferent sympathetic and central vasomotor center abnormalities. Therapy of this disorder is directed primarily at maneuvers to increase plasma volume and to improve peripheral vascular resistance.

Diabetic autonomic neuropathy, particularly when it involves the cardiovascular system, is a grave prognostic sign and may occur in as many as 30% of diabetics. Diabetic autonomic neuropathy most commonly involves lesions in sympathetic efferents and baroreceptors; resistance of the end organ to norepinephrine is an intriguing but uninvestigated possibility at present.

Dialysis patients with autonomic neuropathy most frequently have abnormalities of afferent/baroreceptor function which contribute to episodes of dialysis hypotension.

The various tests of autonomic function provide a unique opportunity for the precise definition of the location of an abnormality in the autonomic nervous system. The routine utilization of these tests will be necessary to fully characterize the natural history of diseases and drugs with autonomic effects, and therefore to establish the benefits of therapeutic intervention.

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