

WHAT ARE DYSAUTONOMIAS?

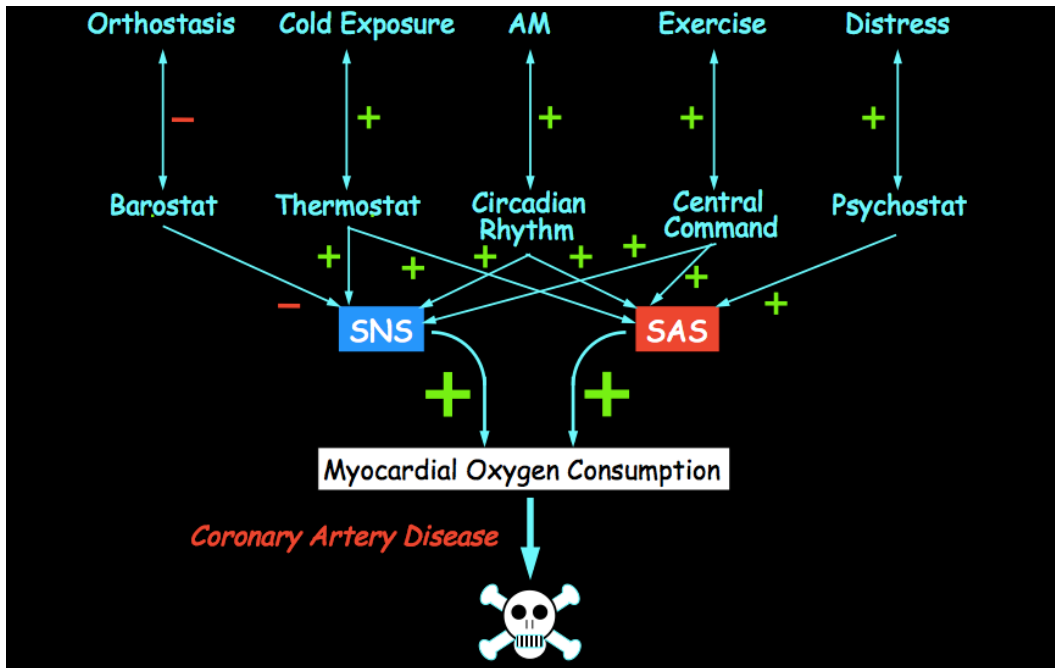
IN DYSAUTONOMIAS WHAT GOES WRONG?

“Dysautonomia” refers to a condition in which altered functions of one or more components of the autonomic nervous system adversely affect health.

Probably the most common types of dysautonomia involve compensatory, normal autonomic nervous system responses that worsen an independent disease process, rather than involving an abnormality of the autonomic nervous system itself. Changes in activities of components of the autonomic nervous system can even be harmful when the changes compensate for abnormal functioning of a different body system.

For instance, in heart failure, the heart fails to deliver an appropriate amount of blood to body organs. Among several compensatory adjustments, one is increased sympathetic noradrenergic system outflow to heart. This improves the pumping function of the heart; however, compensatory activation of the sympathetic noradrenergic system also promotes overgrowth of heart muscle, which can stiffen the heart walls and worsen the heart failure.

Autonomic nervous system failure occurs relatively commonly in diabetes, alcoholism, amyloidosis, AIDS, and cancer treatment with



In coronary artery disease, what normally would be appropriate changes in autonomic functions can be lethal.

particular drugs. In several diseases, such as diabetes, the patients do worse in the long run if they have autonomic failure.

“Dysautonomia” usually refers to a disorder of one or more components of the autonomic nervous system itself.

In other forms of dysautonomia, the problem is from abnormal function of the autonomic nervous system itself. This is the form of dysautonomia emphasized for much of the rest of this book.

Autonomic failure is characteristic of multiple system atrophy and pure autonomic failure.

We know much more about what goes wrong with the sympathetic noradrenergic system than with other parts of the autonomic nervous system in dysautonomias.

In general, there are two ways dysautonomias can result from altered function of the sympathetic noradrenergic system (SNS). The first is when the system is activated to take over when another system fails. This is called compensatory activation. The second is when there is an abnormality of the SNS itself. There are also two general ways that function of the SNS can be abnormal. The first is underactivity of the system, and the second is overactivity of the system. Both underactivity and overactivity of the SNS can be persistent and long-term or can be occasional and short-term—in other words, chronic or episodic.

An example of acute sympathetic noradrenergic failure is fainting associated with decreased sympathetic noradrenergic system outflow to skeletal muscle. An example of chronic sympathetic noradrenergic failure is neurogenic orthostatic hypotension associated with loss of sympathetic noradrenergic nerves. An example of acute sympathetic noradrenergic activation is paroxysmal hypertension during a hemorrhagic stroke with increased sympathetic noradrenergic

Four Types of Dysautonomia

Autonomic Failure Acute	Autonomic Failure Chronic
Autonomic Stimulation Acute	Autonomic Stimulation Chronic

One approach to classifying dysautonomias is based on failure vs. stimulation and acute vs. chronic.

outflows. An example of chronic sympathetic noradrenergic activation is hypernoradrenergic hypertension.

The same 2 X 2 approach based on acute vs. chronic and failure vs. stimulation applies to other components of the autonomic nervous system.

The Ironic Case of John Hunter

Normal changes in activities of the autonomic nervous system can be harmful or even lethal in the setting of an independent disease state.

For instance, in patients with coronary heart disease, what would otherwise be considered physiologic responses to emotional distress can provoke attacks of chest pressure (angina pectoris) and even sudden death. One of the earliest and best-documented—and surely the most ironic—illustrations of this phenomenon was the case of Dr. John Hunter, the renowned academic surgeon considered to be the father of experimental pathology in England.

His colleague, William Heberden, gave the first clear description of angina pectoris as a symptom of coronary artery disease. In March, 1775, Hunter performed an autopsy on one of Heberden's patients who had died suddenly during a violent spell of anger. Hunter described coronary arteriosclerosis when he observed, "The two coronary arteries, from their origin to many of their ramifications upon the heart, were become one piece of bone."

Hunter was notoriously prone to defensive argument, irrational outbursts, obstinance, and impatience—what in modern times would be called a "hostile Type A." In 1785, Hunter began to experience the same angina pectoris that Heberden had described. Hunter's brother-in-law, Everard Home, wrote:

...the first attack of these complaints was produced by an affection of the mind, and every future return of any consequence arose from the same cause; and although bodily exercise, or distention of the



Dr. John Hunter, from a portrait by Sir Joshua Reynolds

stomach, brought on slighter affections, it still required the mind to be affected to render them severe; and as his mind was irritated by trifles, these produced the most violent effects on the disease. His coachman being beyond his times, or a servant not attending to his directions, brought on the spasms, while a real misfortune produced no effect....

Home described eloquently the prolonged episodes of severe chest pain from which Hunter suffered. These episodes were accompanied by pallor followed by swooning:

I was with him during the whole of this attack, and never saw anything equal to the agonies he suffered; and when he fainted away, I

thought him dead...

Heberden himself diagnosed Hunter with angina pectoris, and Hunter claimed, “My life is in the hands of any rascal who chooses to annoy or tease me.”

This proved to be one of the most ironic statements in the history of medicine. As Home wrote:

“On October 16, 1793, when in his usual state of health, he went to St. George's Hospital, and meeting with some things which irritated his mind, and not being perfectly master of the circumstances, he withheld his sentiments, in which state of restraint he went into the next room, and turning around to Dr. Robertson, one of the physicians of the hospital, he gave a deep groan and dropt down dead.”

The story—and irony—does not end here. Hunter’s body was autopsied, and Home supervised the procedure. The examination confirmed the cause of Hunter’s death to be atherosclerosis. His myocardium was scarred, and his coronary arteries were so calcified Home described them as “bony tubes.”

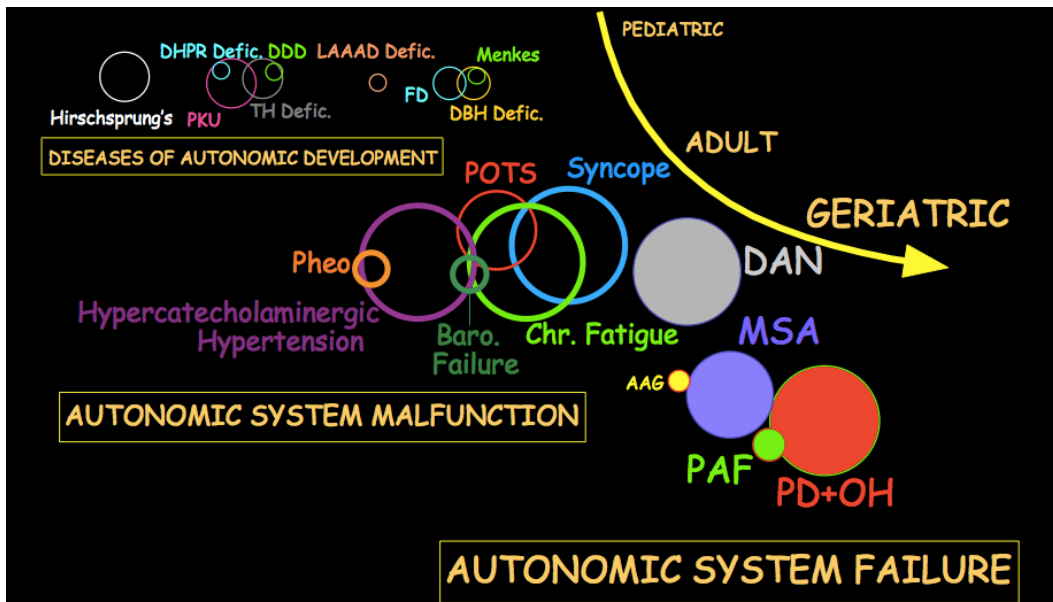
Bony tubes, but not tubes clogged with clot. Hunter did not die of a coronary thrombosis. He also did not die of congestive heart failure, which produces cardiac enlargement, since according to Home, “The heart itself was very small, appearing too little for the cavity in which

it lay, and did not give the idea of its being the effect of an unusual degree of contraction, but more of its having shrunk in its size.”

Given Hunter’s previous prolonged episodes of emotion-provoked severe chest pain accompanied by pallor and followed by faintness and collapse, one may speculate that adrenaline release in the setting of coronary artery disease incited a lethal positive feedback loop. That is, emotion evoked sympathetic adrenergic system activation. The adrenaline-induced increase in myocardial oxygen consumption was not balanced by an increase in oxygen supply because of the rigidified coronary arteries. The imbalance elicited angina pectoris. The angina pectoris exacerbated the distress and thereby the adrenaline secretion, precipitating a lethal arrhythmia.

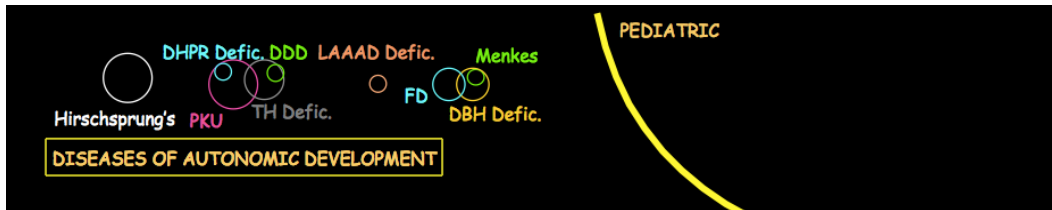
WHEN IN LIFE DO DYSAUTONOMIAS OCCUR?

Different types of dysautonomia occur in the different stages of life.



The Dysautonomias "Universe." There are many forms of dysautonomia, which can occur at any age.

In infants and children, dysautonomias often reflect problems in the development of the autonomic nervous system.



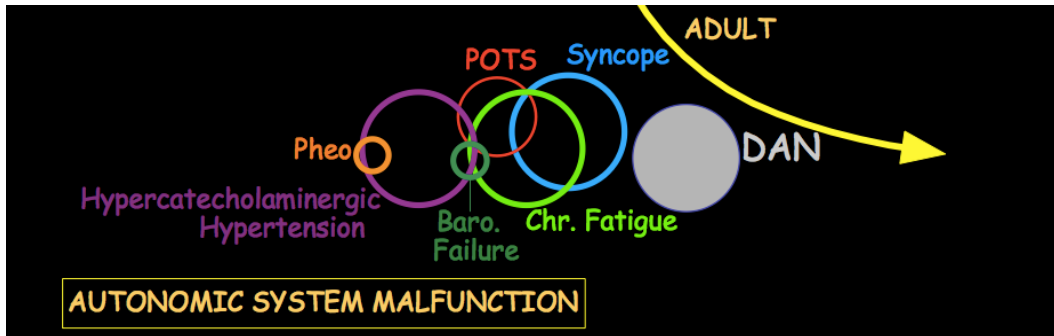
In infants and children, dysautonomias often reflect disorders of development of the autonomic nervous system.

Frequently the cause is a genetic change, called a mutation. A mutation is like a “typo” in the genetic encyclopedia. One type of mutation, found in people of Ashkenazi extraction, causes familial dysautonomia. Another mutation produces dysautonomias in children because of a type of phenylketonuria (PKU). Another causes “kinky hair disease” (Menkes disease). There are also genetic diseases of proteins required for synthesizing or storing catecholamines. In general, dysautonomias from genetic mutations are rare.

In Hirschsprung’s disease, there is a lack of development of nerve cells of the enteric nervous system in the colon, usually without an identified mutation.

In adults, dysautonomias usually reflect functional changes in a generally intact autonomic nervous system.

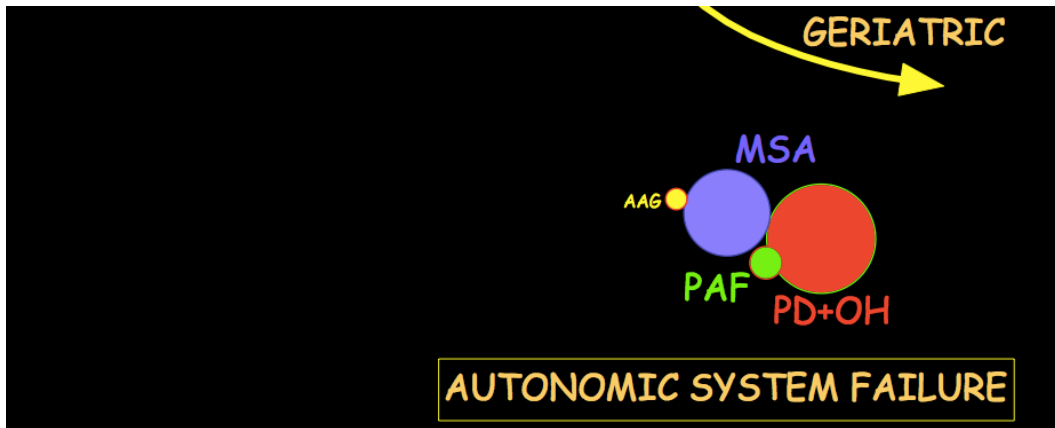
Examples are neurocardiogenic syncope (also called autonomically mediated syncope or reflex syncope), in which the person suffers from



In adults, dysautonomias usually reflect functional changes in a generally intact autonomic nervous system.

frequent episodes of fainting or near fainting, postural tachycardia syndrome, in which the person cannot tolerate standing up for long periods and has a rapid pulse rate during standing, and hypernoradrenergic hypertension, in which overactivity of the sympathetic noradrenergic system causes a form of high blood pressure.

Dysautonomias in adults often are associated with—and may be secondary to—another disease process or with a drug. Common secondary causes include medications, diabetes (diabetic autonomic neuropathy, or DAN), chemotherapy for cancer, irradiation of the neck, and alcoholism. Less commonly, activities of components of the autonomic nervous system change in an attempt to compensate for dehydration or low blood volume, a viral infection impacts the



In the elderly, dysautonomias often result from neurodegeneration, loss of nerve cells in the brain or in the autonomic nervous system itself.

autonomic nervous system, or the body attacks itself (as in autoimmune autonomic ganglionopathy, or AAG).

Rarely, dysautonomias in adults reflect genetic mutations. Examples are a rare form of postural tachycardia syndrome (POTS) that is associated with a mutation that decreases the ability to inactivate norepinephrine, the major chemical messenger of the sympathetic nervous system; and failure of sympathetic nervous system due to a mutation of the gene for dopamine-beta-hydroxylase (DBH), which is required to make norepinephrine.

In the elderly, dysautonomia typically reflects a neurodegenerative disease. The degeneration may be in the form of lesions in the central nervous system, as in multiple system atrophy, or in loss of autonomic

nerves, as in Parkinson disease.

We will return to these dysautonomias later in more detail.

HOW ARE DYSAUTONOMIAS CLASSIFIED?

Since dysautonomias can be somewhat mysterious and controversial, doctors can disagree about the diagnostic classification of these disorders.

Doctors can disagree about how to classify dysautonomias.

As you read about the dysautonomias, keep in mind that the particular labels given for many of these conditions are often best guesses. Such labels can refer to essentially the same set of symptoms. Even with the same label, different people can have very different symptoms. Finally, actual mechanisms for many of these conditions are not well understood. Further research will lead to discoveries about the causes of these conditions, and to new, more definitive names for the conditions.

Often—but not always—a diagnosis is made; occasionally the process causing a dysautonomia can be detected early or reversed; and, rarely, development of a dysautonomia can be prevented.

The primary concern for both the patient and the doctor should be symptom management, because effective symptom management provides relief and improves quality of life

CONDITIONS ASSOCIATED WITH AUTONOMIC FAILURE

The autonomic nervous system has component sub-systems, which can be affected differently in dysautonomias. It is quite rare for the entire autonomic nervous system to fail.

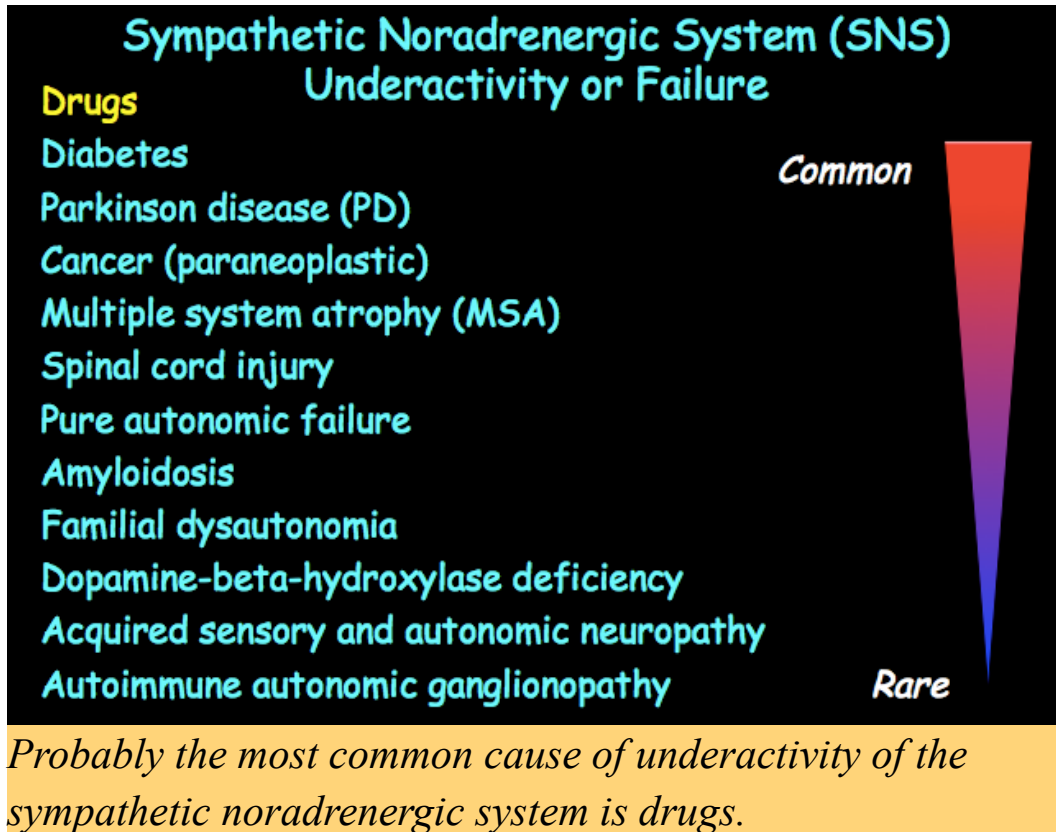
Underactivity of the entire autonomic nervous system as part of a disease is rare.

This section describes the symptoms and signs of underactivity of the sub-systems.

Probably the most common cause of underactivity or failure of the sympathetic noradrenergic system (SNS) is drugs.

Several drugs are known to inhibit functions of the sympathetic noradrenergic system. These include adrenoceptor blockers, tricyclic antidepressants, clonidine, and prednisone.

Among diseases, diabetes probably is the most common cause of sympathetic nervous system underactivity. Primary causes of sympathetic nervous system failure, such as familial dysautonomia and autoimmune autonomic ganglionopathy, are rare. SNS failure



may occur in the setting of a cancer or as a side effect of chemotherapy.

Sympathetic noradrenergic system failure typically manifests as orthostatic hypotension. It can also produce low blood pressure after eating a meal (post-prandial hypotension), after exercising, or upon exposure to warm temperature. SNS failure is associated with a tendency to have less than the normal increase in the force and rate of the heartbeat during exercise. This could manifest clinically as

fatigue, shortness of breath with exercise, or exercise intolerance.

A fall in blood pressure when the patient stands (orthostatic hypotension) is an important sign of failure of the sympathetic noradrenergic system.


In some forms of dysautonomia there is a loss of nerves of the SNS, and the loss is associated with orthostatic hypotension. About 1/3 of patients with Parkinson disease have orthostatic hypotension, and all such patients have at least some loss of sympathetic noradrenergic nerves. By definition, pure autonomic failure patients have sympathetic noradrenergic deficiency.

The parasympathetic nervous system is underactive in some common conditions, including heart failure, diabetes, and Parkinson disease. These conditions can also feature underactivity of the sympathetic noradrenergic system (diabetes is an example) or overactivity of the sympathetic noradrenergic system (heart failure is an example).

Parasympathetic nervous system functions tend to decrease also with normal aging. Underactivity of the parasympathetic nervous system probably mainly reflects decreased nervous system outflow from the brain, rather than loss of parasympathetic nerves.

When the parasympathetic nervous system is underactive, the person

Parasympathetic Nervous System (PNS) Underactivity or Failure

Drugs	
Diabetes	
Heart failure	
Aging	
Sjogren's syndrome	
Parkinson disease (PD)	
Multiple system atrophy (MSA)	
Pure autonomic failure (PAF)	
Autoimmune autonomic ganglionopathy	
	<i>Common</i>
	<i>Rare</i>

Some conditions associated with parasympathetic nervous system (PNS) underactivity or failure

has a dry mouth (and consequently a raspy voice), constipation, a tendency to retain urine in the bladder, a relatively fast pulse rate, dry eyes, and, in men, erectile failure. Several drugs can cause these symptoms, such as drugs for urinary incontinence or diarrhea.

Parasympathetic nervous system underactivity produces many symptoms, such as dry mouth, constipation, urinary problems, decreased tear production, and (in men) inability to have an erection.

Since acetylcholine is the main chemical messenger used by the sympathetic nervous system for sweating, while norepinephrine is the main chemical messenger used by the sympathetic nervous system to tighten blood vessels and maintain blood pressure during standing, a patient with a specific problem in the production, release, or receptors for norepinephrine could have orthostatic hypotension and yet sweat normally; and a patient with a specific problem in the production, release, or receptors for acetylcholine could have decreased sweating and yet not have orthostatic hypotension.

Sweating and blood pressure are “automatic” functions controlled by different chemicals.

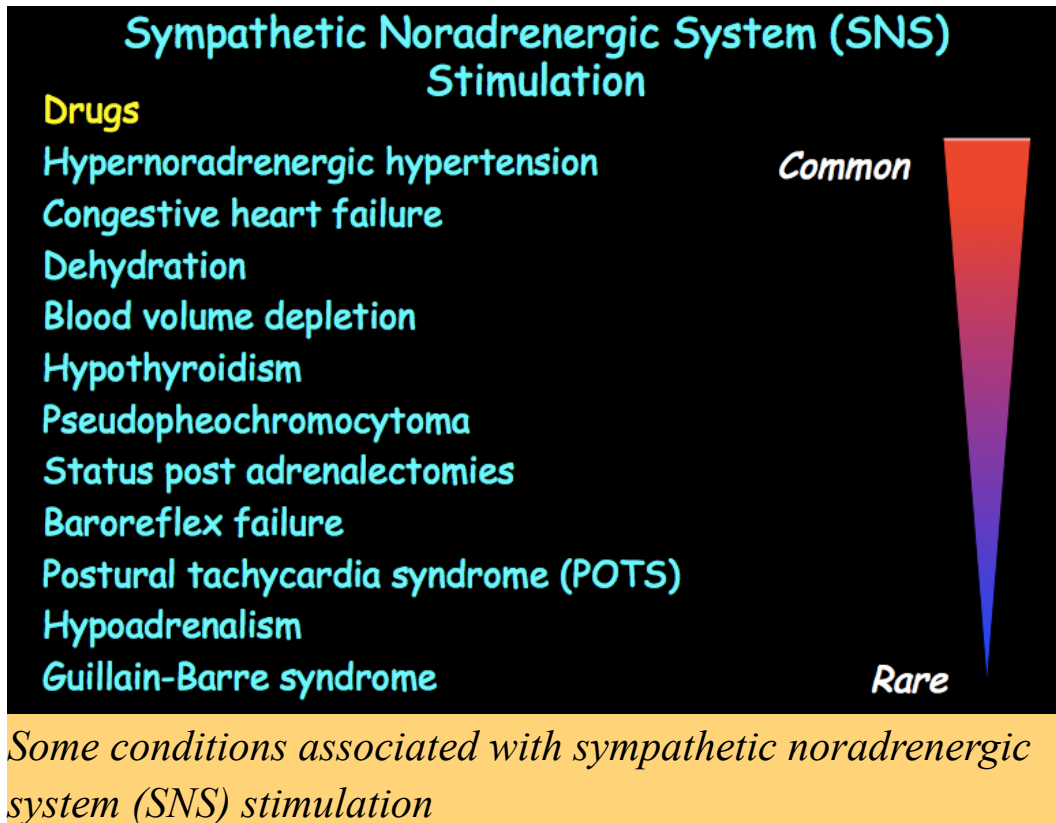
Unlike the parasympathetic cholinergic system and the sympathetic noradrenergic system, which play important roles in everyday activities such as digesting and standing up, the sympathetic adrenergic system is associated with responses to global metabolic challenges or threats to survival. When you are at rest, your adrenal glands release very little adrenaline into the bloodstream, and plasma adrenaline levels are so low that until relatively recently they were below the limit of detection of available assay methods. It is unclear if under resting conditions there are any symptoms from sympathetic adrenergic system failure.

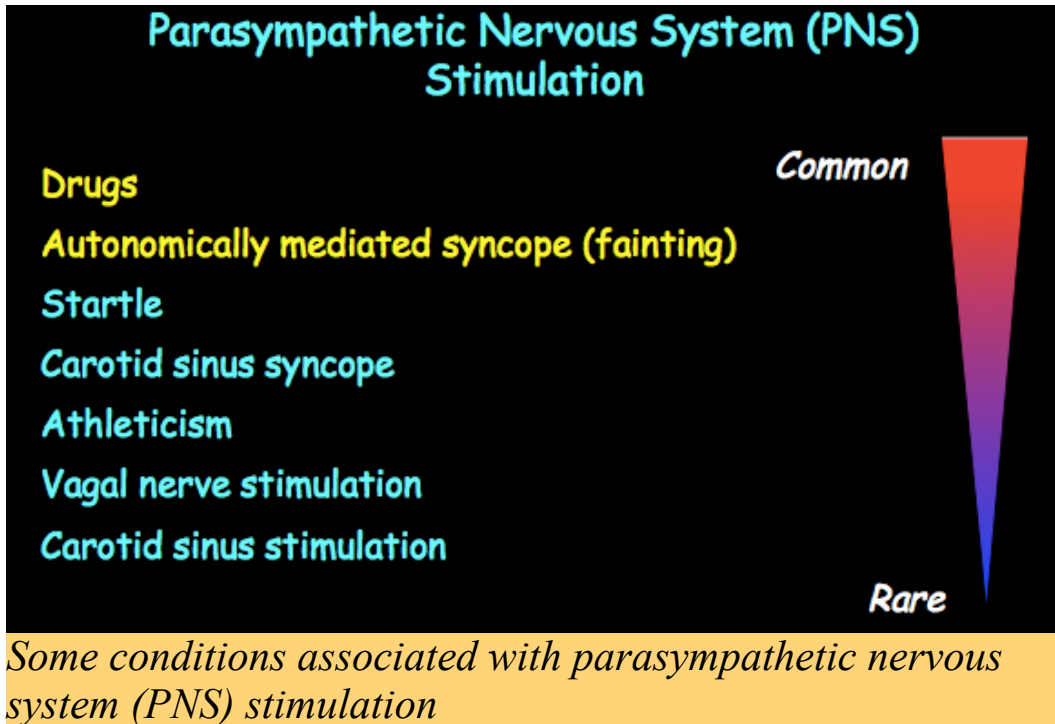
Adrenaline is one of the body’s main hormones for regulating blood levels of glucose, which is a key metabolic fuel. Hypoglycemia evokes profound increases in plasma adrenaline levels. Effects on the

sympathetic noradrenergic system in this setting are more subtle. Failure of the sympathetic adrenergic system therefore might be expected to cause a tendency to low glucose levels. In patients who have diabetes and take injections of insulin, failure or blockade of the sympathetic adrenergic system can result in susceptibility to severe hypoglycemia reactions to the insulin.

Failure of the adrenomedullary hormonal system might cause a tendency to low glucose levels (hypoglycemia).

CONDITIONS ASSOCIATED WITH AUTONOMIC STIMULATION





Sympathetic Adrenergic System (SAS) Stimulation

Drugs

Autonomically mediated syncope (fainting)

Distress

Panic/terror

Hypoglycemia

Postural tachycardia syndrome (POTS)

Shock

Asphyxia

Stress cardiopathy

Hypothermia

Adrenomedullary hyperplasia

Common

Rare



Some conditions associated with sympathetic adrenergic system (SAS) stimulation

Sympathetic Cholinergic System (SCS) Stimulation

Drugs

Heat exposure

Gustatory stimulation (chili peppers)

Emotion

Menopause

Frey's syndrome in diabetes

Hyperhidrosis

Common

Rare

Some conditions associated with sympathetic cholinergic system (SCS) stimulation

WHAT IS ORTHOSTATIC HYPOTENSION?

Normally when you stand up you don't notice much that is different. Nevertheless, there are several automatic, largely unconscious, reflexive changes that are required for maintaining delivery of blood to the brain in response to the seemingly simple act of standing up. When the reflexes fail, you can't tolerate standing still upright.

Orthostatic hypotension is a sign, something a doctor can observe or measure that provides objective evidence of a disease. Inability to tolerate standing up, or orthostatic intolerance, is a symptom, a complaint about something abnormal a person notices that provides subjective evidence of a disease.

Orthostatic hypotension: a 20 point or larger fall in blood pressure after a person stands up for a few minutes from lying down.

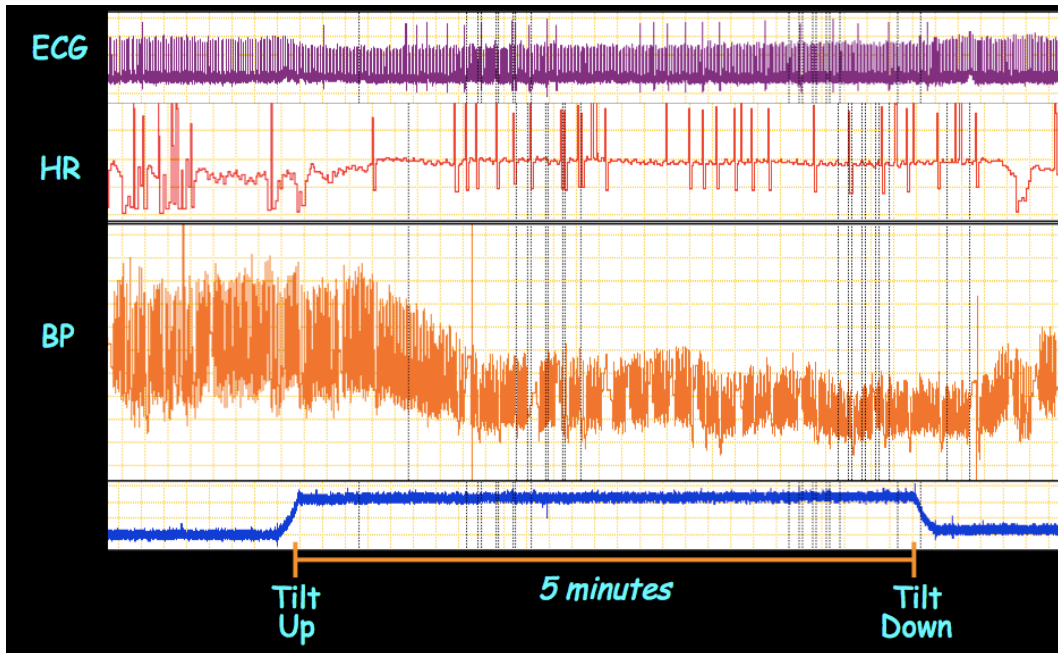
Orthostatic hypotension refers to a persistent, consistent problem, not episodes. If the systolic blood pressure persistently and consistently falls by more than 20 millimeters of mercury (mmHg) between lying flat and standing up, this is orthostatic hypotension. By consensus, experts define orthostatic hypotension in terms of a fall in the systolic blood pressure by at least 20 mmHg and a fall in diastolic blood pressure by at least 10 mmHg between lying down and standing up at least 3 minutes. Doctors sometimes use different definitions, but the

20 mm Hg fall in systolic blood pressure seems to be a common theme in research reports. If the blood pressure while lying down is very high, then more than a 20 mmHg fall in systolic pressure may be required for the doctor to diagnose orthostatic hypotension.

The level of the blood pressure, as well as levels of all the main numbers of the body, such as your temperature, your oxygen level, and your glucose level, are kept in check by reflexes. You can think of reflexes in terms of negative feedback loops. When your blood pressure falls, such as because of injection of a drug that relaxes blood vessels, sensors convey this information to the brain. The brain directs activation of the sympathetic noradrenergic system, which tightens the blood vessels, tending to bring the blood pressure back up.

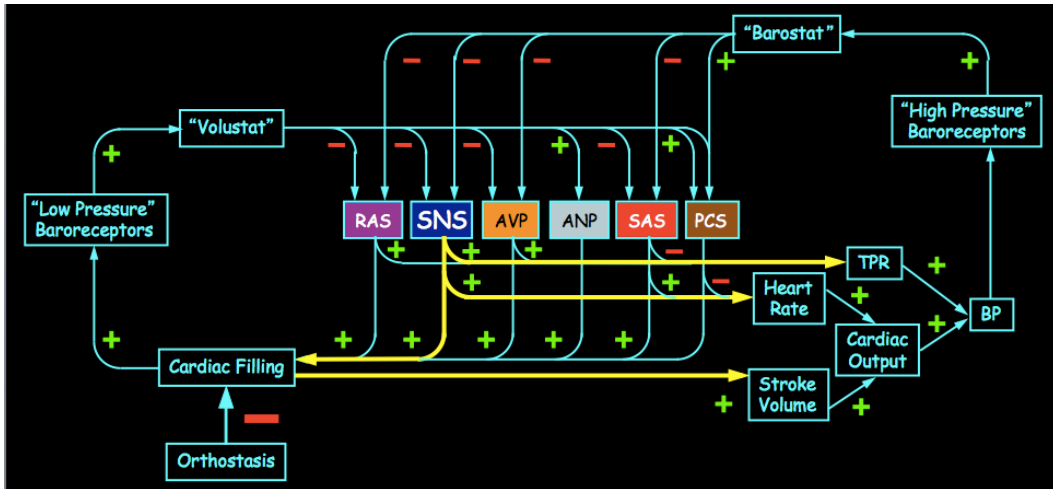
Orthostatic hypotension is a key sign of failure to tighten blood vessels reflexively by activation of the sympathetic noradrenergic system. In other words, orthostatic hypotension is a sign of sympathetic neurocirculatory failure.

Because of the importance of the sympathetic noradrenergic system (SNS) for automatic responses of the blood vessels, when this part of the sympathetic nervous system is underactive the blood pressure falls when the person stands up. This phenomenon is called neurogenic orthostatic hypotension.



A fall in blood pressure when the patient stands up or is tilted head-up on a tilt table (orthostatic hypotension) is an important sign of failure of the sympathetic noradrenergic system.

Many factors besides failure of the sympathetic noradrenergic system, however, can cause orthostatic hypotension. Prolonged bed rest for virtually any reason can do this. Indeed, in the American space program, a study of normal volunteers found that after prolonged bed rest with the head slightly down, healthy people can have orthostatic hypotension. It should not be surprising that elderly, bedridden patients also often have orthostatic hypotension.



A complex neuroendocrine network maintains blood pressure during upright posture (orthostasis). The sympathetic noradrenergic system (SNS) is the main effector system in this network.

Orthostatic hypotension can also result from conditions that cause depletion of blood volume, such as heavy menstrual periods or gastrointestinal hemorrhage from a bleeding ulcer. Any of several drugs can do this, including tricyclics, monoamine oxidase inhibitors, and ganglion blockers.

There are many causes of orthostatic hypotension besides sympathetic noradrenergic system failure.

Doctors may have different opinions about the amount of orthostatic hypotension that is clinically significant. Normally the systolic blood

pressure falls slightly during standing up, because the heart is ejecting less blood, and normally the diastolic pressure does not fall at all, because of the constriction of blood vessels in the body as a whole by way of the baroreflex and activation of the sympathetic noradrenergic system.

Some people have a fall in blood pressure, accompanied by lightheadedness, as soon as they get up, but then the blood pressure comes up to normal. Most experts do not consider this to be orthostatic hypotension, because the fall in blood pressure is not sustained. To diagnose orthostatic hypotension, the fall in blood pressure with standing should be a consistent, persistent finding.

Any of several diseases can produce orthostatic hypotension from sympathetic neurocirculatory failure. These include diabetes, amyloidosis, pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson disease (PD), and autoimmune autonomic ganglionopathy (AAG).

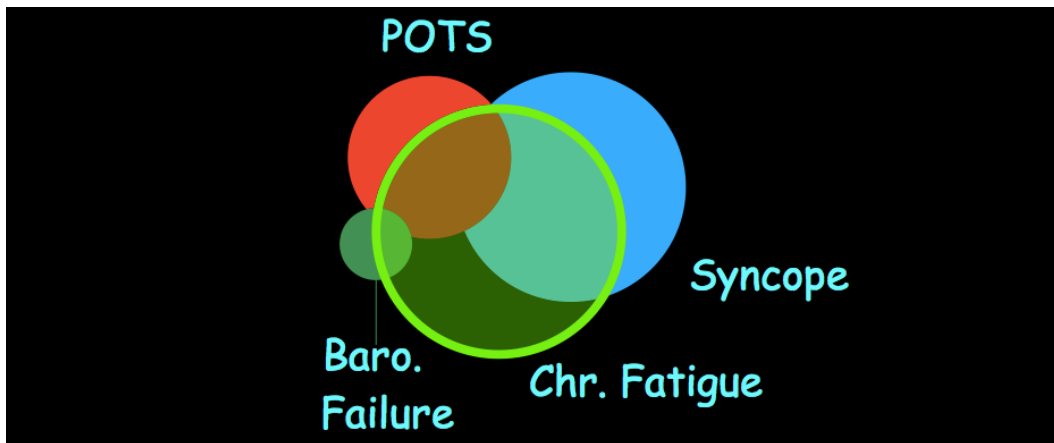
There are several other dysautonomias in which the patients cannot tolerate prolonged standing, even though they do not have persistent, consistent orthostatic hypotension. These disorders come under the heading of chronic orthostatic intolerance.

WHAT IS ORTHOSTATIC INTOLERANCE?

A major way dysautonomias cause problems is by producing orthostatic intolerance.

Patients with orthostatic intolerance can't tolerate prolonged standing.

Neither orthostatic intolerance nor orthostatic hypotension is a diagnosis, which is a decision about the cause of a specific case of



Chronic orthostatic intolerance occurs as part of several conditions. About 60% of patients with chronic fatigue syndrome have chronic orthostatic intolerance.

disease.

About 60% of patients with chronic fatigue syndrome have chronic

orthostatic intolerance, with postural tachycardia syndrome (POTS), neurocardiogenic syncope (fainting), or both. Much less commonly, chronic orthostatic intolerance can be a manifestation of arterial baroreflex failure.

Remember that orthostatic intolerance is based on symptoms, such as dizziness or lightheadedness while standing. Orthostatic intolerance is not a sign, because it isn't something an observer can measure objectively. And it isn't a disease, although there are many diseases that produce orthostatic intolerance.

The fact that there are many possible causes of orthostatic intolerance poses a challenge to any doctor trying to come up with a diagnosis to explain orthostatic intolerance in a particular patient. A starting point in identifying a cause of orthostatic intolerance is to determine whether the patient has failure of the sympathetic nervous system to regulate the heart and blood vessels correctly. We call this sympathetic neurocirculatory failure. In dysautonomias that produce chronic sympathetic neurocirculatory failure, the patient always has a fall in blood pressure during standing, or orthostatic hypotension.

In other forms of chronic orthostatic intolerance, the person does not have sympathetic neurocirculatory failure, and the blood pressure does not fall consistently when the person stands up (although the person can have delayed orthostatic hypotension after many minutes of standing). Instead, the person feels dizzy or lightheaded during standing, even while the blood pressure is maintained. Orthostatic

hypotension can produce orthostatic intolerance, but orthostatic intolerance can occur without orthostatic hypotension.

In the evaluation of a patient with chronic orthostatic intolerance, in which the patient does not have evidence of sympathetic neurocirculatory failure, doctors often prescribe a tilt table test. The chapter about testing for dysautonomias discusses the tilt table test. In general, there are two types of positive tilt table test result. If the patient has an excessive, progressively more severe increase in pulse rate during the tilting, then this would be consistent with postural tachycardia syndrome, or POTS. If the patient suddenly has a decrease in level of consciousness or actually loses consciousness (syncope), then this would be consistent with neurocardiogenic syncope (also called autonomically mediated syncope, reflex syncope, or fainting). The loss of consciousness is virtually always associated with a fall in blood pressure, (neurally mediated hypotension). A tilt table test can also yield results consistent with both POTS and neurocardiogenic syncope, such as when the patient has a large increase in pulse rate, followed by a sudden fall in pulse rate back to normal, but with neurally mediated hypotension and syncope.

Once a diagnosis of POTS is made, the workup may continue, to determine if the rapid pulse is part of a primary problem or is part of a compensation in which activity of the sympathetic noradrenergic system outflow to the heart is increased. The section about POTS discusses this workup.

Fainting involves sudden changes in autonomic functions that, taken together, decrease blood flow to parts of the brain required for consciousness. Between episodes of fainting, patients with repeated bouts of neurocardiogenic syncope often do not feel well, and they complain of non-specific symptoms such as fatigue, heat intolerance, headache, chronic pain, exercise intolerance, and orthostatic intolerance.

Doctors often do tilt table testing in patients who cannot tolerate standing (orthostatic intolerance) and do not have a fall in blood pressure during standing (orthostatic hypotension).

Uncommonly, orthostatic intolerance reflects failure of the baroreflex. In this situation, the sympathetic noradrenergic system is not activated appropriately in response to a decrease in blood pressure or in response to a decrease in venous return to the heart.

Baroreflex failure does not consistently cause orthostatic hypotension, but it always causes large swings in blood pressure, both high and low, because of the inability of the baroreflex to keep the blood pressure within limits. Baroreflex failure occurs in some people years after irradiation of the neck, such as for treating a cancer. The radioactivity exposure accelerates aging-related stiffness of the carotid arteries in the neck—arteriosclerosis. Since the baroreceptors are distortion receptors, the stiffening interferes with the ability of the

baroreceptors to sense changes in blood pressure.

Without this information, the brain cannot reduce swings in blood pressure. Baroreflex failure is also a known complication of tumors and surgery for tumors in the lower brainstem, because this is the location of the “barostat” for blood pressure regulation.

Orthostatic intolerance can be associated with abnormal levels of adrenaline-like chemicals.

Measurements of plasma levels of norepinephrine and adrenaline can provide useful information in the evaluation of chronic orthostatic intolerance. In patients with chronic orthostatic intolerance from orthostatic hypotension, failure to increase plasma norepinephrine by the normal amount during standing (more than 60% by 5 minutes) can indicate failure to activate the sympathetic noradrenergic system, and an increase in plasma norepinephrine to a high level can indicate recruitment of the sympathetic noradrenergic system as part of an attempt to compensate for decreased venous return to the heart, such as from dehydration. Among patients with chronic orthostatic intolerance who do not have orthostatic hypotension, those with POTS often have high plasma norepinephrine levels when the patients are upright; patients with neurocardiogenic syncope (fainting), with or without POTS, have high plasma adrenaline levels at the time of fainting.

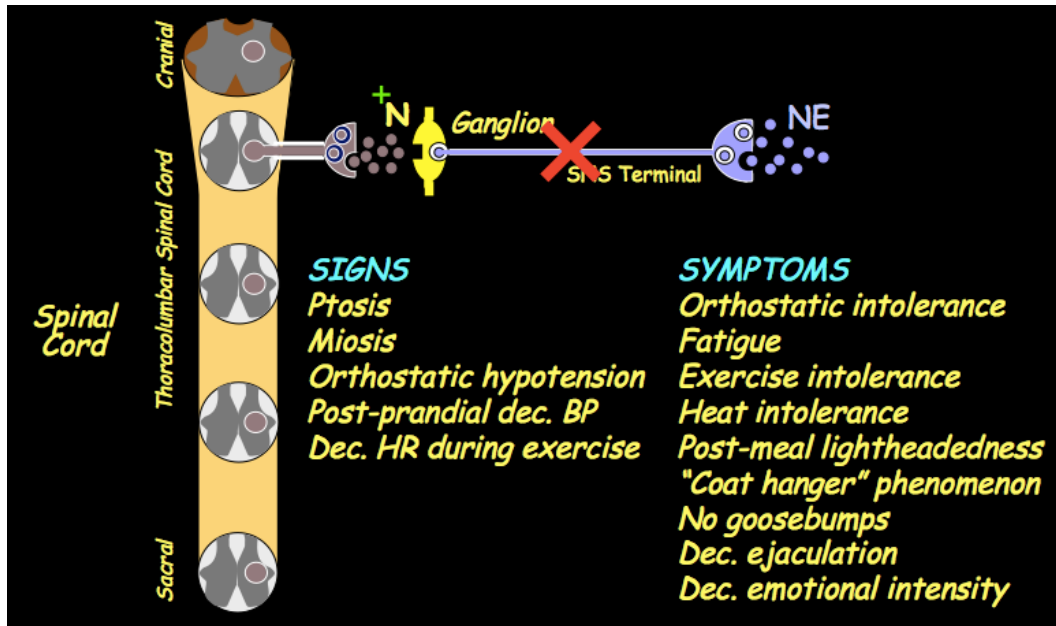
WHAT ARE THE SYMPTOMS AND SIGNS OF DYSAUTONOMIAS?

Symptoms and signs of dysautonomias result from alterations in activities of one or more components of the autonomic nervous system.

Activation or inhibition of the different components of the autonomic nervous system produces different effects on the body.

Symptoms of failure of the sympathetic noradrenergic system include orthostatic intolerance, intolerance of heat or cold, lightheadedness after eating a large meal, fatigue, and exercise intolerance. The main signs of failure of the sympathetic noradrenergic system are inability to maintain blood pressure during standing (orthostatic hypotension), after a meal (post-prandial hypotension), after exercise, or during exposure to heat.

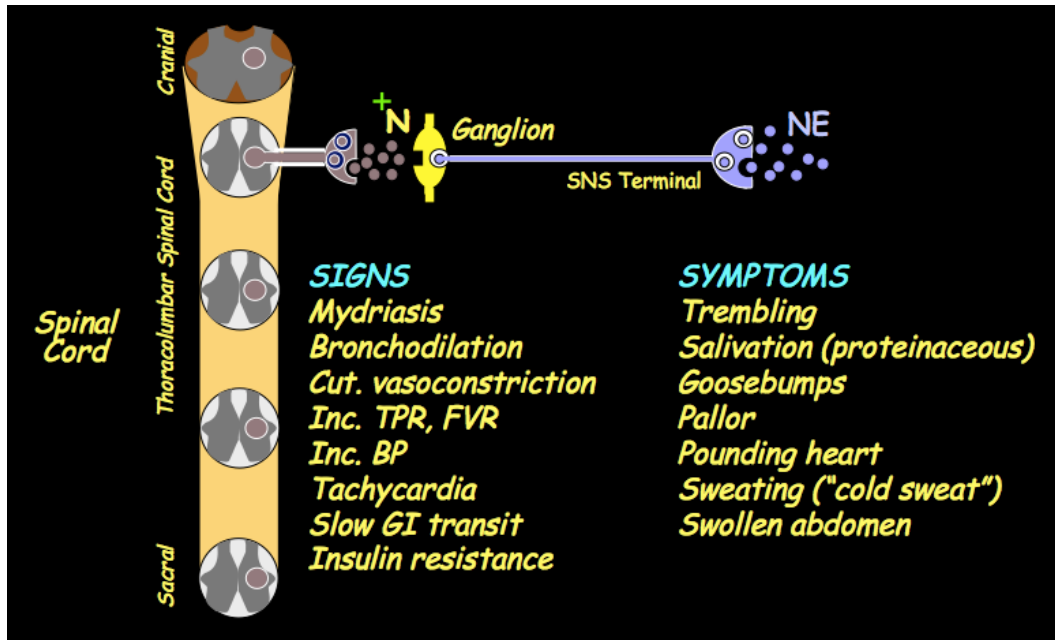
Increased activity of the sympathetic noradrenergic system (SNS) produces its effects via the release of norepinephrine, especially in the blood vessels and heart. The released norepinephrine tightens blood vessels in the skin, kidneys, gut, and skeletal muscle. Because of the constriction of blood vessels in the skin the patient may look pale.



Symptoms and signs of sympathetic noradrenergic system (SNS) underactivity or failure

Norepinephrine released from sympathetic nerves in the skin also causes the hair to stand up and causes goose bumps. Stimulation of the sympathetic nerves in the salivary glands increases the flow of thick saliva. Signs of increased activity of the sympathetic noradrenergic system include increased blood pressure or heart rate, pallor, and trembling.

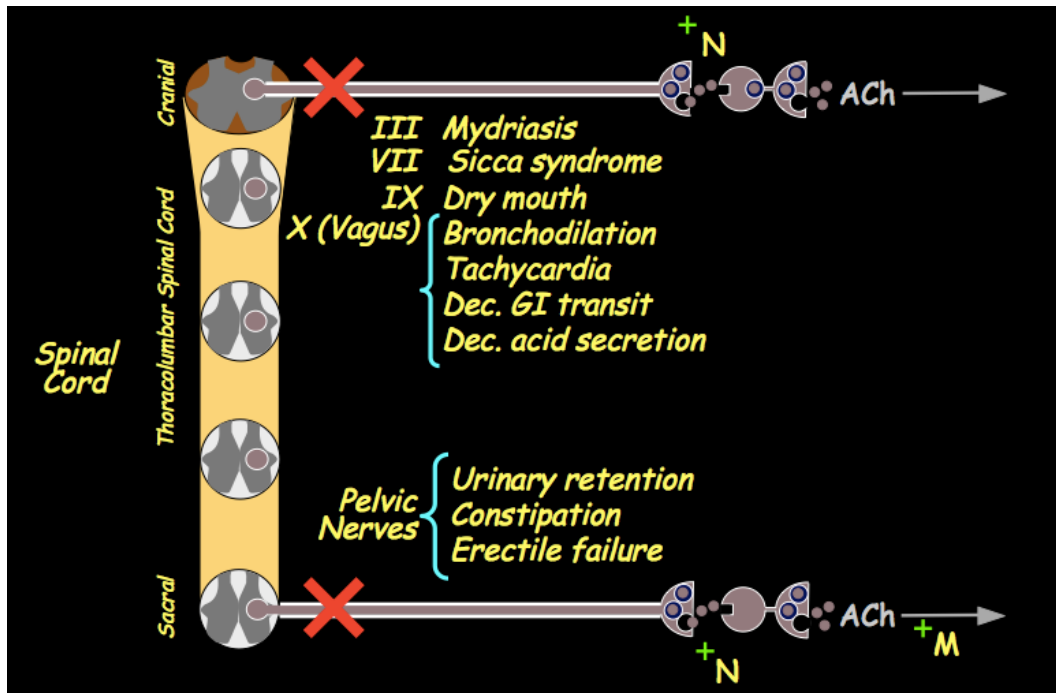
Increased activity of the parasympathetic nervous system produces its effects via release of acetylcholine in several organs of the body.



Symptoms and signs of sympathetic noradrenergic system (SNS) overactivity or stimulation

The patient notes increased gut motions, nausea, urinary urgency or frequency, increased production of watery saliva, increased tear production, and decreased visual adaptation to the dark. Signs of increased activity of the parasympathetic nervous system include slow heart rate, increased bowel sounds, increased salivation and tear production, and constricted pupils.

Symptoms of failure of the parasympathetic nervous system include constipation, dry mouth, dry eyes, difficulty beginning urination, and

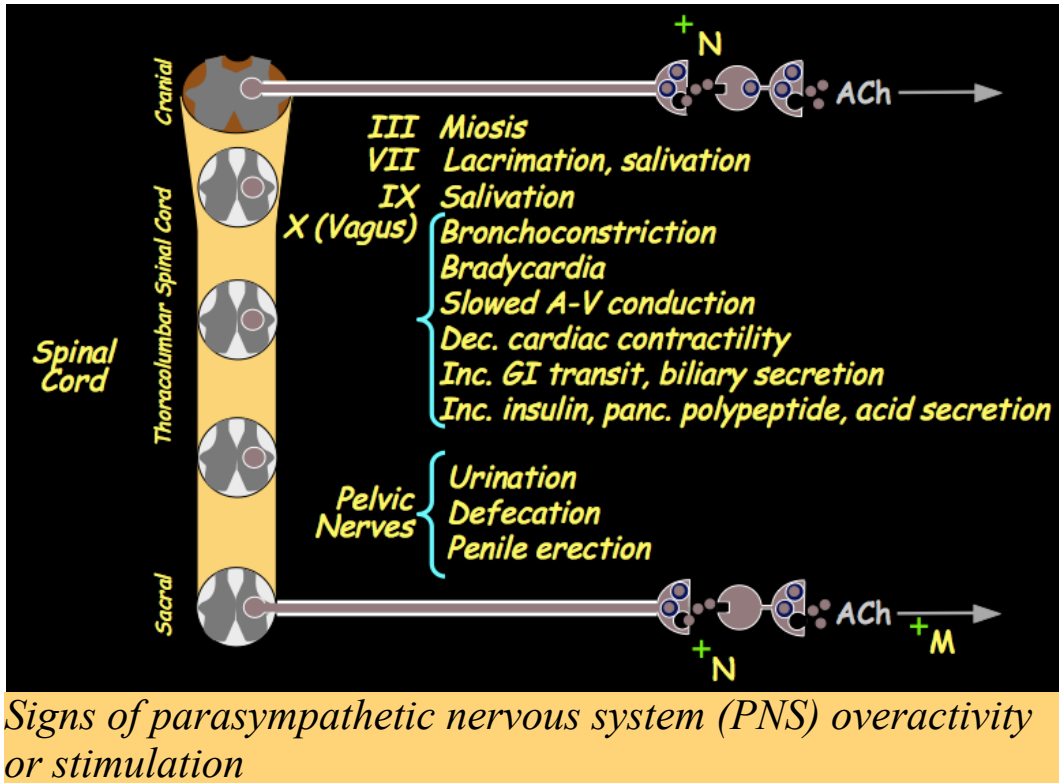


Symptoms and signs of parasympathetic nervous system (PNS) underactivity or failure

erectile failure in men.

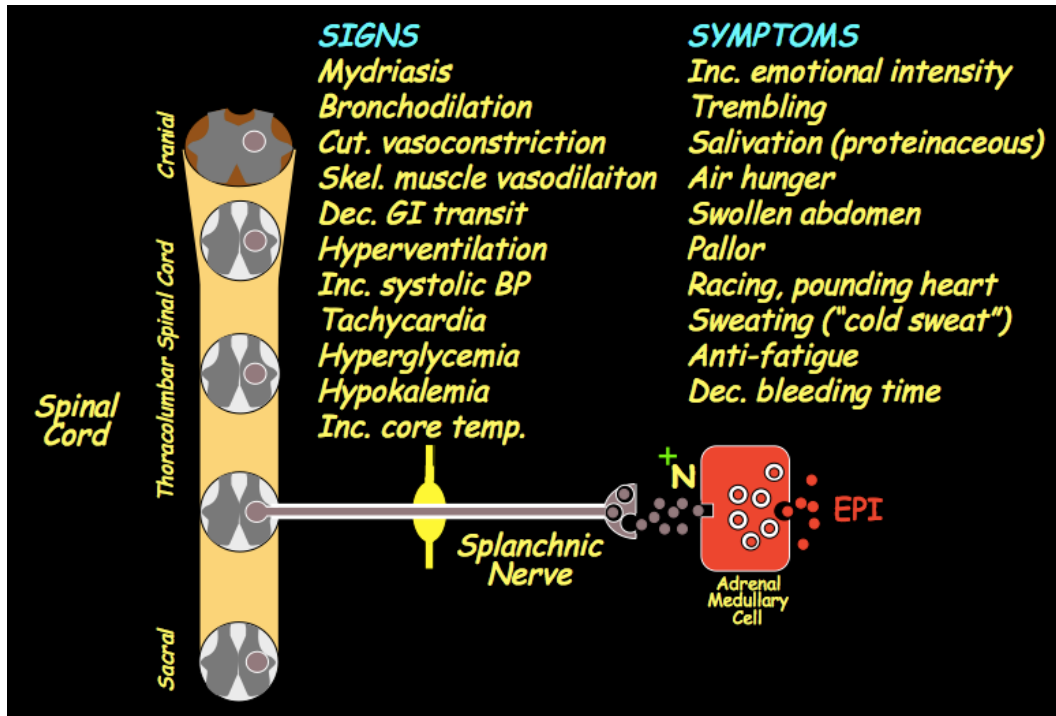
Signs of failure of the parasympathetic nervous system include decreased salivation, a dry, raspy voice, decreased bowel sounds, increased heart rate, and enlarged urinary bladder.

Increased activity of the sympathetic cholinergic system produces its effects via release of acetylcholine at sweat glands. The patient



reports increased sweating, during heat exposure, exercise, after eating (gustatory sweating), during emotional distress, or at rest. The main symptoms and signs of failure of the sympathetic cholinergic system are from decreased sweating.

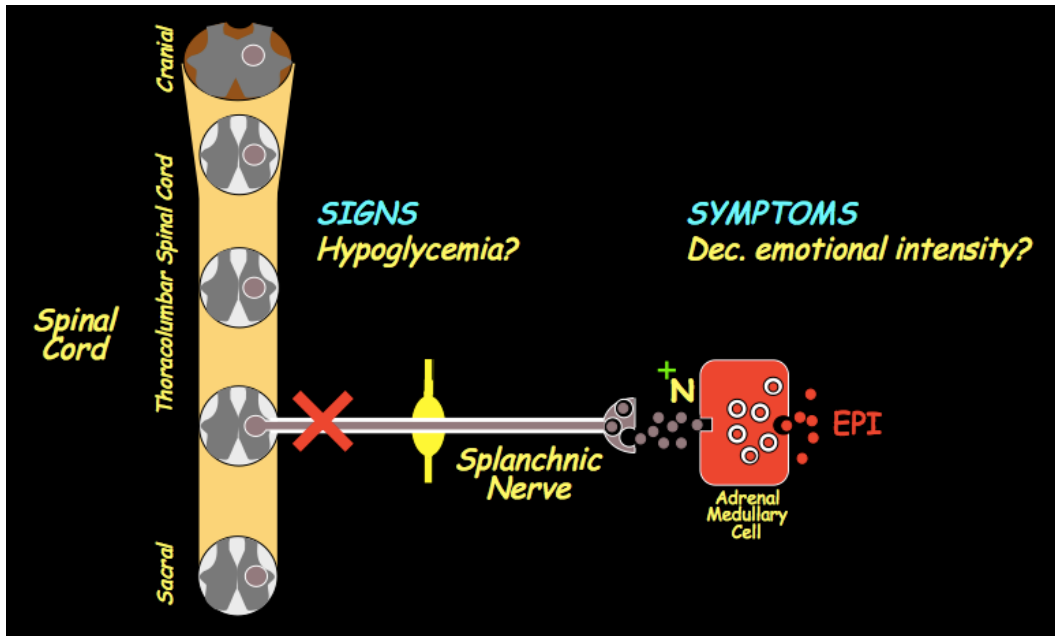
Increased activity of the sympathetic adrenergic system (adrenomedullary hormonal system) produces its effects via release of adrenaline from the adrenal glands. Symptoms of such activation may



Symptoms and signs of sympathetic adrenergic system (SAS) overactivity or stimulation

include a sense of energy or increased emotional intensity, anxiety, a sense of the heart beating (palpitation), or an increased rate or depth of breathing. Signs include paleness of the skin, due to constriction of local blood vessels, trembling, a tendency to decreased bleeding time due to platelet activation, sweating, and increased blood glucose levels.

It is difficult to distinguish alterations in enteric nervous system



There seem to be few symptoms or signs of sympathetic adrenergic system (SAS) underactivity or inhibition.

activity from alterations in parasympathetic nervous system activity in the gut.

Symptoms and signs of altered activities of components of the autonomic nervous system do not necessarily mean that these components are functioning abnormally, since any of a variety of disorders and drugs affect those components.