

**STARS
IN
THE
DYSAUTONOMIAS
UNIVERSE**

In this part you will learn about several specific forms of dysautonomia. The approach is not encyclopedic. The presentation generally follows the sequence in the “dysautonomias universe,” beginning with pediatric, then adult, then geriatric conditions. Within each domain the more common conditions come first.

Although for teaching purposes emphasis is placed on diseases that are known or suspected to involve a primary abnormality of the autonomic nervous system, most dysautonomias in general medical practice reflect harm because of worsening of an independent pathologic state, secondary consequences of another disease, or effects of a drug or other treatment.

Recall the definition of dysautonomia as a condition in which altered function of one or more components of the autonomic nervous system adversely affects health. The old man who has a heart attack while shoveling snow provides an example of damage because of an interaction with an independent disorder—coronary artery disease. Common, chronic disorders such as diabetes, heart failure, kidney failure, and neurodegenerative diseases are all associated with dysautonomias of one kind or another. Drugs and other treatments for any of a variety of problems, from hypertension to benign prostatic hypertrophy to cancer to the common cold, can cause harm by stimulating or inhibiting parts of the autonomic nervous system.

Please bear in mind that the descriptions here are not meant to be

exhaustive, and individual patients can have symptoms that overlap across several disorders.

INHERITED OR CONGENITAL DYSAUTONOMIAS

Several inherited or congenital diseases have been described that feature dysautonomia. The following discussion describes a few of them. Most are severe and become manifest in infancy or childhood.

Inherited forms of dysautonomia are rare.

To understand genetic causes of these diseases you have to know what a mutation is.

A mutation is like a typo in the genetic encyclopedia.

The encyclopedia consists of two sets of 23 volumes (chromosomes) each. The last two volumes are the same size in girls (each volume is X), whereas the last two differ in size in boys (the larger volume X, the smaller Y).

In autosomal dominantly transmitted diseases, even one copy of the mutated gene is sufficient to produce the disease. One-half the family members will inherit the mutation and have the disease (assuming perfect “penetrance”).

In autosomal recessive diseases, both parents have the mutated gene

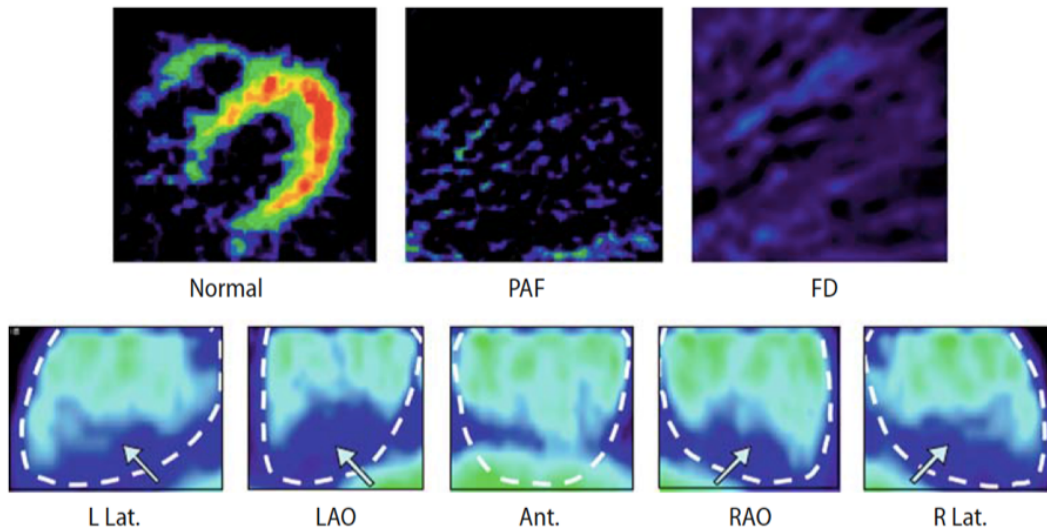
on one of their chromosomes. They are carriers. Since each parent donates one chromosome, the chances are 1/2 that they will donate the chromosome carrying the mutation, and the chances are 1/4 that their offspring will carry the mutation on both chromosomes and have the disease.

In X-linked recessive diseases involving a mutation on the X chromosome, the disease is expressed in boys but not in girls, because the other X chromosome does not carry the mutation. The mothers of boys with an X-linked recessive inherited disease are carriers, because the affected X-chromosome is coming from the mothers. If a known carrier is pregnant with a boy, the chances are 50% that he will have the disease and 50% that he won't—and neither will any of his descendants.

Familial Dysautonomia

The prototype of an inherited dysautonomia is familial dysautonomia (FD), also known as Riley-Day syndrome and hereditary sensory and autonomic neuropathy type III (HSAN III). FD is a rare inherited disease that features abnormalities in sensation and in functions of the autonomic nervous system. FD runs in families of Ashkenazi extraction.

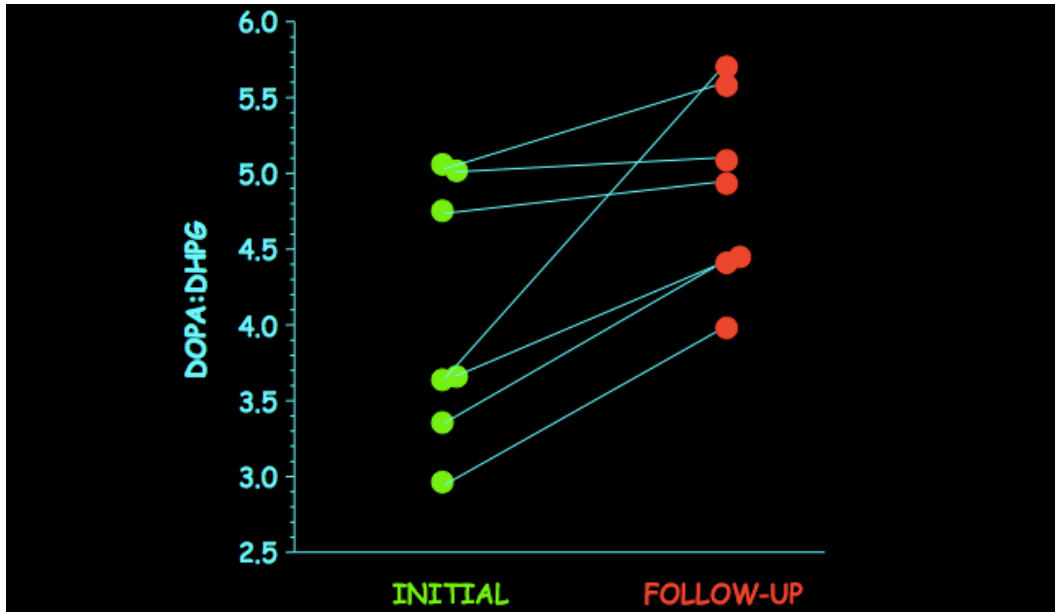
The cause of FD is a mutation of the gene, IKBKAP. The mutation



Familial dysautonomia involves decreased cardiac noradrenergic innervation, especially in the more distal regions of the heart.

results in decreased levels of the protein, IkappaB kinase-associated protein (IKAP), especially in nervous system tissue. The functions of IKAP remain unknown, but it may have something to do with the development of small nerve fibers, such as those of the sympathetic nervous system. With supportive treatment, the outlook for FD patients has improved greatly over recent years; many patients are over 20 years old.

Children with FD have a few signs that are diagnostic, including lack of overflow tears, lack of lingual fungiform papillae, and absence of a



There is evidence for progressive neurodegeneration of sympathetic noradrenergic neurons in FD.

histamine flare reaction. Adult FD patients typically have orthostatic hypotension, associated with subnormal increments in plasma levels of the sympathetic neurotransmitter, norepinephrine, when the patient stands up.

FD patients are prone to crises of vomiting, sweating, fast heart rate, and high blood pressure. The crises can be life-threatening. The patients often have severe orthopedic problems. Because of inability to sense heat, they are at high risk of burns of the mouth or esophagus due to drinking scalding hot liquid.

With genetic screening tests, FD can be detected in utero.

FD seems to involve incomplete development of sympathetic noradrenergic nerves. Adult FD patients have neuroimaging evidence for decreased cardiac sympathetic innervation, especially in the left ventricular free wall. The ratio of DOPA:DHPG in plasma is increased in all FD patients, probably reflecting decreased norepinephrine synthesis. Over the course of the disease there is evidence for progression of the sympathetic noradrenergic denervation, as plasma DOPA:DHPG ratios increase.

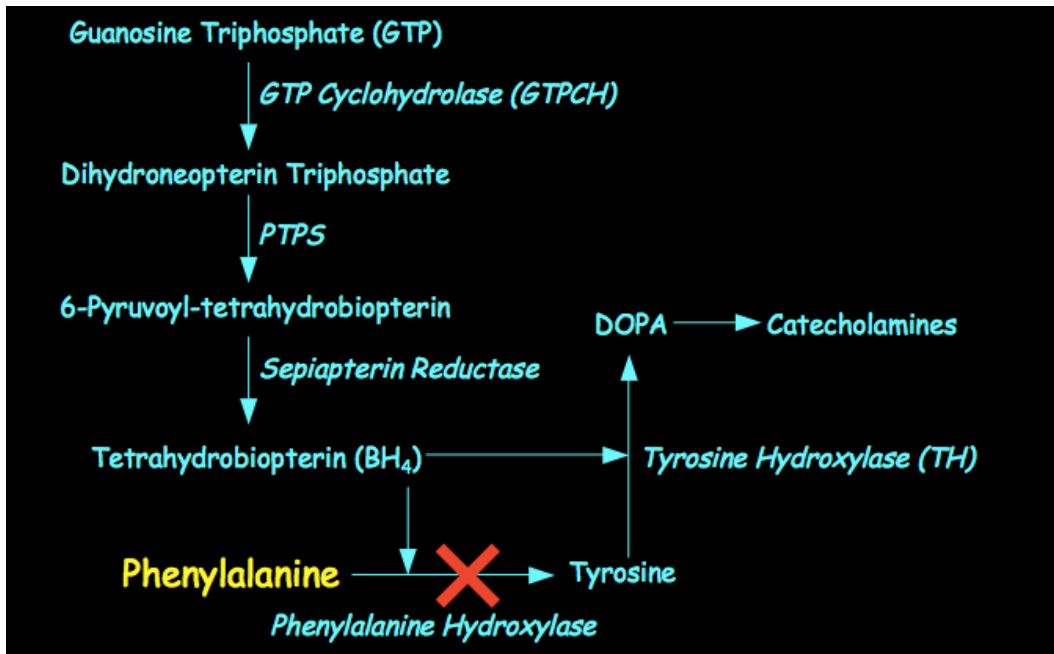
Blood pressure lability in FD patients has been linked with baroreflex failure, due to decreased information coming to the brain from baroreceptors—an afferent lesion.

Diseases of Catecholamine Synthesis

PKU

If you have read the label on a can of diet soda pop that contains the sweetener, aspartame, you have noticed a warning for people with a disease called phenylketonuria (PKU).

People with classic PKU have a deficiency of phenylalanine hydroxylase, the enzyme that converts the amino acid phenylalanine to tyrosine. Due to this deficiency, ingesting foods rich in



PKU results from phenylalanine hydroxylase deficiency.

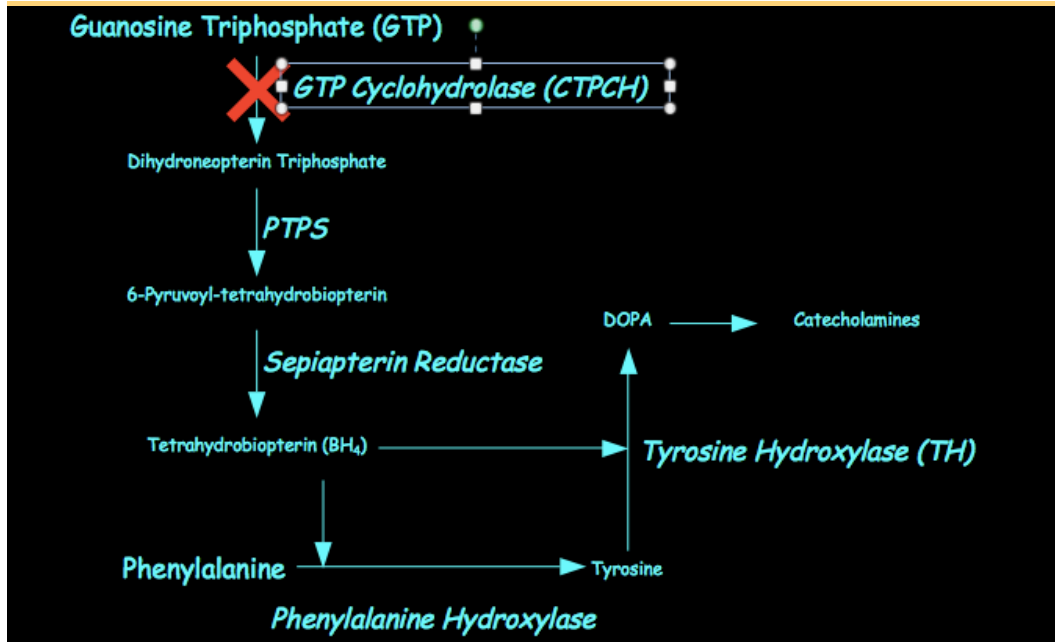
phenylalanine can lead to a buildup of phenylalanine, and too much phenylalanine is toxic, especially in infants and children. Aspartame is broken down to phenylalanine in the body, and so drinking the diet soda pop could cause damage.

For phenylalanine hydroxylase to work requires a co-factor called tetrahydrobiopterin (BH₄). BH₄ is also a required co-factor for tyrosine hydroxylase (TH), so that BH₄ is required for synthesizing catecholamines in the body. BH₄ is also a co-factor for the synthesis of serotonin and nitric oxide.

In dihydropteridine reductase deficiency there is an inability to recycle BH₄. This causes an atypical form of PKU in which even restricting phenylalanine does not protect the infant from developing a neurodegenerative disease, and death occurs in childhood.

DOPA-Responsive Dystonia

GTP cyclohydrolase (GTPCH) is the first enzyme in the synthetic cascade leading to tetrahydrobiopterin (BH₄). Since BH₄ is a co-factor for tyrosine hydroxylase (TH), GTPCH deficiency manifests as a form of parkinsonism with dystonia, called DOPA-responsive dystonia (also called Segawa's disease). The symptoms get worse as the day goes on. Autosomal-dominant DRD comes from mutation of the GTPCH gene. Autosomal-recessive forms of the disease come from mutations of the genes encoding sepiapterin reductase or TH. The disease usually manifests in childhood.

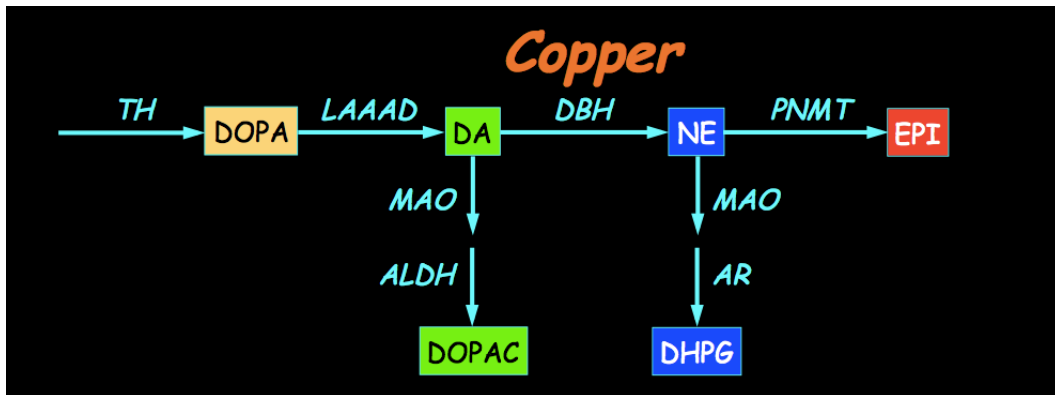


Deficiency of GTP cyclohydrolase results in decreased DOPA synthesis and manifests with DOPA-responsive dystonia.

Menkes Disease

Menkes disease, also known as “kinky hair disease,” is an inherited disorder of copper metabolism. A baby with this disease can seem normal at birth, except for peculiar hair that is a light tan-orange and kinky and exhibits twisted hair shafts. The baby soon fails to meet milestones of development, deteriorates neurologically, and dies in childhood.

The gene that regulates copper metabolism and is mutated in Menkes



Menkes disease is due to abnormal copper handling in the body. DBH is a copper enzyme.

disease is located on the X-chromosome. This means that the disease is confined virtually exclusively to boys.

Copper is required for several important processes in the body. If copper treatment is begun soon enough, Menkes disease patients can have marked improvement in development. In at-risk pregnancies, it is important to diagnose the disease soon after birth, because if the baby had the disease and the disease were caused by a particular mutation, then the baby could respond to injections of copper, but the treatment must begin within a few weeks of birth.

In particular, copper is necessary for normal activity of the enzyme, dopamine-beta-hydroxylase (DBH), which in turn is required for production of norepinephrine in the body. Patients with Menkes

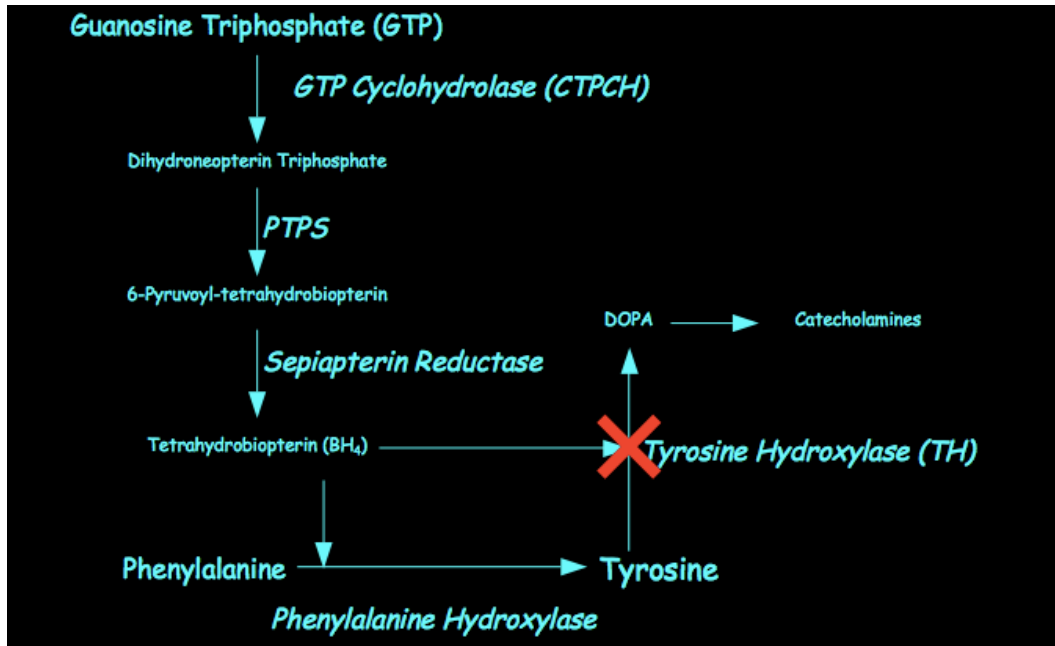


Early copper treatment can markedly improve outcome in Menkes disease.

disease all have a characteristic abnormal neurochemical pattern in the plasma, with elevated levels of DOPA, dopamine and its neuronal metabolite DOPAC, compared to levels of norepinephrine and its neuronal metabolite DHPG. Detecting this pattern has so far proven perfectly sensitive and specific in diagnosing the disease in at-risk newborns, enabling successful early copper treatment.

The enzyme, tyrosinase, catalyzes the first step in the synthesis of melanin, the black pigment in skin and hair. Tyrosinase, like DBH, is a copper enzyme. Low tyrosinase activity probably accounts for the odd hair color in Menkes disease patients.

TH Deficiency



In tyrosine hydroxylase deficiency there is decreased ability to synthesize catecholamines.

Tyrosine hydroxylase (TH) is the rate-limiting enzyme in the biosynthesis of the catecholamines dopamine, norepinephrine, and epinephrine.

TH deficiency is a rare genetic disorder transmitted as an autosomal recessive trait. The deficiency manifests along a wide spectrum from a mild parkinsonian movement disorder developing during childhood to a life-threatening neurological disorder in infancy. As for autosomal Segawa's disease, patients with TH deficiency respond to levodopa treatment.

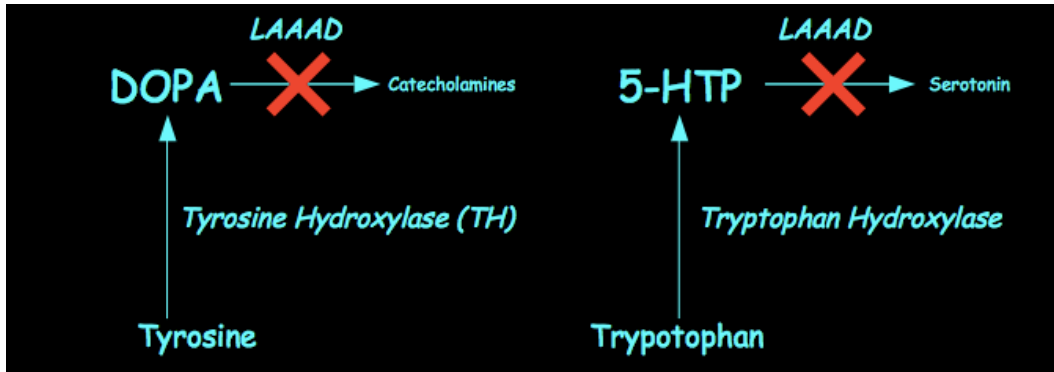
LAAAD Deficiency

L-aromatic-amino-acid decarboxylase (LAAAD, AADC, also called DOPA decarboxylase) catalyzes the conversion of DOPA to the catecholamines and 5-hydroxytryptophan to serotonin (5-hydroxytryptamine). LAAAD uses pyridoxal phosphate (vitamin B6) as a co-factor.

LAAAD deficiency presents as a severe neurological disease in the first year of life. The disease is transmitted as an autosomal recessive trait. The affected infant feeds poorly, startles easily, has disturbed sleep, and experiences episodes of abnormal rotation of the eyeballs (oculogyric crises), irritability, muscle spasms, and involuntary movements.

Because of the inability to synthesize norepinephrine and epinephrine, the patients have low blood pressure (hypotension), a tendency to low blood sugar (hypoglycemia), droopy eyelids (ptosis), nasal congestion, and poor regulation of core temperature. Due to unopposed parasympathetic nervous system influences the pupils are constricted (miosis), and often there is gastroesophageal reflux.

Patients with LAAAD deficiency have a characteristic neurochemical pattern, with high DOPA and 5-hydroxytryptophan levels and low



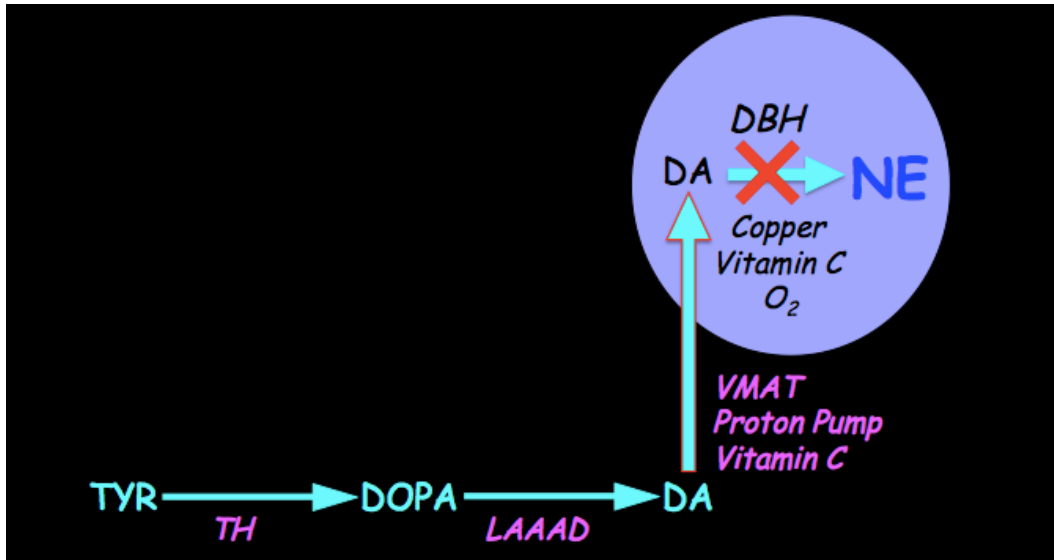
Deficiency of L-aromatic-amino-acid decarboxylase (LAAAD) causes deficiency of catecholamines and serotonin.

levels of catecholamines, catecholamine metabolites, serotonin, and 5-hydroxyindoleacetic acid (5-HIAA).

Treatment with levodopa, 5-hydroxytryptophan, dopamine receptor agonists, serotonin receptor agonists, and cholinergic receptor antagonists may be tried. It has been proposed recently that the patients might benefit from a form of gene therapy based on an adeno-associated virus to increase LAAAD activity.

DBH Deficiency

The enzyme, dopamine-beta-hydroxylase (DBH), is required for production of norepinephrine in the body. Patients with DBH deficiency have orthostatic hypotension and very low plasma norepinephrine levels, even though the sympathetic nervous system is



Patients with DBH deficiency have decreased synthesis of norepinephrine.

intact.

Treatment with L- dihydroxyphenylserine (L-DOPS) bypasses the enzyme deficiency and results in remarkable improvement in patients with DBH deficiency.

The sympathetic cholinergic system is intact in patients with DBH deficiency. They therefore have normal sweating, even though they have sympathetic neurocirculatory failure.

Mice with DBH deficiency on a genetic basis do not survive to birth. How it is that people with DBH deficiency survive and, with

norepinephrine precursor treatment, thrive remains a medical scientific mystery.

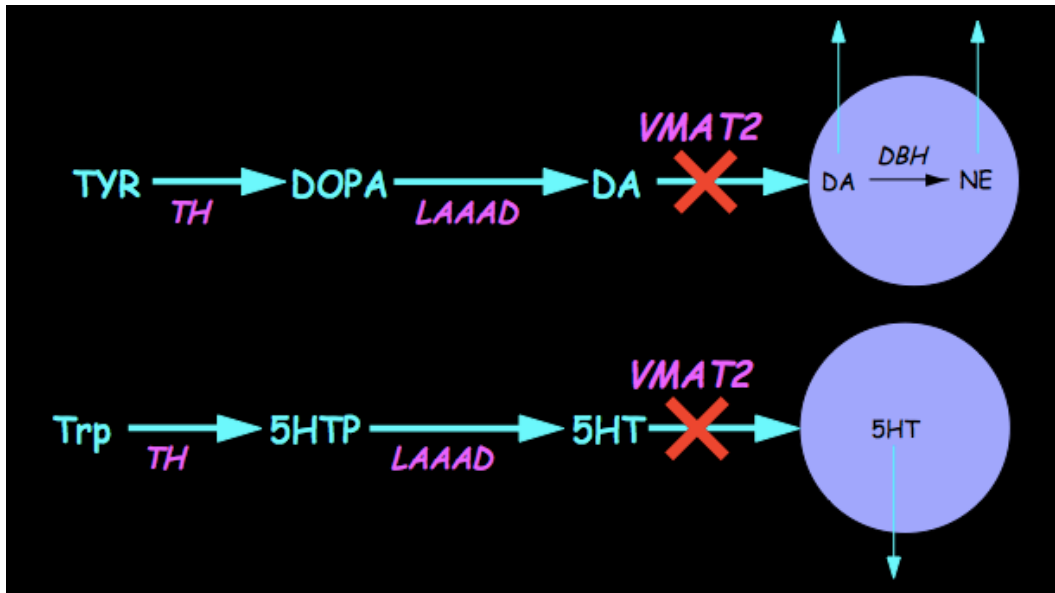
VMAT2 Deficiency

The type 2 vesicular monoamine transporter (VMAT2) transports the monoamines dopamine (DA), norepinephrine (NE), epinephrine (EPI), and serotonin (5-hydroxytryptamine, 5HT) into storage vesicles. Release of these chemical messengers occurs by exocytosis of the contents of the vesicles, so interference with VMAT2 causes dysfunction of all the monoaminergic systems.

Predictably, mutation of the gene encoding VMAT2 produces a severe, lethal pediatric disease. Among several manifestations of congenital VMAT2 deficiency, one is parkinsonism.

In mice, knocking out the VMAT2 gene is incompatible with life. A mouse strain has been created with about a 90% decrease in VMAT2 activity. This strain develops aging-related movement abnormalities resembling those in Parkinson's disease. Conversely, mice that over-express VMAT2 are relatively resistant to manipulations that produce parkinsonism.

One explanation for why VMAT2 deficiency in mice produces aging-related parkinsonism is that the DA synthesized in the neuronal



The monoamines dopamine (DA), norepinephrine (NE), and serotonin (5HT) are stored in and released from vesicles. VMAT2 deficiency interferes with the functions of all three monoaminergic systems.

cytoplasm cannot be taken up into vesicles and instead undergoes spontaneous and enzyme-catalyzed oxidation; the oxidation products are toxic and destroy the neuron.

The NET Result

The cell membrane norepinephrine transporter (NET) plays a key role in inactivating norepinephrine. Normally, about 90% of the norepinephrine released from sympathetic nerve terminals is recycled

by being taken back up into the nerve terminals. When the transporter is underactive, more norepinephrine is delivered to its receptors in the heart and blood vessel walls for a given amount of norepinephrine release, producing an exaggerated increase in pulse rate and blood pressure when the sympathetic noradrenergic system is activated. One kindred has been described in which POTS runs in the family because of inherited decreased NET deficiency.

NET deficiency is a very rare cause of POTS.

Although NET deficiency is an extremely rare cause of POTS, it is important scientifically and, in a way, culturally. If POTS can have a genetic cause, then it cannot only reflect a psychiatric or psychosomatic disorder. The various symptoms and signs and continual life challenges of POTS from NET deficiency are essentially the same as those in much more frequent forms of POTS, illustrating that disorders of regulation such as POTS can arise from any of multiple causes. Different determinants can lead to essentially the same syndrome, and the syndrome is real.

I'm still puzzled about why decreased NET activity produces orthostatic intolerance, but I know from my own experience that it does. Once as part of my research I took a dose of 125 mg of desipramine, a drug that temporarily blocks the NET. For hours afterward I had orthostatic intolerance, tachycardia, brain "fog," and dysphoria (sour mood) to boot.

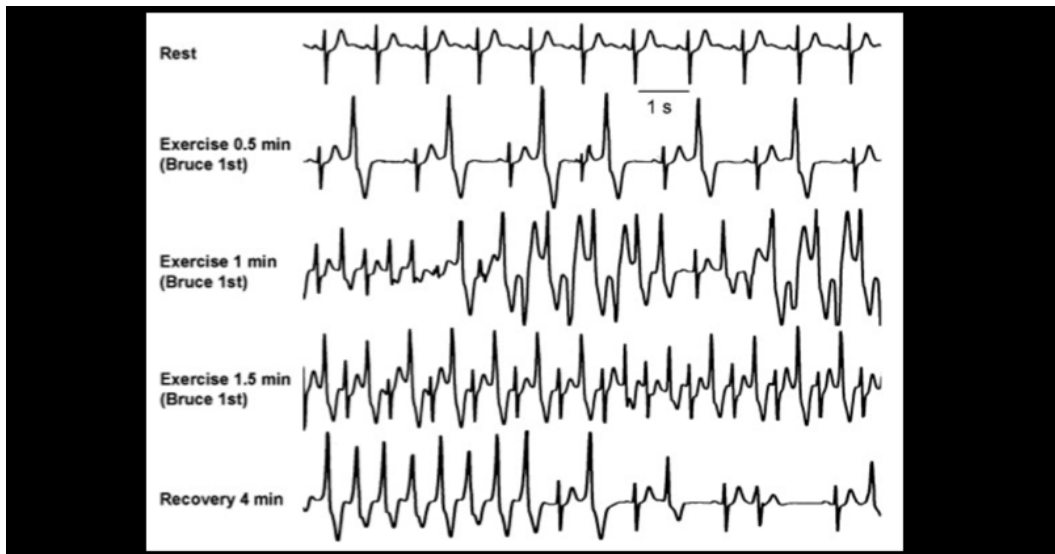
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a rare genetic disorder in which life-threatening abnormal heart rhythms can be evoked whenever sympathetic noradrenergic system (SNS) or sympathetic adrenergic system (SAS) activity is increased.

CPVT is a rare form of inherited fainting that involves a high risk of sudden death from abnormal heart rhythms.

Polymorphic ventricular tachycardia can degenerate rapidly to ventricular fibrillation and sudden death. CPVT manifests primarily as emotion- or exercise-related fainting or seizure activity in children and young adults. Importantly, under resting conditions the electrocardiogram is normal.

There are two modes of inherited transmission of CPVT, a more common autosomal dominant form and a less common autosomal recessive form. In both forms the basis for increased susceptibility to ventricular arrhythmias is enhanced accumulation of ionized calcium in the cytoplasm during SNS activation. In about a half of CPVT patients a specific causal mutation can be identified.



Exercise-induced ventricular tachycardia in a patient with CPVT.

Autosomal dominantly transmitted CPVT is caused by mutations of the cardiac ryanodine receptor, encoded by the RYR2 gene.

Autosomal recessively transmitted CPVT is caused by homozygous mutations (both parents are carriers of the same mutation) or compound heterozygous (the parents have different mutations) in the CASQ2 gene, which encodes calsequestrin 2.

The main treatment of CPVT is beta-adrenoceptor blockade.

Implanted electric cardioverter-defibrillators are also used. Other proposed treatments include the anti-arrhythmic drug flecainide and left cardiac sympathetic denervation.

AUTONOMICALLY MEDIATED SYNCOPE

Synopsis:

Mainly young adult women or children.

Normal pulse rate during standing.

Can be associated with several non-specific associated problems (inability to tolerate prolonged standing, heat intolerance, fatigue, chest pain, heart “flip-flops,” exercise intolerance).

Variable outlook, can improve.

Not life-threatening.

Syncope is sudden loss of consciousness (you black out) that is associated with loss of muscle tone (you go limp) and reverses rapidly (you wake up quickly.)

Syncope is sudden loss of consciousness associated with loss of muscle tone and the regaining of consciousness within seconds to minutes. In pre-syncope, the patient feels like he or she will faint but does not actually lose consciousness.

In people with intact adrenal glands, autonomically mediated syncope is characterized by an increase in plasma adrenaline levels.

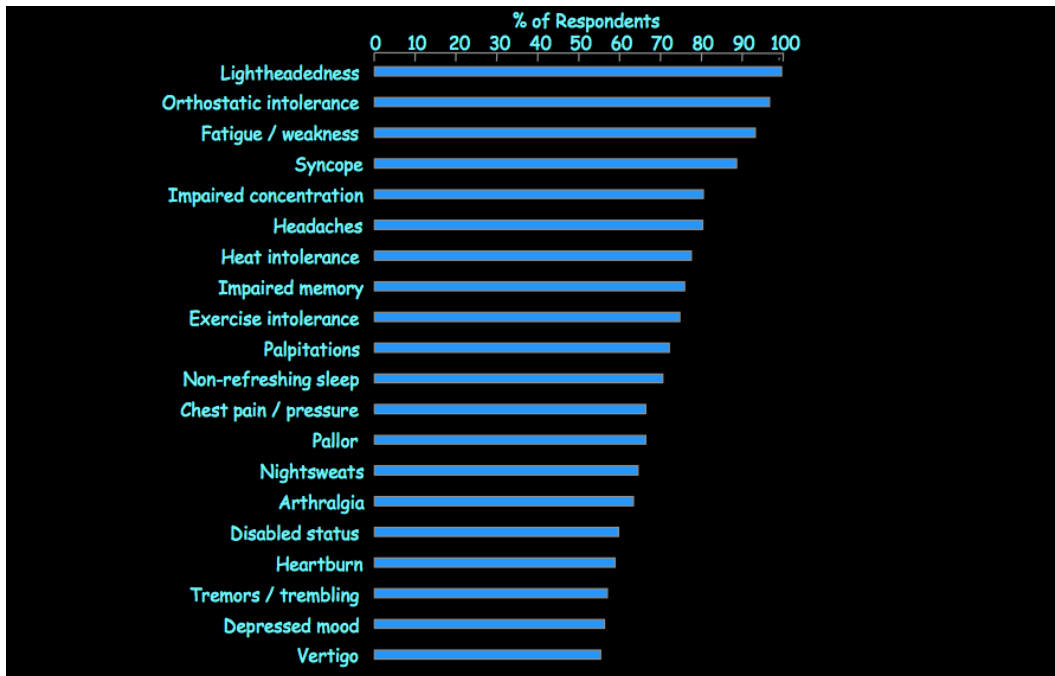
I use the term, autonomically mediated syncope because of the key role of alterations in activities of the components of the autonomic nervous system in fainting.

Most patients with frequent episodes of autonomically mediated syncope recognize early signs of fainting coming on and are usually able to abort the episode before syncope actually occurs.

Autonomically mediated syncope is fainting. Other names are vasovagal syncope, vasodepressor syncope, neurally mediated hypotension, reflex syncope, and neurocardiogenic syncope. Pre-syncope is near-fainting but without actual loss of consciousness.

Fainting is by far the most common cause of sudden loss of consciousness in the general population. It occurs predominantly in young adults and is more common in women than in men. In elderly adults, syncope is more likely to be a sign of a heart problem (abnormal heart rhythm, abnormal conduction of electrical impulses in the heart, or heart valve problem) or orthostatic hypotension.

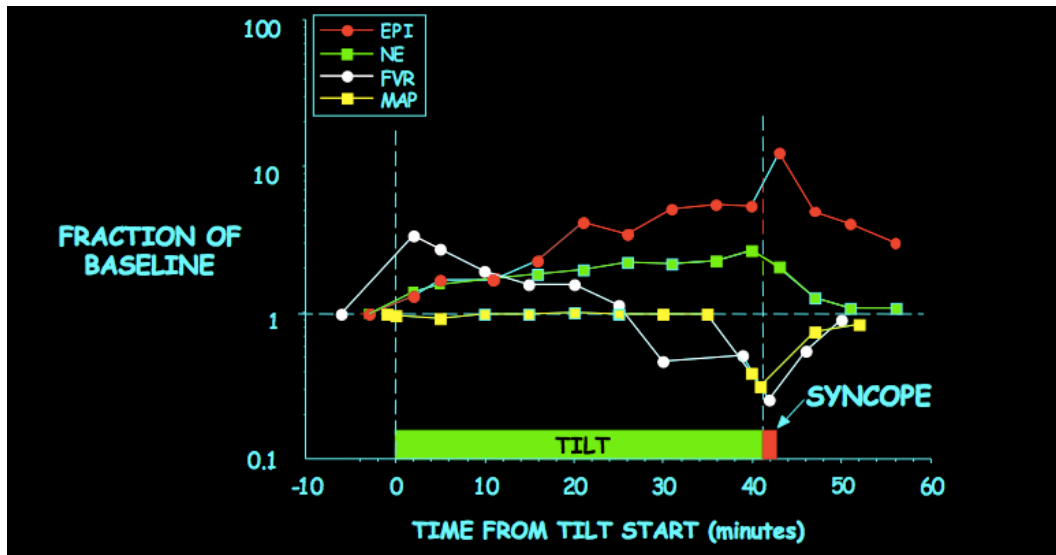
Patients in whom autonomically mediated syncope is a frequent problem often feel unwell between episodes, with an inability to tolerate prolonged standing, chronic fatigue, headache, “brain fog,” or chest pain.



Patients with frequent episodes of autonomically mediated syncope have many other symptoms.

Frequent autonomically mediated syncope can resemble POTS. Both conditions mainly involve young adult women, and both are associated with inability to tolerate prolonged standing, chronic fatigue, headache, and chest pain. POTS more commonly involves symptoms of dysfunction in multiple body systems.

Tilt table testing can provoke a sudden fall in blood pressure, called neurally mediated hypotension (NMH), in patients with POTS or



Tilt-induced neurally mediated hypotension and syncope. Note the decrease in forearm vascular resistance (FVR) and mirror image increase in plasma epinephrine (EPI) and greater increase in EPI than norepinephrine (NE)—i.e., “sympathoadrenal imbalance”—before the fall in mean arterial pressure (MAP).

autonomically mediated syncope.

Treatments for autonomically mediated syncope are about the same as for POTS: Florinef™ and liberal salt and water intake, β -adrenoceptor blockers, midodrine, calf muscle resistance training, or exercise training. In patients with syncope that is associated with actual cessation of the heartbeat (asystole), insertion of a pacemaker

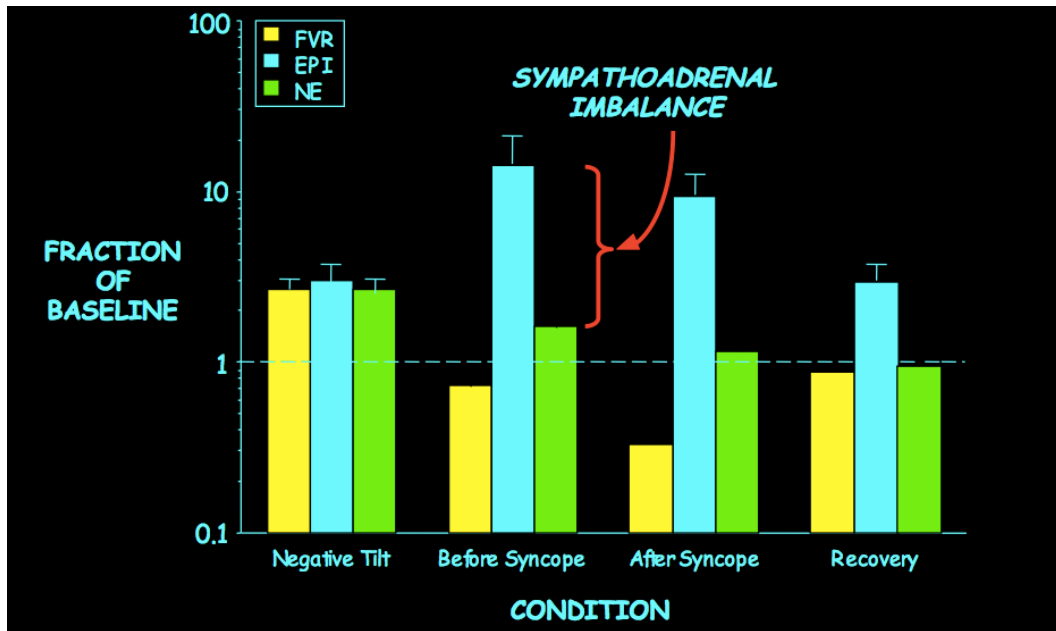
may be indicated. Consistent with the notion that decreased sympathetic nerve traffic or decreased norepinephrine release predisposes to neurocardiogenic syncope, some patients note improvement with sympathomimetic amines such as d-amphetamine or methylphenidate (Ritalin™).

As in POTS, in autonomically mediated syncope there does not seem to be much risk of the later development of a chronic cardiovascular or neurodegenerative disease.

Sympathoadrenal Imbalance

Regardless of the underlying diagnosis, acute autonomically mediated syncope seems to have the same proximate mechanism. There is a larger increase in sympathetic adrenal system (SAS) outflow than in sympathetic noradrenergic system (SNS) outflow—“sympathoadrenal imbalance,” or SAI. The neurochemical hallmark of SAI is a proportionately greater increase in plasma adrenaline than in simultaneously measured plasma norepinephrine. SAI typically not only accompanies but precedes episodes of autonomically mediated syncope, suggesting that SAI is a causal factor in fainting.

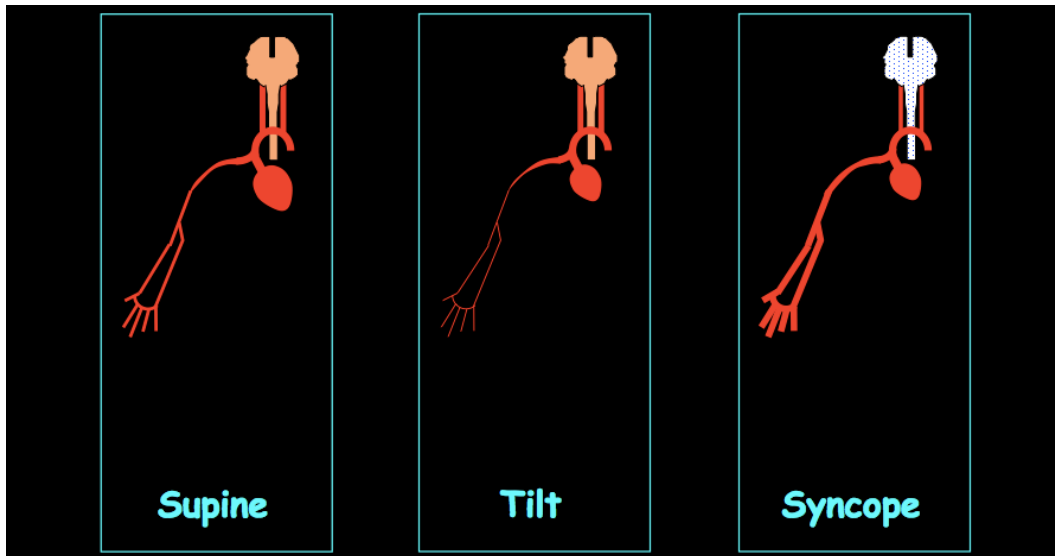
It has been proposed that in SAI, adrenaline-induced skeletal muscle vasodilation is not countered by increased SNS outflow. The cardiac output is redistributed toward the skeletal muscle, at the expense of



Autonomically mediated syncope involves pattern where before the acute episode, epinephrine (adrenaline) levels are high, while the sympathetic noradrenergic system is less activated or even shuts down.

delivery of blood to the brain.

Injection of adrenaline into a healthy person does not evoke fainting. This probably is because skeletal muscle vasodilation produced by adrenaline's action at beta-2 adrenoceptors on the vascular smooth muscle cells is normally countered by reflexive stimulation of sympathetic noradrenergic system (SNS) outflows. Norepinephrine



Changes in blood flow distribution accompanying tilt-induced syncope

(NE) is then released at an increased rate from SNS nerves supplying the skeletal muscle, and the released NE occupies alpha-1 adrenoceptors on the vascular smooth muscle cells, resulting in a counter-balancing vasoconstrictor effect. In autonomically mediated syncope, SNS outflow does not keep up with the adrenaline-induced skeletal muscle vasodilation.

Increased sweating also precedes autonomically mediated syncope. Although this can occur at the same time as SAI, it has not yet been shown that adrenaline evokes the sweating. Pallor constitutes another classic sign in autonomically mediated syncope. Pallor in this setting may be due to the cutaneous vasoconstriction evoked by high

circulating adrenaline levels. High circulating adrenaline levels could also explain the dilated pupils typically noted when people faint.

Do Snakes Faint?

The ability to stand up enabled the evolution of some of the defining characteristics of us humans. Adopting an upright posture, however, has also posed a novel challenge—maintaining blood flow to the brain despite gravitational pooling of blood in the legs and pelvic organs. To redistribute blood rapidly and appropriately in this setting, hormonal systems do not suffice; a nerve network is required.

In evolutionary terms, our ancestors began standing upright relatively recently. This may help explain why only one such nerve network seems to have evolved in humans—the sympathetic noradrenergic system (SNS). Each time you stand up, the SNS is activated markedly, rapidly, unconsciously, and automatically. By release of the chemical messenger, norepinephrine (NE), from nerve terminals in the walls of blood vessels in the limbs, kidneys, and gut, blood vessels in these organs constrict, while blood vessels in the heart, lungs, and brain do not. Blood flows to the brain, heart, and lungs therefore are preserved during standing up, despite the fall in venous return to the heart.

In forms of dysautonomia where the SNS fails, norepinephrine release



Harvey B. Lillywhite and examples of climbing and water snakes

does not increase adequately when the patient stands up. Possibly because of the novelty of the challenge in evolution, there are no alternative effectors for immediate compensatory activation. The tone of blood vessels in the skeletal muscle, kidneys, and gut does not increase, and as the venous return to the heart falls, so does the blood pressure. This explains why orthostatic hypotension constitutes a cardinal manifestation of failure of the SNS.

Climbing snakes often wriggle up trees, while water snakes spend their lives horizontal, surrounded by about the same pressure from head to tail. Many years ago, Dr. Harvey B. Lillywhite, of the University of Florida at Gainesville, placed snakes into cylindrical plastic tubes and then tilted them head-up. Among climbing snakes, nothing much happened, but among water snakes, during the tilting blood pooled in the tail end, the blood pressure at the midpoint of the body fell, and the heart rate increased compensatorily but

inadequately to maintain the blood pressure at the level of the head. If kept in this situation, with a brain blood flow of zero, water snakes would have to lose consciousness eventually.

Structural and functional differences between climbing and water snakes help explain their different abilities to maintain blood flow to the brain during head-up tilting. Climbing snakes have thin, tapered bodies, with the heart located relatively close to the brain. Water snakes have wider and more cylindrical bodies, with the heart close to the longitudinal center. Climbing snakes have higher blood pressure than water snakes, even when horizontal. Climbing snakes writhe when tilted, squeezing blood in the veins toward the heart like squeezing toothpaste up a tube.

Analogously, in humans who are about to faint while standing up, voluntary muscle pumping, by curling the toes, twisting the legs, and tightening the buttocks, can deliver enough blood to the heart and brain to prevent loss of consciousness temporarily. A patient with frequent fainting I evaluated many years ago obtained virtual cure of the problem by a regimen of isometric calf muscle training.

Climbing snakes when tilted constrict blood vessels to organs and muscles in the lower half of the body but not to vital anterior organs such as the lung, brain, and heart. The blood vessels tailward of the heart in climbing snakes have a substantial nerve supply—presumably sympathetic noradrenergic nerves—consistent with the ability to

constrict local blood vessels reflexively. In climbing snakes, as in humans, the sympathetic noradrenergic system seems to have afforded a survival advantage, by helping counter effects of gravity on delivery of blood to vital organs and enabling occupation of a particular environmental niche. Considering that water snakes evolved from terrestrial snakes, in evolutionary history the ability to adapt to gravitational stress must have devolved in the species that took to the water.

Some patients who have chronic orthostatic intolerance appear to have a structural problem that predisposes them to fainting while upright. These patients can have evidence for increased flexibility of joints and of blood vessel walls, probably because of altered protein fibers. The blood vessels have increased “give.” When the patient stands up, blows against a resistance, or carries out any activity that impedes the return of blood to the heart, too much blood collects in the veins, decreasing delivery of blood to the brain.

Both POTS and autonomically mediated syncope are far more prevalent in women than in men. Given the account of the climbing snakes and water snakes, maybe the greater prevalence of these syndromes in women relates also to structural and functional gender differences, such as lower centers of gravity, lower blood pressure, less well developed skeletal muscle below the level of the heart, a larger pool of venous blood in the pelvis, and greater inherent stretchability of blood vessels. I comment on this further later in the

section on apples and pears.

Fainting While Lecturing to Autonomics Experts

In October of 2007 a combined meeting of the American Autonomic Society and the European Federation of Autonomic Societies took place in Vienna. I was in the audience when a remarkable demonstration of autonomically mediated syncope occurred—the lecturer fainted.

The lecturer was (and still is) an expert on autonomic changes accompanying exercise. When her turn came, she strode to the lectern to give her talk. Soon afterward, though, she paused and then slumped slowly to the floor. Colleagues and I immediately rushed to her aid. She was barely conscious. Initially her pulse was present but almost impalpable. She was pale and sweaty. Her pupils were dilated. After a minute or two of her being supine, her pulse returned and became bounding and full, and about the same time she regained alertness and began to speak lucidly. As I recall, her talk was deferred.

Ironically, in 2009 she published an article about sympathetic neural mechanisms in human cardiovascular health and disease. In the article she wrote:

“Movement from a supine or sitting position to an upright position requires complex adjustments in blood flow and blood pressure, and these adjustments are ultimately coordinated by sympathetic nerves in conjunction with parasympathetic modulation of heart rate. Without such adjustments, blood flow to the brain would fall below autoregulatory limits, and standing up would consistently cause syncope.”

DIABETES

Diabetes is probably the most common cause of autonomic neuropathy. Among patients with diabetes, the occurrence of autonomic neuropathy is an adverse prognostic factor.

Dysautonomia is common in diabetes and is associated with worse outcome.

Diabetes often involves chronic pain in the feet (painful diabetic neuropathy). Loss of sympathetic noradrenergic innervation in the feet accompanies the neuropathy.

Diabetics can also have neurogenic orthostatic hypotension, with evidence of failure of baroreflex regulation of sympathetic noradrenergic system outflows.

Poor control of the urinary bladder is another sign of diabetic

autonomic neuropathy. Patients have difficulty starting the urinary stream or have urinary retention that can require self-catheterization.

Other manifestations of diabetic autonomic neuropathy include erectile dysfunction, resting tachycardia, diarrhea or constipation, esophageal dysfunction, and decreased stomach contractions (gastroparesis).

Cardiac sympathetic neuroimaging often cannot accurately assess the status of cardiac sympathetic innervation in patients with diabetes, because the disease also involves patchy narrowing of coronary arterioles. Since injected cardiac sympathetic imaging agents are delivered to the heart by way of the coronary arterial tree, it is difficult or impossible to distinguish loss of sympathetic innervation from decreased delivery by the bloodstream.

Mechanisms of dysautonomia in diabetes are poorly understood.

The high prevalence, multiple manifestations, and prognostic significance of diabetic autonomic neuropathy contrast with remarkably poor understanding of the mechanisms.

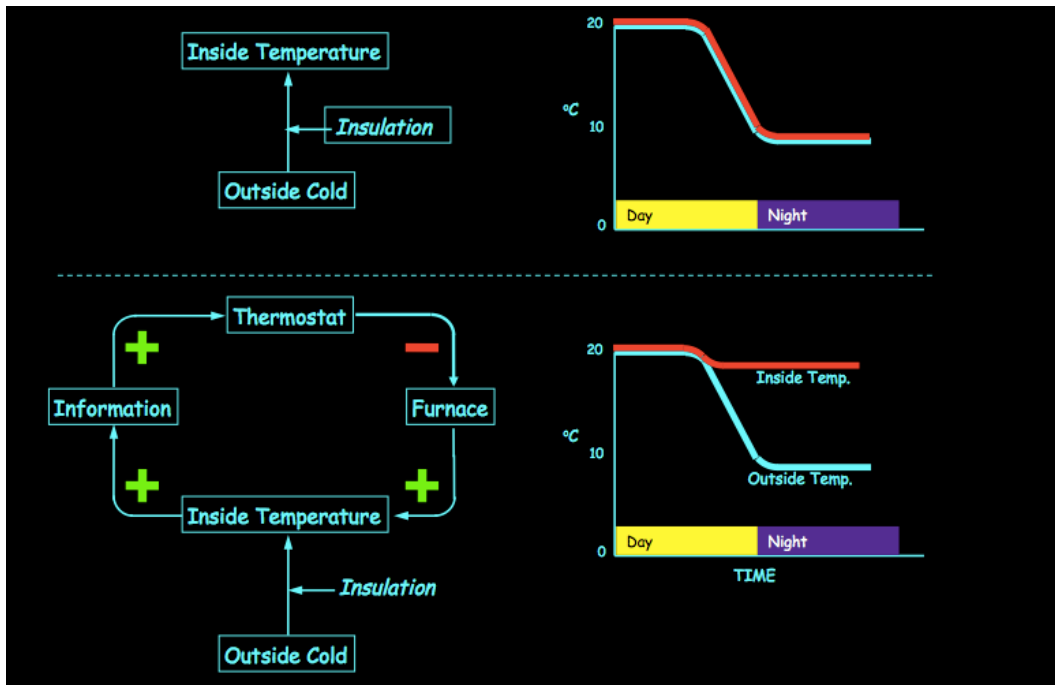
HYPERTENSION

Hypertension, or chronic high blood pressure, increases the risks of serious conditions such as stroke, heart attack, and heart or kidney failure. High blood pressure is basically defined by abnormal numbers. The systolic pressure is the maximum pressure in the arteries when the heart is ejecting blood. The diastolic pressure is the minimum pressure when the heart is filling with blood between heartbeats.

A person with blood pressure persistently more than 140/90 mmHg may be considered to be hypertensive; however, the medical risks, and therefore the need for treatment, depend not only on the blood pressure itself but also on other factors such as age, gender, ethnicity, and co-morbidities such as coronary artery disease, diabetes, or obesity.

In order to understand the role of the autonomic nervous system in hypertension, you have to know about negative feedback regulation.

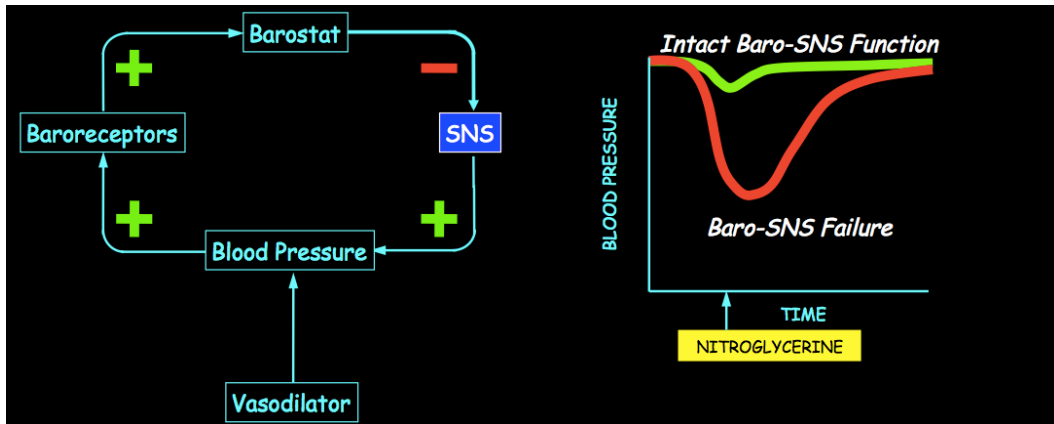
According to Cannon's concept of homeostasis, the body's many internal variables, such as blood pressure, are not allowed to vary by much or for long. This is because of negative feedback regulation. In



A thermostatic system is a classic example of negative feedback regulation.

a negative feedback loop, there are an odd number of negative relationships in the loop. The level of the monitored variable is maintained.

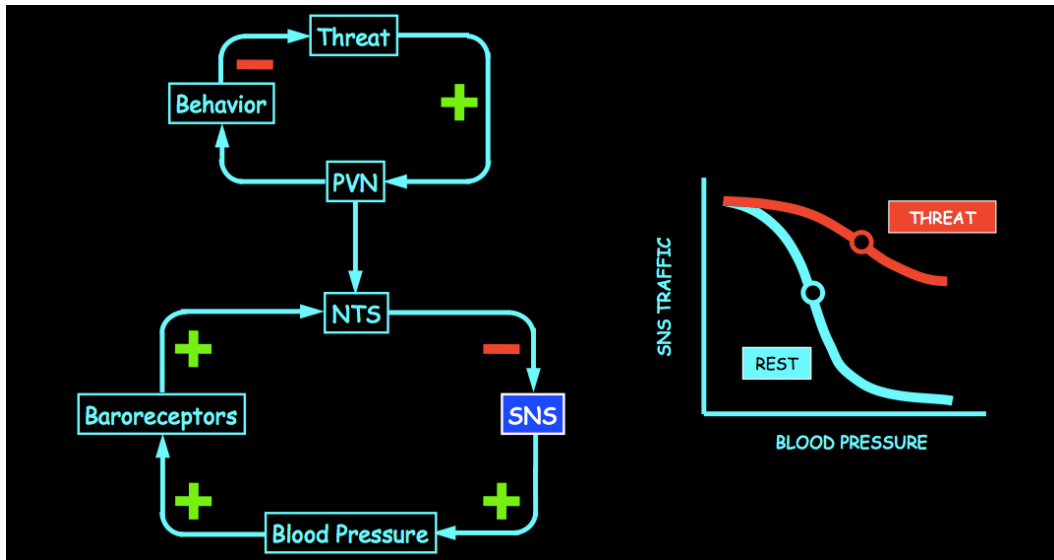
Think of the thermostat in your house. The thermostat compares the information coming in about room temperature with the setting determined by a controller—namely, you. When the room temperature decreases sufficiently and for long enough, the thermostat



In a patient with baroreflex-sympathoneural failure, nitroglycerine produces a large, sustained fall in blood pressure.

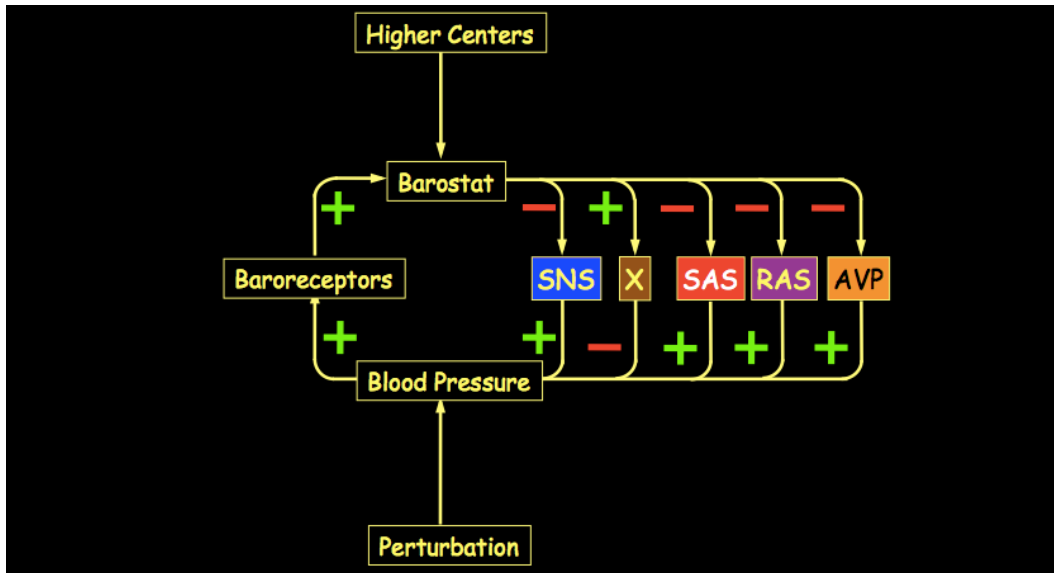
senses the discrepancy between what the room temperature is and what the thermostat setting is. The furnace is then instructed to turn on, and the room temperature increases toward the set value.

There is a theory that the brain has many comparators that act like thermostats. Taken together, they are called homeostats. According to this theory, a “barostat” in the lower brainstem compares information coming in from baroreceptors about blood pressure with settings determined by higher centers in the brain, and when the discrepancy between what is sensed and what is set is detected, traffic in the sympathetic noradrenergic system (SNS) changes, so that the blood pressure stays within range.



A system that contains a higher level negative feedback loop superimposed on a lower level negative feedback loop can behave as if the lower level loop contained a “homeostat.”

For instance, i.v. injection of nitroglycerine relaxes blood vessels and causes them to dilate (vasodilation), and the blood pressure falls. The barostat receives less baroreceptor afferent information, and the SNS is stimulated reflexively. Because of the increased sympathetic nerve traffic, the rate of release of norepinephrine, the sympathetic neurotransmitter, increases. Then there is more binding of the norepinephrine to alpha-adrenoceptors in the walls of blood vessels, the blood vessels constrict, and the blood pressure rapidly returns to baseline. In the setting of baroreflex-sympathoneural failure, nitroglycerine injection produces a much larger, more sustained

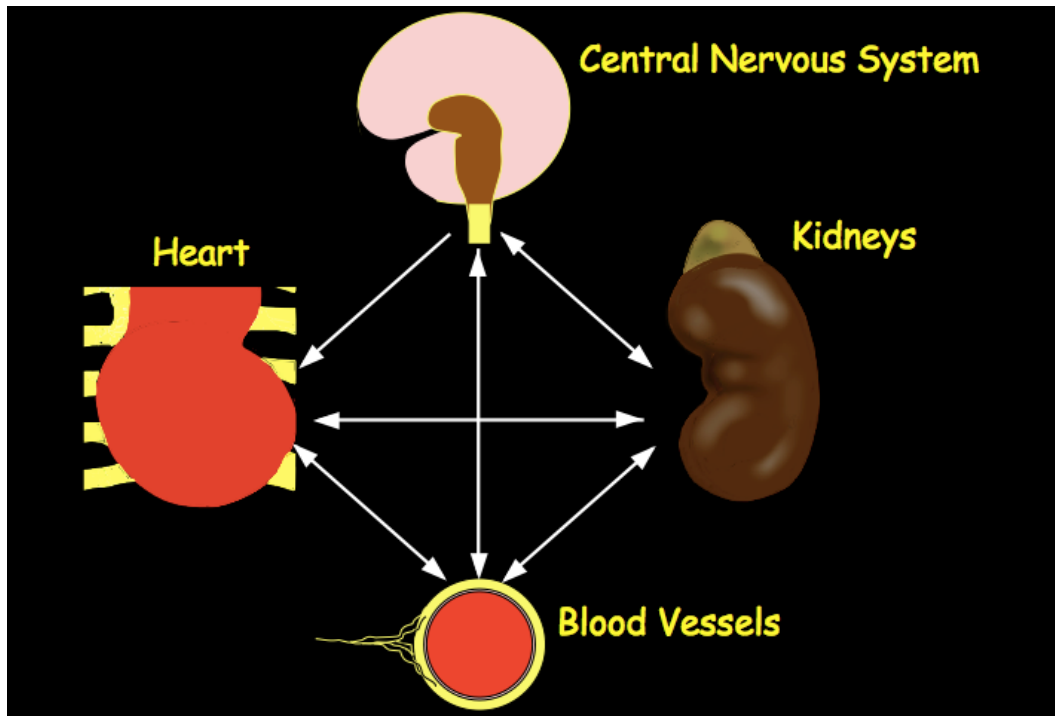


Some effectors of the arterial baroreflex

decrease in blood pressure.

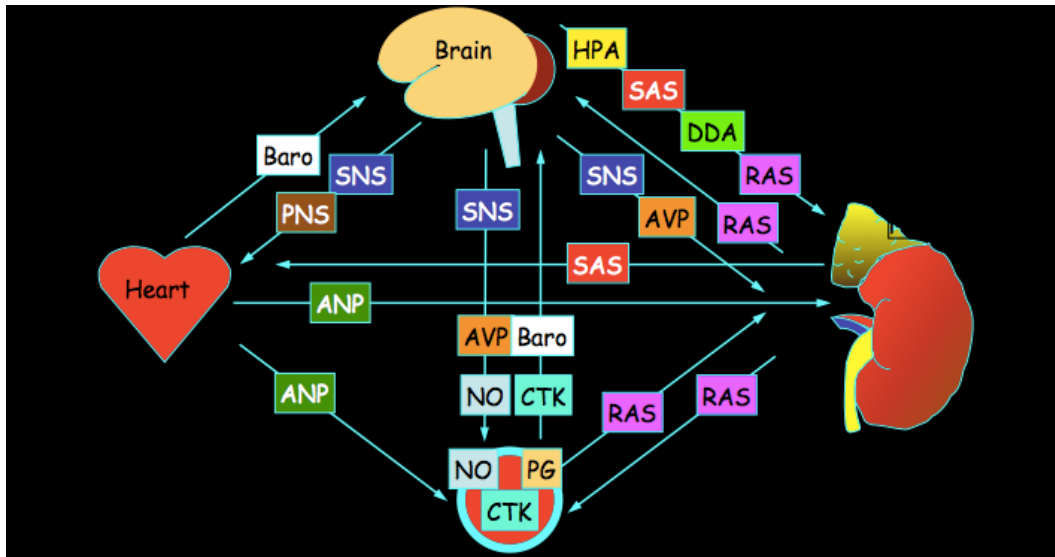
It is important to bear in mind that the barostat, as all homeostats, is conceptual and not real. There are no known physiological comparators, for temperature, blood pressure, glucose, or any other monitored variable of the body. Instead, it is likely that there are negative feedback loops at higher centers in the nervous system that affect the functions of those lower down, giving the appearance of altered “instructions” or “set points” for responding.

For instance, the nucleus of the solitary tract (NTS) is the site in the lower brainstem that receives all the baroreceptor afferent



Blood pressure is determined by interactions among the central nervous system, heart, kidneys, and blood vessels.

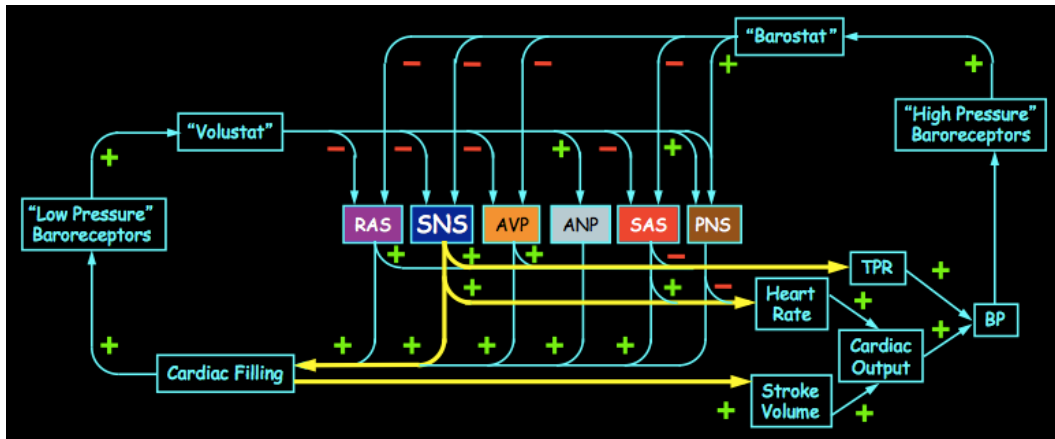
information. When the NTS neurons receive this information, they direct changes in SNS outflow. In an emotionally threatening situation, activity higher in the brainstem, at the level of the paraventricular nucleus of the hypothalamus (PVN) increases, as part of a kind of neuroendocrine negative feedback loop to enable the organism to deal with the threat. PVN stimulation affects the stimulus-response relationship between blood pressure and the afferent baroreceptor information to the NTS.



Many effectors contribute to blood pressure regulation.

The body has several effectors besides the sympathetic noradrenergic system for regulating blood pressure by negative feedback. You probably recognize two of them in the diagram—the parasympathetic nervous system, via the vagus nerve, the tenth cranial nerve, for which acetylcholine is the neurotransmitter, and the sympathetic adrenergic system, for which adrenaline is the hormone. Other effectors include the renin-angiotensin-aldosterone system and the arginine vasopressin system. Because of the importance of the renin-angiotensin-aldosterone system in blood pressure regulation and in hypertension management, the next section describes this system in more detail.

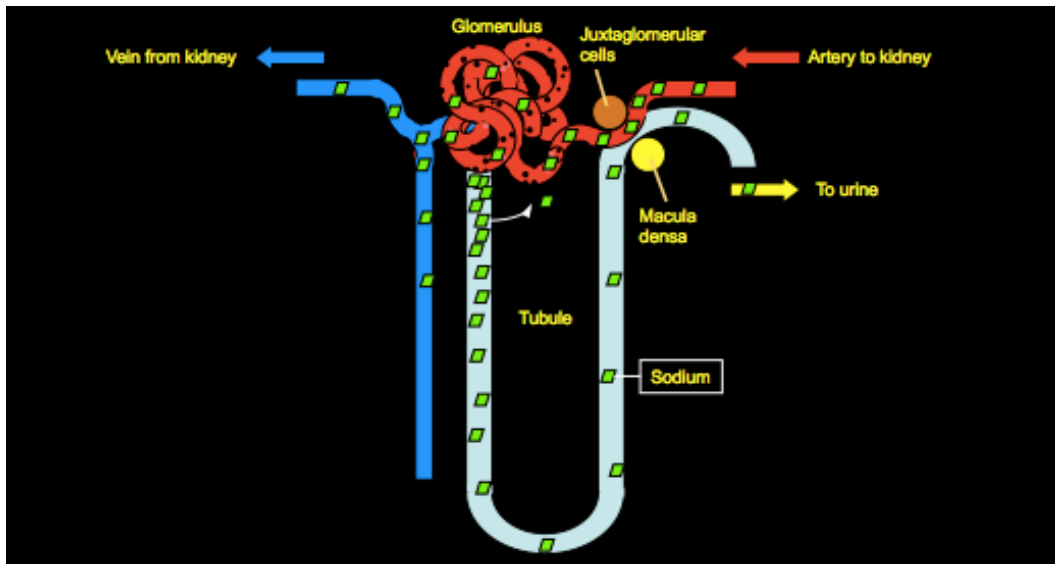
The renin-angiotensin-aldosterone system (RAS) plays a dominant



A complex network of effectors and negative feedback loops determines the blood pressure. One of the most important effectors is the sympathetic noradrenergic system (SNS).

role in the maintenance of sodium balance in the body. Dietary sodium restriction stimulates RAS activity; sodium loading virtually shuts it down.

The kidneys filter the blood by millions of leaky blood vessels coiled into tiny ball-like tufts called glomeruli (singular, glomerulus). Blood cells themselves normally cannot pass through the holes in the glomeruli, but the watery part of the blood, containing sodium, does pass through. The filtered fluid (filtrate) then enters tiny tubes, tubules. Cells lining the tubules take up the filtered sodium and put it back into the bloodstream. The sodium that escapes this recycling stays in the filtrate and eventually leaves the body in the excreted

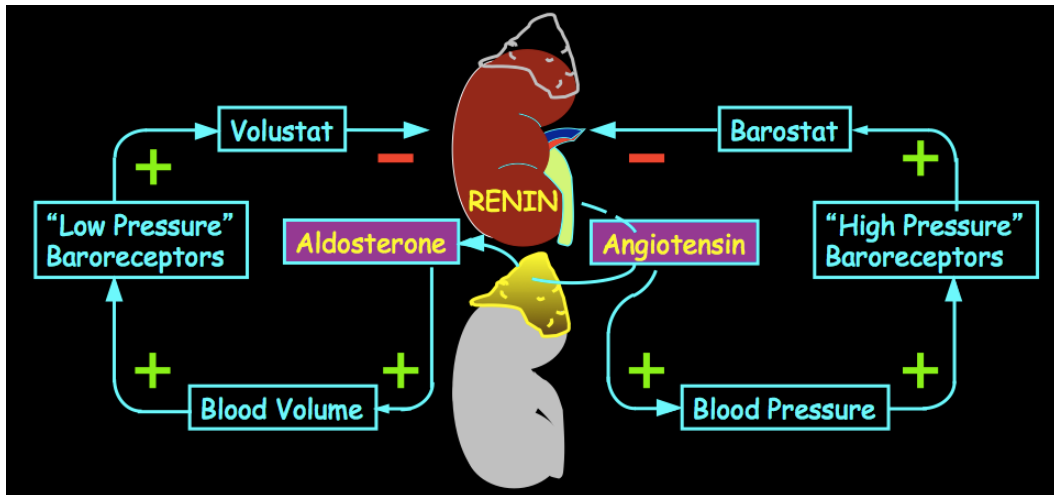


Kidney nephron, emphasizing the juxtaglomerular apparatus

urine.

Specialized tubule cells called the macula densa (or "dense spot") monitor the concentration of sodium in the filtrate that has passed through the glomeruli. When the amount of sodium falls below a certain level, the macula densa cells send a message to other nearby cells, called juxtaglomerular cells, located in the walls of the blood vessels heading toward the glomeruli. The juxtaglomerular cells release into the bloodstream the first effector chemical of the RAS, renin.

The same juxtaglomerular cells also act as sensors themselves. They



Relationships of components of the renin-angiotensin-aldosterone system to the “volustat” and “barostat”

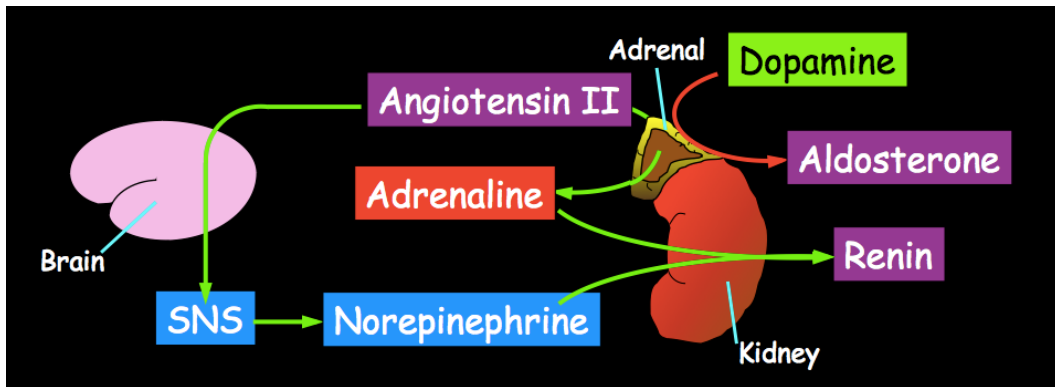
detect stretch, and therefore the distending pressure, in the blood vessels. A fall in the distending pressure leads to release of renin. This means that not just one but at least two homeostats regulate the RAS in the kidneys. The main monitored variables for regulation of the RAS are the pressure in the blood vessels approaching the glomeruli and the concentration of sodium in the glomerular filtrate.

Stretch receptors in two other places outside the kidneys also contribute to regulation of release of renin, and we’ll discuss them now.

“Low-pressure” baroreceptors are located in the walls of the chambers and veins at the entry to the heart. “High-pressure” baroreceptors are

located in major arteries, especially in the carotid sinus, where the common carotid artery splits into the external and internal carotid arteries. When the amount of blood filling the heart falls, such as by a fall in blood volume, or when the blood pressure in the carotid arteries falls, such as from relaxation of blood vessels, the brain acts on this information to direct an increase in renin release. Conceptually, the homeostat that regulates renin release to maintain blood volume as monitored by the low-pressure baroreceptors can be called the “volustat,” and the homeostat that regulates renin release to maintain blood pressure as monitored by the high-pressure baroreceptors can be called the “barostat.”

Renin has no known activity of its own, but it does act as an enzyme to speed up the conversion of a protein, angiotensinogen, to a peptide (a short chain of amino acids) called angiotensin I. Angiotensin I also has no known physiological action, but another enzyme, angiotensin-converting enzyme (ACE), speeds up the conversion of angiotensin I to angiotensin II. Angiotensin II is one of the most potent chemicals of the body that constrict blood vessels. Angiotensin II therefore increases blood pressure. Predictably, both ACE inhibitors and angiotensin II receptor blockers are effective and widely used to treat hypertension. Another key effect of angiotensin II, which establishes the RAS as the body’s main system regulating sodium balance, is to stimulate the adrenal cortex to release aldosterone. Aldosterone increases reabsorption of sodium from the tubules in the kidneys.



Interactions between catecholamine systems and the renin-angiotensin-aldosterone system

Activation of the RAS therefore increases the blood pressure by constricting blood vessels, via the vasoconstrictor effect of angiotensin II, and also increases the blood volume and cardiac filling, via the sodium retention produced by aldosterone. Thus, the renin-angiotensin-aldosterone system is a key effector for two homeostatic systems, the barostat and the volustat.

Catecholamine systems of the body interact with the renin-angiotensin-aldosterone system in several ways. First, stimulation of the sympathetic noradrenergic system increases renin secretion. Second, angiotensin II acts in the brain to increase sympathetic nervous outflows. Third, there are abundant angiotensin II receptors in the adrenal medulla. Angiotensin II can evoke release of adrenaline directly, and adrenaline increases renin secretion. Fourth, dopamine, which is the chemical precursor of norepinephrine and adrenaline,

inhibits aldosterone secretion from the adrenal cortex in response to angiotensin II.

Blood pressure is determined by two variables. The cardiac output is the amount of blood ejected by the heart in one minute. This corresponds to the total blood flow in the circulation. The total peripheral resistance is the amount of resistance to blood flow in the circulation as a whole. To get a grasp of cardiac output and total peripheral resistance, think of the pressure in a garden hose. Turning on the faucet increases both the flow of water and the pressure in the hose. If you turned down the faucet, this would decrease the pressure and the flow. You could bring the pressure back up by tightening the nozzle, but the flow would decrease further. If the nozzle remained tightened, turning the faucet up would increase the flow, but now the pressure in the hose would be high. In most people with chronic hypertension, the cardiac output is normal or even decreased. This means that in hypertension, the high blood pressure is usually from high total peripheral resistance. The vascular nozzle is too tight.

Just as two variables determine blood pressure, two variables determine cardiac output. These are the heart rate and the stroke volume. The heart rate is the number of beats per minute. The stroke volume is the amount of blood ejected by the heart in one heartbeat. This presentation has emphasized that blood pressure is regulated by negative feedback. Input to the brain from arterial baroreceptors causes reflexive changes in activities of effectors, and this tends to

buffer the effects of a perturbation of blood pressure. The sympathetic noradrenergic system and the renin-angiotensin-aldosterone system are two of the most important effectors in blood pressure regulation. The vagus nerve, the tenth cranial nerve, contributes to blood pressure regulation especially by modulation of heart rate. The sympathetic adrenergic system plays a major role in the high blood pressure commonly found in emergency situations. In addition to the barostat, a volustat regulates blood volume and thereby cardiac filling and cardiac output, based on information from low pressure baroreceptors. Although the diagram of negative feedback regulation of blood pressure seems very complex, what is depicted actually is a relatively simple model compared to models hypertension researchers have developed.

One may ask, if the body has available so many negative feedback loops and effectors to control blood pressure, why does hypertension even exist? What goes wrong with the negative feedback regulation, such that the blood pressure becomes persistently high? Somehow the complex interplay of the blood vessels, heart, kidneys, and the central nervous system goes awry. No one knows exactly what goes wrong, how, or why.

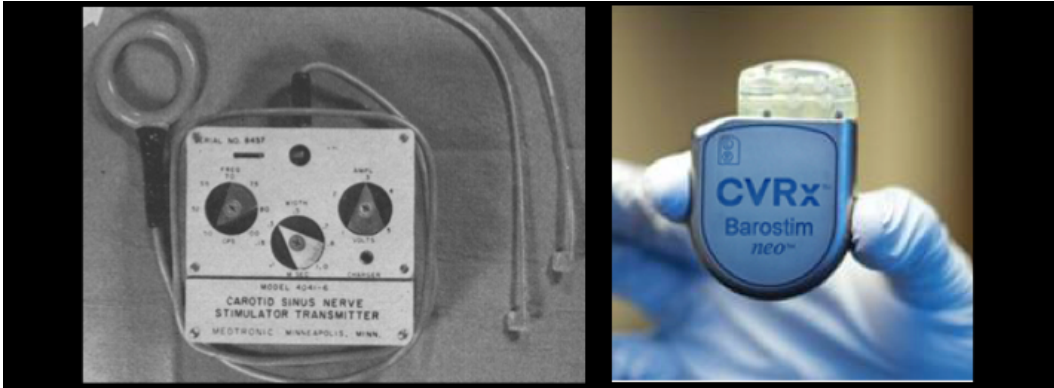
A guess—and it's only a guess—is that the effectors that regulate blood pressure evolved to maintain homeostasis of other monitored variables and not blood pressure per se. Throughout human evolution, systems evolved to counter infection, to endure emergencies, to

maintain the core temperature of the body, to distribute blood flows to body organs appropriately in different circumstances, to convert ingested food to energy and get rid of waste, to have correct levels of several electrolytes such as sodium, and to conserve water. These all have offered clear survival advantages. The side effect of increased blood pressure may have had relatively little significance. In modern society, these needs no longer are pressing, but the homeostatic systems may still operate in a manner that biases toward high intake of fat, sugar, salt, and water, with attendant increased blood pressure. Hypertension might then be a consequence of modern civilization.

Carotid Sinus Stimulation

Until relatively recently it was thought that despite the importance of the arterial baroreflex for keeping the blood pressure within a pre-specified range acutely, the arterial baroreflex does not contribute to the long-term regulation of blood pressure, because of “resetting” of the reflex as a consequence of hypertension. Findings from recent studies about carotid sinus stimulation have forced reconsideration of the dismissal of the arterial baroreflex as a determinant of blood pressure in patients with hypertension.

Modern day carotid sinus stimulation is a descendant of the “Baropacer,” which was an external pacemaker developed in the 1960s. The electrodes of the Baropacer were wrapped around the



Modern implanted carotid sinus stimulators are descendants of “baropacer” devices of the 1960s.

carefully dissected carotid sinus nerve. Stimulation of the carotid sinus nerve reflexively inhibits sympathetic noradrenergic nervous outflows and decreases blood pressure. This approach was successful, but the approximately concurrent introduction of effective drugs to treat high blood pressure led to the demise of the Baropacer.

Early in my career, the Cardiology Branch of the National Heart, Lung, and Blood Institute was located on the 7th floor of Building 10, the NIH Clinical Center. I was allowed to use a Baropacer from the Branch’s animal lab for an experiment to try to stimulate the carotid sinus nerve of a cat and map out brain pathways mediating the baroreflex. The experiment was a failure, mainly because of the inability to maintain the integrity of the nerve over time. Modern implanted baropacers such as the CVRx neo™ are placed on the carotid sinuses—a much simpler approach than wrapping the

electrodes around the nerves—but this still seems to be an effective approach.

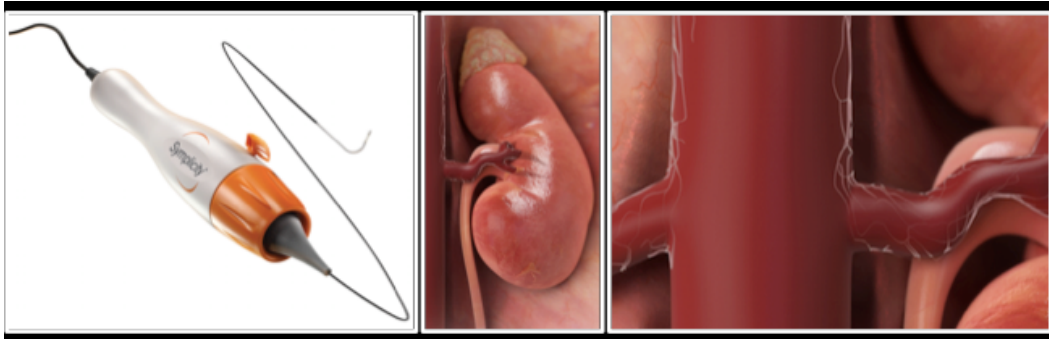
Carotid sinus stimulation is currently undergoing clinical trials to treat refractory hypertension. The stimulation is continuous. It has several other potential uses (excuse the egregious pun), including treatment for heart failure, some arrhythmias, and metabolic syndrome, all based on inhibition of sympathetic noradrenergic outflows.

Similar technology might be developed to treat supine hypertension in patients with neurogenic orthostatic hypotension from chronic autonomic failure—a very difficult condition for which no drug is effective.

Renal Nerve Ablation

Another technology undergoing testing to treat refractory hypertension is based on destroying the sympathetic nerves supplying the kidneys. The procedure involves percutaneous cannulation of the renal arteries and delivery of radiofrequency energy in a spiral through the walls of the arteries. This destroys the nerves that travel in the outer layer of the arterial walls.

Medtronic, the company that manufactured the Baropacer in the 1960s, sponsored a recent large trial of its Symplicity™ device for



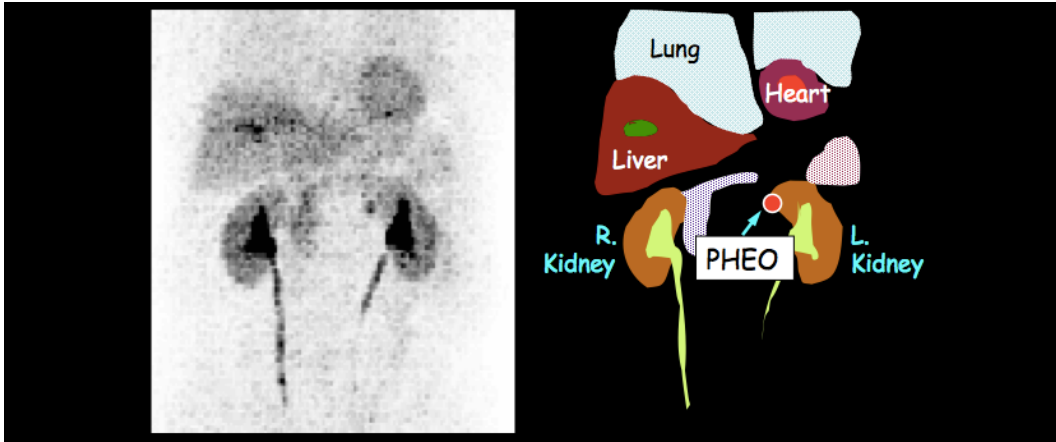
Medtronic's Symplicity system for renal sympathetic nerve ablation.

renal nerve ablation. The trial was stopped because of lack of efficacy. Further development of this technology may require devising means to test the extent of renal denervation actually produced by the procedure.

Hypertension has many mechanisms. It is possible that only patients with a substantial sympathoneural contribution to their high blood pressure (hypernoradrenergic hypertension) would benefit from renal nerve ablation. Such patients can be identified by clonidine suppression testing.

Pheochromocytoma (Pheo)

Pheochromocytomas (“pheos”) are rare but clinically and scientifically important tumors of cells that produce and secrete



Pheochromocytomas (“pheos”) usually are in an adrenal gland.

catecholamines.

“Pheos” are rare tumors of cells that make catecholamines.

Most pheos are located in the adrenal gland. Because of the potent effects of catecholamines on the cardiovascular system, pheos often present with signs and symptoms of high circulating catecholamine levels. These include high blood pressure, headache, pallor, and sweating.

A patient harboring a pheo can have unexpected, paroxysmal hypertension upon exposure to relatively mild perturbations, such as anesthesia induction, or drugs such as sympathomimetic amines.

Most pheos are benign and can be removed surgically. This means that pheos represent a form of curable hypertension.

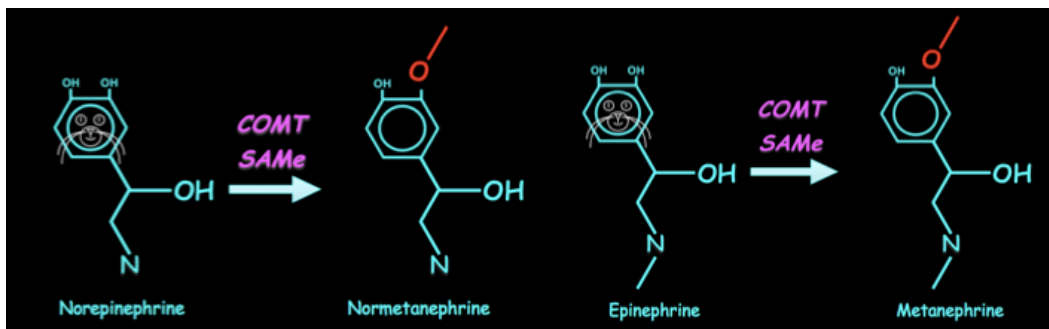
In a patient with clinical findings suggestive of a pheo, measuring plasma levels of free (unconjugated) metanephrines (normetanephrine and metanephrine) is a valuable screening test, because of the extremely low frequency of false-negative results. That is, if plasma metanephrines are normal, one can rule out pheo.

If the screening biochemical testing is positive, then MRI, CT scanning, clonidine suppression testing, or imaging with a ligand for the cell membrane norepinephrine transporter (e.g., ^{123}I -MIBG) may be done.

Clonidine decreases sympathetic noradrenergic outflows and thereby decreases plasma norepinephrine (NE) levels. If a patient had high blood pressure due to high sympathetic noradrenergic system outflows, then clonidine would produce a large decrease in the plasma NE. In a positive clonidine suppression test for a pheo, the plasma NE level fails to decrease between baseline and 3 hours after 0.3 mg of oral clonidine.

Plasma Metanephrines

In a patient with symptoms or signs suggesting a pheo, the most efficient screening test is measuring plasma levels of free (unconjugated) metanephrines.



COMT catalyzes the conversion of norepinephrine to normetanephrine and of epinephrine to metanephrine.

The term, “metanephrines,” refers to the O-methylated metabolite of norepinephrine, which is normetanephrine (NMN) and the O-methylated metabolite of epinephrine, which is metanephrine (MN). The enzyme, catechol-O-methyltransferase, or COMT, catalyzes the transfer of a methyl group from the methyl donor, S-adenosyl methionine (SAME) to the catechol nucleus, so that the -OH hydroxyl group is replaced by an -OCH₃ methoxy group.

Unlike the sympathetic nerves, the catecholamine-producing cells in the adrenal medulla express COMT. This means that under resting conditions norepinephrine (NE) that leaks from the vesicles into the cytoplasm in adrenomedullary cells can be metabolized to normetanephrine (NMN), but NE that leaks from the vesicles into the cytoplasm in sympathetic nerves cannot. Plasma NMN therefore provides a more sensitive, specific test for pheo than does plasma NE. In the case of epinephrine (EPI), there is very little ongoing release of

EPI into the bloodstream, whereas there is ongoing release of metanephrine (MN) due to the continuous leakage of EPI from the vesicles into the cytoplasm.

If there were a high rate of sympathetic noradrenergic nerve traffic, plasma NMN could be increased, due to O-methylation of some of the released NE that is taken up by non-neuronal cells. If a patient with hypertension had hyperactivity of the sympathetic noradrenergic system, clonidine administration would drop the rate of sympathetic nerve traffic and decrease plasma NMN levels; but if a patient had a pheo, clonidine administration would fail to decrease plasma NMN.

Stress Cardiopathy in a Senator

Pheochromocytomas exert several adverse effects on the cardiovascular system, due to massive increases in circulating levels of catecholamines in response to seemingly minor manipulations.

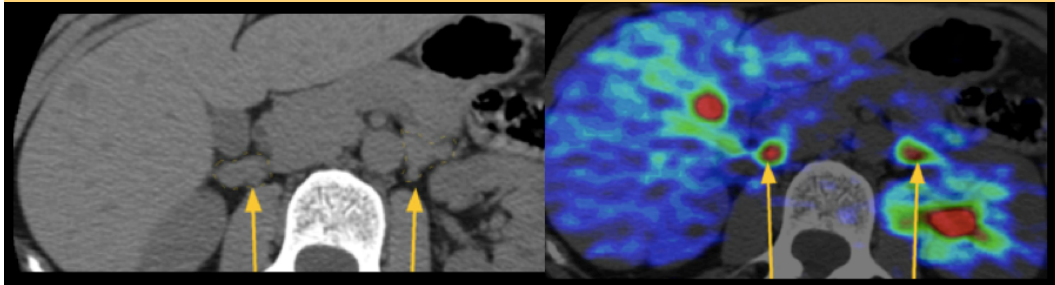
A US Senator went in for routine thyroid surgery but had severe hypertension upon anesthesia induction, and so the surgery was called off. Subsequently he again had a hypertensive episode evoked by anesthesia induction. He went into acute heart failure and had to be treated in an intensive care unit. In an attempt to increase the pumping efficiency of his heart, i.v. adrenaline was infused. Unexpectedly, this worsened his heart failure. The infusion was stopped, and gradually the patient recovered.

He then underwent a workup for pheo. The workup included ^{18}F -dopamine PET scanning and measurement of plasma metanephrines at the NIH Clinical Center, and both tests were positive. A pheo was identified surgically and removed. Subsequently he had the thyroid surgery he had originally planned on, without complications.

This case teaches a few lessons. First, sudden, unexpected hypertension should raise a suspicion of pheo. Second, increases in plasma levels of catecholamines by a pheo can be sufficiently massive to cause a form of heart failure that resembles *takotsubo* cardiopathy (stress cardiopathy). Third, instead of stimulating the heart, adrenaline can precipitate or worsen heart failure due to toxic effects on the myocardial cells. Whether these effects reflect occupation of adrenoceptors on the surface of the cells or entry of adrenaline into the cells and intracellular toxicity remains unclear.

"Pseudopheo"

Pheos are rare. Most patients who undergo a diagnostic workup for a pheo prove not to harbor the tumor. The term, "pseudopheochromocytoma," or "psuedopheo," refers to a condition in which the patient has episodes of severe high blood pressure and symptoms suggestive of a pheo, but the patient doesn't actually have a pheo. Sometimes pseudopheo overlaps clinically with orthostatic intolerance syndromes such as arterial baroreflex failure or postural



CT and ^{18}F -dopamine scans in a patient with pseudopheo. The arrows point to enlarged adrenal medullas.

tachycardia syndrome.

Patients with pseudopheo have a pattern of normal sympathetic noradrenergic system outflow, adrenomedullary activation, and augmented adrenoceptor-mediated cardiovascular responses to released catecholamines.

It has been reported that glucagon injection into pseudopheo patients produces a large increase in plasma adrenaline levels. This is not seen in pheo patients or healthy volunteers. Glucagon stimulation testing might therefore be considered in the diagnostic evaluation; however, the sensitivity and specificity of the testing have not been established.

POSTURAL TACHYCARDIA SYNDROME (POTS)

Synopsis:

Mainly young adult women.

Too rapid pulse rate during standing.

Several non-specific associated problems (inability to tolerate prolonged standing, chronic fatigue, faintness, exercise and heat intolerance, headache, neuropathic pain, slowed gastrointestinal movements, chest pain, heart “flip-flops,” tendency to panic)

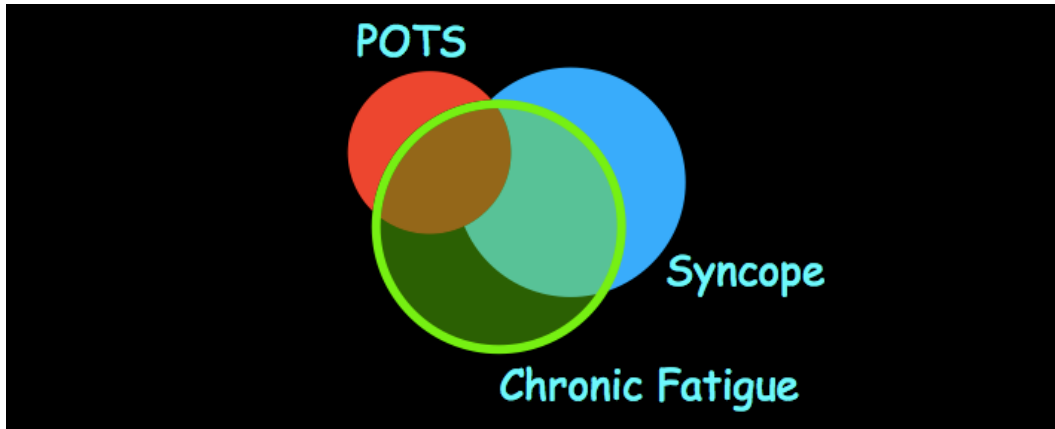
Variable outlook, can improve.

Not life-threatening.

Patients with the postural tachycardia syndrome (postural orthostatic tachycardia syndrome, POTS) have an excessive increase in pulse rate when they are standing.

POTS is a syndrome, not a single disease, and can have any of several causes.

Different research groups have different views about the classification of dysautonomias and especially about POTS and chronic orthostatic intolerance. Some investigators view POTS as synonymous with



POTS, autonomically mediated syncope, and chronic fatigue often occur together.

chronic orthostatic intolerance. The condition has features that are also suggestive of hyperdynamic circulation syndrome or “neurasthenia.” The many terms that have been used probably reflect different emphases at different centers and gaps in knowledge about underlying mechanisms.

POTS patients have too rapid a pulse rate when they stand, as well as several other non-specific problems.

At least some of these symptoms are thought to reflect increased effects of the catecholamines, norepinephrine or adrenaline, in the heart, from overactivity of the sympathetic noradrenergic system, the sympathetic adrenergic system, or both.

The orthostatic tachycardia usually occurs without orthostatic hypotension. The finding of orthostatic hypotension does not exclude a diagnosis of POTS, however, as delayed orthostatic hypotension can occur in this condition.

In general medical practice, the finding of an excessive increase in heart rate with standing, postural tachycardia, is usually secondary to identifiable problems, such as medications or dehydration from chronic illness. It is only when the cause is not readily identified, and the patient has some of the other complaints discussed below, that the patient is thought to have postural tachycardia syndrome, or POTS.

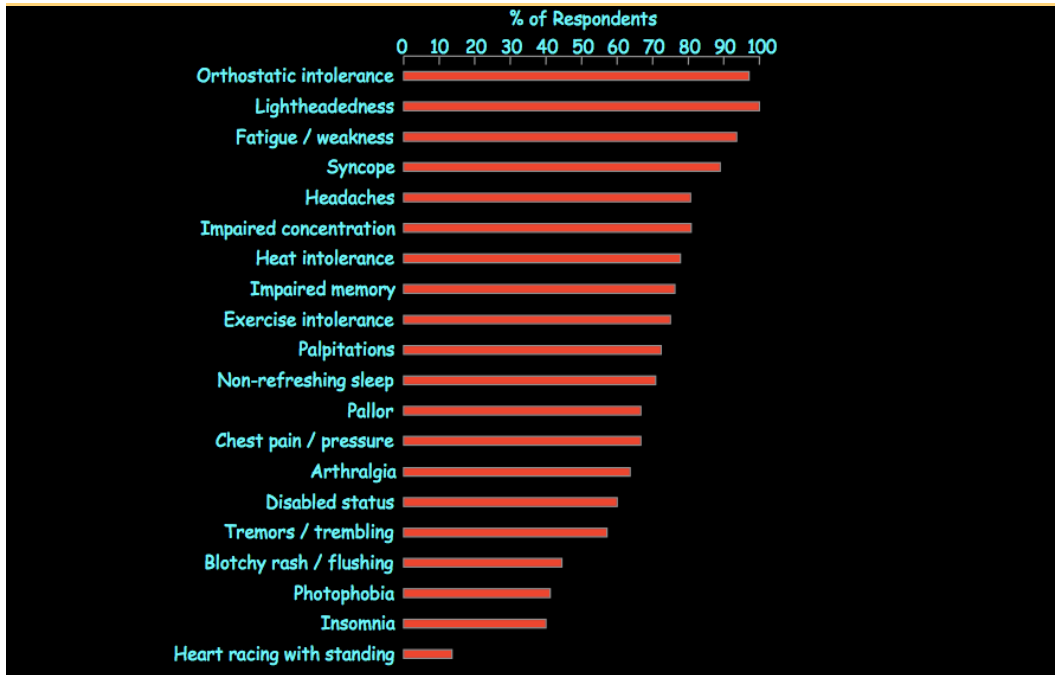
The Key is the "S"

The key word in postural tachycardia syndrome is “syndrome.”

A syndrome is a set of symptoms that occur together. Merely having a fast pulse rate while standing is not a syndrome, which always involves more than a single symptom or sign.

The occurrence of a rapid pulse rate when a person stands is necessary but is not sufficient to diagnose POTS.

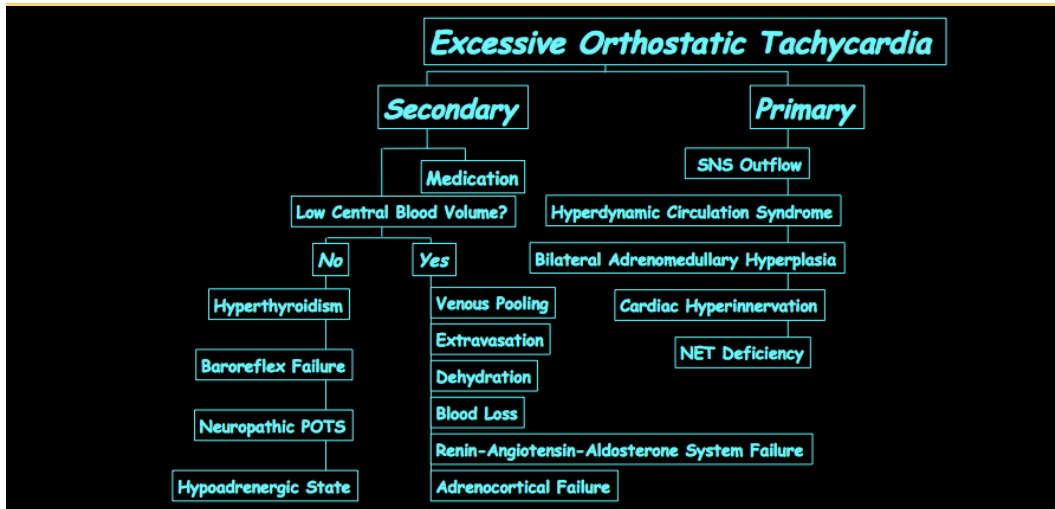
POTS is a syndrome, because it is associated with a variety of symptoms that, when thought of individually, are not specific for any



POTS patients usually have many non-specific symptoms.

particular disease process. Patients with POTS not only have a rapid pulse rate when they stand up, they also have several other symptoms, such as orthostatic intolerance, chronic fatigue, a tendency to faint, chest pain, pain in the back of the neck or shoulders, headache, cool, sweaty extremities, heat intolerance, exercise intolerance, palpitations, and neuropsychological complaints such as disturbed sleep, panic, anxiety, depression, “brain fog,” and generalized disability.

Primary vs. Secondary Causes of POTS



An algorithm for clinical evaluation of excessive orthostatic tachycardia

Trying to identify a specific cause in a particular patient with POTS can be a great challenge to clinicians. There are probably as many causes of a fast pulse rate as there are of a fever, and the typical symptoms of POTS are not specific for any single disease.

Researchers have thought that usually in POTS, sympathetic nerve traffic to the heart is increased as a compensation. The compensation could be for a decrease in the amount of blood returning to the heart or a decrease in the total peripheral resistance to blood flow when the patient stands up. Either situation could alter information from the baroreceptors to the brain, leading to a reflexive increase in sympathetic noradrenergic system activity directed by the brain.

Blood Volume and POTS

There are many causes for a decrease in the amount of blood returning to the heart when a patient is standing. The possibility of blood volume depletion or excessive pooling of blood in the legs during standing up has drawn particular attention. Indeed, low blood volume was noted in the first reported case of POTS. The response to i.v. infusion of normal saline can be dramatic, at least in the short run.

Dehydration, blood loss, or other causes of decreased blood volume can produce a condition that looks like POTS.

Delayed orthostatic hypotension in POTS is also thought to result from a progressive, exaggerated decline in blood volume during prolonged standing, from leakage of fluid into the tissues through blood vessel walls (extravasation). Consistent with excessive blood pooling in the legs or lower abdomen during orthostasis, inflation of a military anti-shock trousers (MAST) suit reduces substantially the increase in heart rate in response to orthostasis in patients with POTS.

Low blood volume in turn can result from blood loss, from failure of the bone marrow to make an adequate number of red blood cells, or from failure of hormone systems such as the renin-angiotensin-aldosterone system. In addition, blood volume can fall while a person stands, due to leakage of fluid out of the blood vessels into the tissues (extravasation). Finally, an “effective” low blood volume can occur,

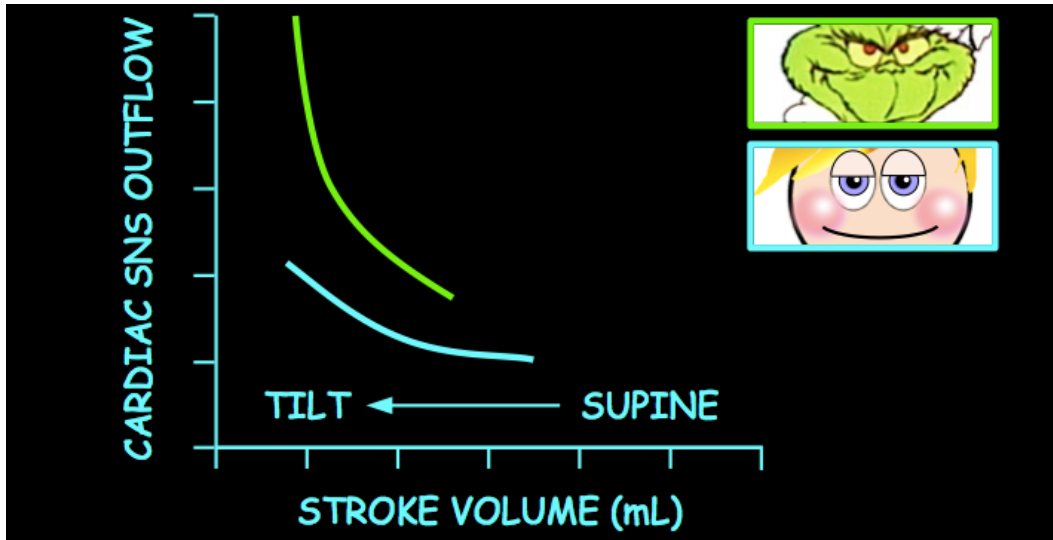
when the blood pools excessively in the veins in the pelvis and abdomen after a person stands, such as because of a lack of muscular “tone” in the vein walls. It is possible that a problem with the protein structure of blood vessel walls could lead to POTS. POTS in Ehlers-Danlos syndrome may be an example of such a condition.

Grinch Syndrome

Drs. Qi Fu and Ben Levine, of the University of Texas Southwestern Medical Center in Dallas, came up with a novel name for a type of POTS: “Grinch syndrome.”

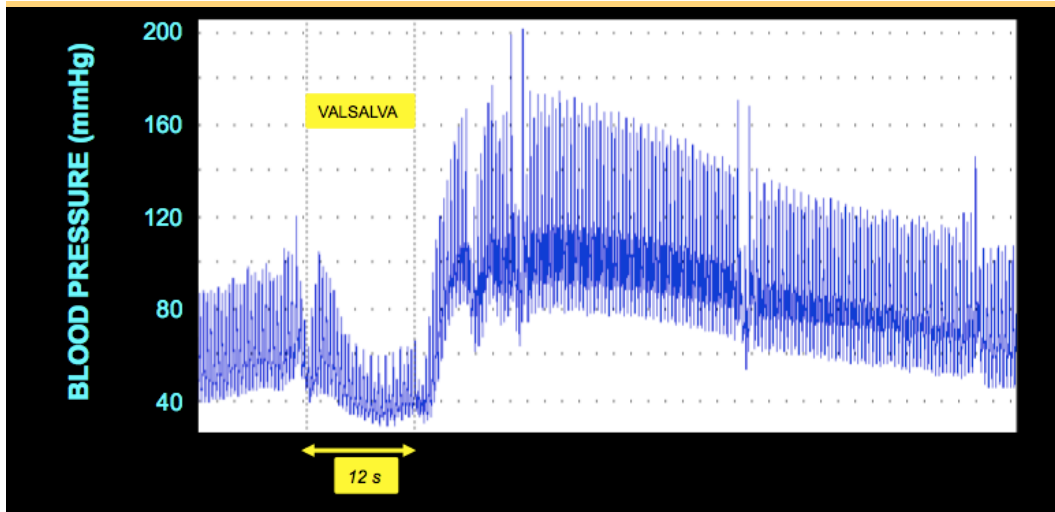
“Grinch syndrome,” refers to the Dr. Seuss character who had a heart that was “two sizes too small.” Fu and Levine proposed that marked tachycardia during orthostasis in Grinch syndrome patients is a compensation for low stroke volume. Exercise training was remarkably helpful in such patients.

We diagnosed Grinch syndrome in a POTS patient—an adolescent with congenital pectus excavatum and a cardiac stroke index below the lower limit of normal. When he performed the Valsalva maneuver, there was a huge, sustained Phase IV overshoot in blood pressure, and when he was tilted head-up on a tilt table, he had an excessive orthostatic increase in the arterial plasma norepinephrine (NE) level, both findings indicating excessive



Grinch syndrome is named for the Dr. Seuss character who had a heart “two sizes too small.” Here is how a patient with Grinch syndrome might respond to head-up tilt.

responsiveness of the sympathetic noradrenergic system. As the tilting proceeded, he had a progressive increase in skin electrical conductance (a measure of sweating). His arterial plasma adrenaline levels continued to increase beyond the proportionate increase in plasma NE—sympathoadrenal imbalance (SAI). As the adrenaline level increased, forearm vascular resistance decreased. This constellation predicts autonomically mediated syncope. Sure enough, soon after the forearm blood flow increased, the patient developed acute neurally mediated hypotension, and the tilting was stopped.



Dramatic Phase IV overshoot of blood pressure in a patient with POTS and Grinch syndrome. In the same patient there was a marked increase in plasma norepinephrine during tilt-table testing. Both abnormalities indicate excessive sympathetic noradrenergic system responses to stimuli that decrease venous return to the heart. Eventually the patient developed sweating and forearm vasodilation, harbingers of neurally mediated hypotension.

Neuropathic POTS

In “partial dysautonomia,” or “neuropathic POTS,” there is thought to be a patchy loss of sympathetic nerves, such as in the legs or splanchnic organs. When the patient stands up, the blood pools in the

veins, and less blood returns to the heart, or else the arterioles fail to constrict, and the total resistance to blood flow decreases. In response to either or both of these abnormalities, the sympathetic noradrenergic system supply to the heart is stimulated reflexively.

In “neuropathic POTS,” sympathetic nerves to the heart are thought to be overactive as a compensation for loss of sympathetic nerves elsewhere.

There are other possible causes of decreased total peripheral resistance that might reflexively increase sympathetic noradrenergic system traffic to the heart. For instance, any of several drugs block receptors for norepinephrine in blood vessel walls; other drugs directly relax blood vessel walls. The recent introduction of analyses of skin biopsies for small fiber neuropathy may help refine the diagnosis of neuropathic POTS.

Hyperadrenergic Orthostatic Intolerance

In “hyperadrenergic orthostatic intolerance,” the problem is thought to be a primary abnormality in the functioning or regulation of the autonomic nervous system itself.

Failure of the baroreflex can produce a condition that looks like POTS. Baroreflex failure is discussed separately.

In a related syndrome, called the hyperdynamic circulation syndrome, the patients have a fast pulse rate all the time, variable high blood pressure, increased heart rate responses to the drug, isoproterenol, and increased plasma norepinephrine and adrenaline levels at rest and during provocative maneuvers. β -Adrenoceptor blockers such as propranolol or benzodiazepines such as diazepam improve the syndrome. It is unclear whether patients with this syndrome have an increased frequency of later development of established hypertension. Episodes of fast pulse rate and increased blood pressure can be associated with blotchy flushing of the face, neck, and upper chest.

“Neurasthenia” a term introduced in the late 1860s. refers to a syndrome initially described in Civil War soldiers. Also called neurocirculatory asthenia, the syndrome consists of a large number of symptoms, including breathlessness, palpitations, chest pain, dizziness, shortness of breath on exertion, fatigue, excessive sweating, trembling, flushing, dry mouth, numbness and tingling feelings, irritability, and exercise intolerance. Most modern research about neurocirculatory asthenia has been conducted in Russia. Western cardiovascular researchers rarely use this term. The symptoms resemble those in POTS, and as in POTS the multiplicity of symptoms contrasts with a relative lack of signs, which all are non-specific—relatively fast pulse rate, relatively rapid breathing, facial and neck flushing, slight tremor, sweaty palms, a “functional” heart murmur, and hyperactive knee jerk reflexes, with generally normal resting blood pressure. Just as in POTS or the hyperdynamic circulation

syndrome, in neurasthenia injections of adrenaline can evoke these symptoms. β -Adrenoceptor blockers often normalize the cardiovascular findings without affecting the other symptoms and signs. Drugs such as caffeine can evoke fast pulse rate, increased ventilation, tremor, and sweatiness in patients with neurocirculatory asthenia.

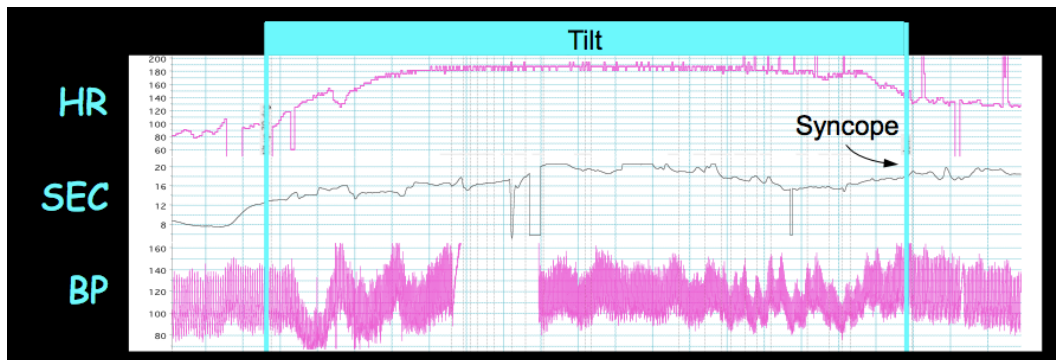
In another related condition, inappropriate sinus tachycardia, the heart rate is increased markedly from normal, even under resting conditions. Radiofrequency ablation of the sinus node, the heart's pacemaker area, is considered for patients with inappropriate sinus tachycardia who are resistant to treatment with medications. Radiofrequency ablation does not usually improve the condition of patients with POTS.

Patients with POTS often have increased plasma levels of norepinephrine, the chemical messenger of the sympathetic noradrenergic system, especially when they are standing up. Indeed, according to one suggestion, criteria for diagnosing POTS include an upright plasma norepinephrine level of 600 pg/ml or more; however, whether increased sympathetic nervous outflows constitute a primary abnormality or compensatory response usually is unknown in an individual patient.

If the orthostatic tachycardia were primary, then treating it would help the patient, but if the orthostatic tachycardia were secondary, then

treating the tachycardia would not help the patient. Keeping this principle in mind can help to understand how one patient may feel better from treatment with a beta-blocker, which forces the pulse rate to go down, while another may not feel better at all, even though the pulse rate has decreased to the same extent.

POTS with Autonomically Mediated Syncope



Polygraphic recording documenting excessive orthostatic tachycardia, sweating (measured by skin electrical conductance, or SEC), and blood pressure variability followed by syncope.

Although POTS and frequent fainting (autonomically mediated syncope, neurocardiogenic syncope, reflex syncope) are considered to be different forms of chronic orthostatic intolerance, when POTS patients are subjected to tilt table testing, a substantial minority have fainting reactions.

When they do, they have the same pattern of “sympathoadrenal imbalance” as found in patients with fainting who do not have POTS. In sympathoadrenal imbalance, there is a dissociation between plasma adrenaline levels, an index of sympathetic adrenergic system (SAS) activity, and plasma norepinephrine levels, an index of sympathetic noradrenergic system (SNS) activity.

Comparing Apples and Pears

Chronic orthostatic intolerance syndromes such as POTS are much more common in women than in men. The basis for this difference remains poorly understood.

One possibility is the body shapes of men and women, as a result of hormonal differences throughout development. In general, a man’s body is shaped like an apple, with broad shoulders, while a woman’s body is shaped like a pear, with broad hips. It seems reasonable to speculate that during orthostasis there would be more of a tendency of blood to pool in the abdomen and pelvis in women than in men. If so, then for the same amount of abnormal increase in the capacitance of veins, there would be a more severe decrease in venous return to the heart in women and consequently more reflexive recruitment of sympathetic noradrenergic outflows, resulting in a larger tachycardia response.



Male and female physiognomies—“apples” and “pears”

During orthostatic stress, whether induced by tilt table testing or lower body negative pressure, women have more blood pooling in the pelvic region than do men. This is probably because women have anastomoses between uterine and ovarian arteries and large plexuses of veins around the uterus, ovaries, and vagina.

People with Klinefelter syndrome (genotypically XXY) are phenotypically men, because they have a Y chromosome, but they are feminized because they have two XX chromosomes. They have broad hips and narrow shoulders. POTS has been reported in a patient with this syndrome.

This physiognomic notion is probably over-simplistic. Among other things, it does not explain easily why chronic fatigue syndrome,

autonomically mediated syncope, migraine, temporomandibular joint disorder, Sjogren's syndrome, and fibromyalgia—which often overlap—are also all more common in women than men.

POTS Treatment

The first step in management of chronic orthostatic intolerance is to search carefully for common, reversible causes, such as diabetes, weight loss, prolonged bed rest, debilitating diseases, and medications.

Treatment of POTS should be tailored to the individual patient.

Drug treatments for POTS generally have attempted to increase blood volume, such as using Florinef™ and liberal salt and water intake, injections of erythropoietin, or infusions of saline intravenously; block fast pulse rates, such as using β -adrenoceptor blocker; decrease exaggerated norepinephrine release, such as using clonidine; or enhance vasoconstriction, such as using midodrine or octreotide. Non-drug treatments include abdominal compression (e.g., a doubled bicycle leotard or abdominal binder), venous compression hose, calf muscle resistance training, exercise training, or even insertion of a pacemaker.

Often these treatments, while helpful, do not bring the patients back to

a sense of normal health. Over the course of months or years, the patients can improve, or else they learn to cope with this chronic, debilitating, but not life-threatening disorder.

In devising an individual treatment plan, it may be worthwhile to consider whether the POTS results from low blood volume, decreased tone of blood vessels, a primary form of hyperactivity of the sympathetic noradrenergic system, or physical de-conditioning. If there were low blood volume, then treatment with water, salt, fludrocortisone, or i.v. saline would be rational. If there were decreased tone of arterioles, then midodrine, a sympathomimetic amine, or L-DOPS would make sense, while if there were decreased tone of veins then compression hose or an abdominal binder could work. If there were a primary increase in sympathetic noradrenergic system outflow to the heart, then a beta-blocker would be in order. Finally, because of the debility caused by POTS, patients can get into a vicious cycle of bed rest, decreased cardiovascular and skeletal muscle tone, worse exercise intolerance and fatigue, and more bed rest. Enrolling in an individualized exercise conditioning program can be very beneficial.

STRESS CARDIOPATHY

All emotions entail changes in heart functions, a fact recognized by one of the giants in the history of medicine and physiology, William Harvey.

In 1628 Harvey described the circulation of the blood for the first time in his book, *On the Circulation of the Blood*, a classic in the history of clinical science. Remarkably, in the same book he stated one of the founding ideas of psychosomatic medicine, neurocardiology, and autonomics: “For every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart.”

Pathological studies about how distress can produce sudden death were not done until the past century. In 1907, about twelve years after the discovery of the cardiovascular stimulatory effects of adrenaline, it was demonstrated that infusion of adrenaline can lead to death of heart muscle. The heart muscle cells rupture and die of overstraining. A particular microscopic change called “contraction band necrosis” develops. In victims of assault who die without sufficient evidence of internal or external injury to explain the death, most have contraction band necrosis as part of the post-mortem findings. Similarly, patients who die from a stroke due to bleeding inside the brain often have contraction band necrosis (also called myocytolysis) of heart muscle



William Harvey, father of clinical science

cells. The extent of loss of heart muscle cells in this setting is related to the extent of increase in plasma levels of catecholamines.

A relatively recently described form of distress-induced acute heart failure is *takotsubo* cardiopathy, so named because of a characteristic abnormal shape of the heart in patients with this condition. A *takotsubo* is a Japanese pottery urn used to catch octopuses. The octopus's head gets stuck in the jar (I guess octopuses are not that smart.) In *takotsubo* cardiopathy, during systole when the heart is ejecting blood, the apex of the heart balloons out while the base of the heart contracts normally. On a ventriculogram the combination of

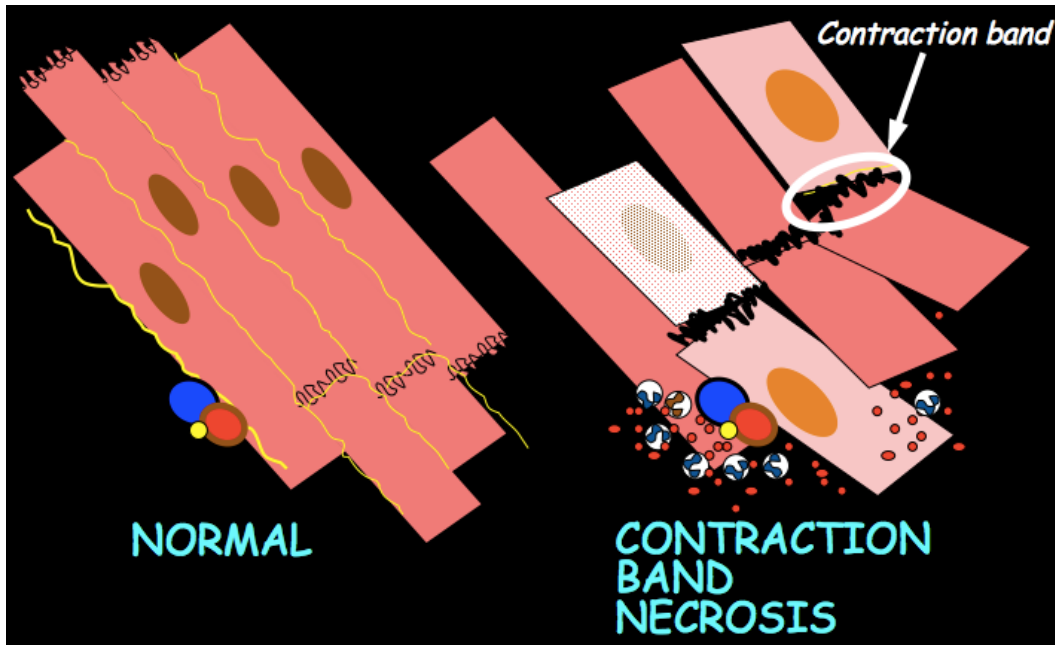
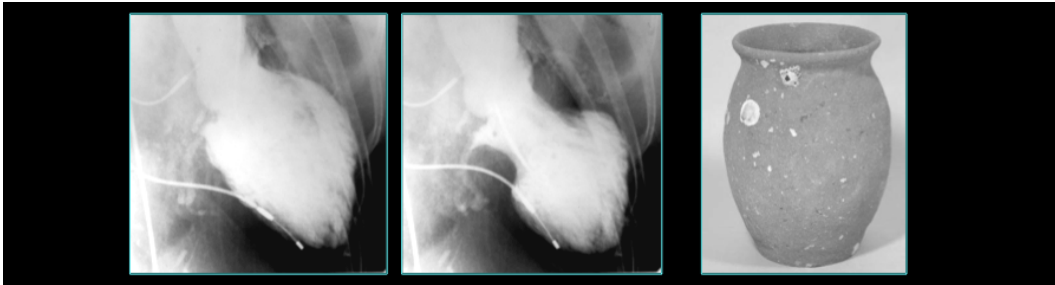


Diagram of contraction band necrosis of heart muscle cells

apical ballooning and basal contraction gives the appearance of a *takotsubo*.

Takotsubo cardiopathy has been reported to occur mainly in post-menopausal women, for reasons that are not yet completely understood. Some patients can have acute catecholamine-induced heart failure without the *takotsubo* heart shape. Remarkably, if the patient survives, heart muscle function can recover over a couple of weeks.



In takotsubo cardiopathy, during systole the apex of the heart balloons out.

Patients with stress cardiopathy have extremely high plasma adrenaline levels—more than 30 times normal. It seems likely that adrenaline levels this high are directly toxic to the heart.

In the setting of circulatory shock related to poor heart muscle pumping, catecholamines such as adrenaline often are given i.v. to try to improve the contractile function of the heart. Sometimes this approach backfires, and the infusion actually worsens the heart's pumping capability. This situation is very tenuous because of the possibility of induction of a lethal positive feedback loop.

Although it is widely accepted that high circulating adrenaline levels can cause or contribute to stress cardiopathy, the mechanisms of adrenaline cardiotoxicity are poorly understood. There are a few possibilities. First, at high concentrations adrenaline may inhibit rather than stimulate production of the second messenger adenylyl cyclase, by a switch from a stimulatory to an inhibitory G-protein.

Second, adrenaline taken up into the heart muscle cells could undergo spontaneous or enzyme-catalyzed oxidation, resulting in formation of autotoxic metabolites that interfere with the functions of numerous proteins required for cellular integrity. Third, adrenaline-mediated, drastically increased entry of ionized calcium into the cytoplasm could so contract the cells that they rupture—hence the term, “contraction band necrosis.”

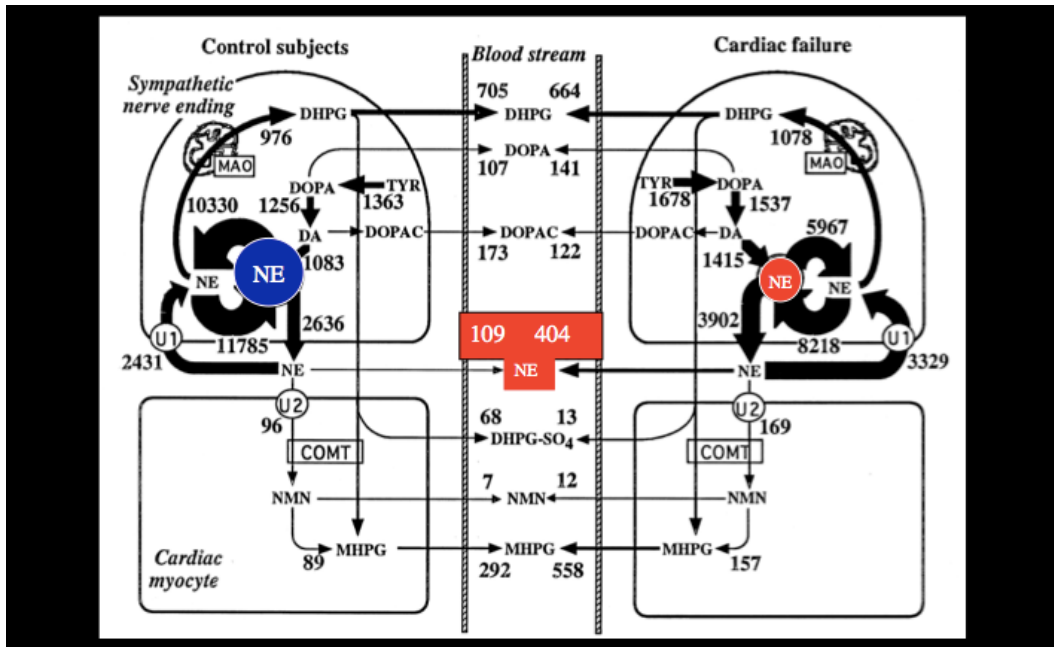
HEART FAILURE

Most dysautonomias are secondary; that is, an alteration in autonomic nervous system function that normally would itself be appropriate, adaptive, and helpful can be rendered maladaptive, harmful, or even lethal in the setting of an independent pathological state.

Heart failure is associated with stimulation of the sympathetic noradrenergic system (SNS).

The situation in heart failure is a prototypical example. In heart failure the heart does not deliver an appropriate amount of blood to body organs. As part of compensation to improve cardiac pump function, the sympathetic noradrenergic system (SNS) is activated. At the same time that this can improve the pump function of the heart, however, SNS activation increases the risk of abnormal heart rhythms, increases the work of the heart, promotes retention of sodium by the kidneys, and promotes overgrowth of heart muscle, which can stiffen the heart walls and worsen the heart failure.

The pattern of pathophysiologic abnormalities of the SNS in heart failure is very complex. At the same time that there is increased release of norepinephrine (NE) in the failing heart, there is also depletion of NE stores.



Heart failure involves increased norepinephrine release from sympathetic nerves at the same time that there is depletion of norepinephrine stores.

Energy-requiring processes such as Uptake-1 and vesicular uptake are less efficient in heart failure. Decreased NE stores in the failing heart appear to result from high NE turnover and reduced efficiency of NE reuptake and storage. Meanwhile, it is thought that the high rate of delivery of NE to its receptors renders the beta-1 adrenoceptors less sensitive.

Scientific integrative medical thinking can help grasp the development of chronic heart failure. Suppose a person had a bicuspid aortic valve

—the most common congenital valvular lesion in humans. The abnormal anatomy would cause turbulent blood flow across the valve. This might produce a “functional” heart murmur, but the individual could develop normally. Over the years of turbulent blood flow with each heartbeat, wear and tear on the valve would cause it to calcify and become stenotic, decreasing aortic filling. Via a negative feedback loop involving release of the SNS from baroreceptor restraint, the brain would direct a compensatory increase in cardiac SNS outflow. Increased NE delivery to its receptors on myocardial cells could help maintain cardiac function for many years.

In the long run, however, these compensatory, adaptive responses could come at a cost. NE promotes myocardial hypertrophy, which increases the demand for oxygen and metabolic fuels delivered by coronary perfusion; it increases cardiac contractility, which in this case would maintain aortic filling at the expense of increased blood flow turbulence and wear and tear on the valve, accelerating the stenosis; and it reduces thresholds for arrhythmias.

Especially in the setting of concurrent coronary artery disease, the increased demand for oxygen by the stimulated, hypertrophied heart could at times of stress exceed the supply—a kind of energy crisis, manifested clinically by easy fatigue and dyspnea on exertion among other symptoms. In sympathetic nerves, NE stored in vesicles leaks spontaneously continuously into the cytosol, and reuptake of NE back into the vesicles requires energy. As a consequence of decreased

energy availability there would be decreased NE recycling and depletion of NE stores. This would limit NE release during stress and escalate further the increases in SNS outflows. Inefficient sequestration of catecholamines that leak passively from the vesicles into the cytosol could result also in buildup of catecholamines in the cytosol, where they are “autotoxic” because of spontaneous and enzymatic oxidation to form toxic byproducts. Destruction of sympathetic nerves due to autotoxicity would diminish further the stores of releasable NE. Reuptake of released NE back into the terminals would be attenuated concurrently, because neuronal reuptake is also an energy-requiring process. The patient would now have congestive heart failure.

Once cardiac pump function declined to below a certain level despite maximal SNS stimulation, blood would back up into the pulmonary veins, bringing on pulmonary edema. The patient would then become short of breath even at rest and, in a distress response, experience the classic “feeling of impending doom,” which has been associated from time immemorial with massive adrenomedullary release of adrenaline. Moreover, rather than augmenting left ventricular myocardial contractility, too much adrenaline is toxic to myocardial cells. Myocardial contractility would decrease further, “stress cardiopathy” would develop, and the pulmonary edema would worsen. In several ways, physiologic negative feedback loops would have given way to pathophysiologic positive feedback loops. Within a sometimes surprisingly short period of time from the onset of symptoms, the

patient could die—within minutes because of a catecholamine-evoked ventricular arrhythmia, hours because of intractable pulmonary edema, or days because of critically decreased perfusion of body organs such as the kidneys.

SJOGREN'S SYNDROME

Sjogren's syndrome is a condition in which the patients have chronically dry mouth and dry eyes, typically in the setting of some form of connective tissue disease like rheumatoid arthritis. There is evidence of autoimmunity directed against the salivary glands and lacrimal glands, with infiltration of the tissue by lymphocytes.

The vast majority of Sjogren's syndrome patients are adult women—just as is the case for postural tachycardia syndrome, autonomically mediated syncope, chronic fatigue syndrome, temporomandibular joint disorder, and migraine. One of the most famous patients with the condition is the professional tennis player, Venus Williams, who also has reported chronic fatigue associated with her Sjogren's syndrome. Since having to drop out of the US Open in 2011, she has returned to close to her former performance, with a vegan diet and exercise regimen.

Sjogren's syndrome has long been suspected of involving a form of dysautonomia. A recent report suggested dysfunction of the parasympathetic cholinergic system; however, sympathetic noradrenergic nervous system function seems intact.



The professional tennis player, Venus Williams, had to drop out of the US Open in 2011 due to fatigue related to Sjogren's syndrome.

AMYLOIDOSIS

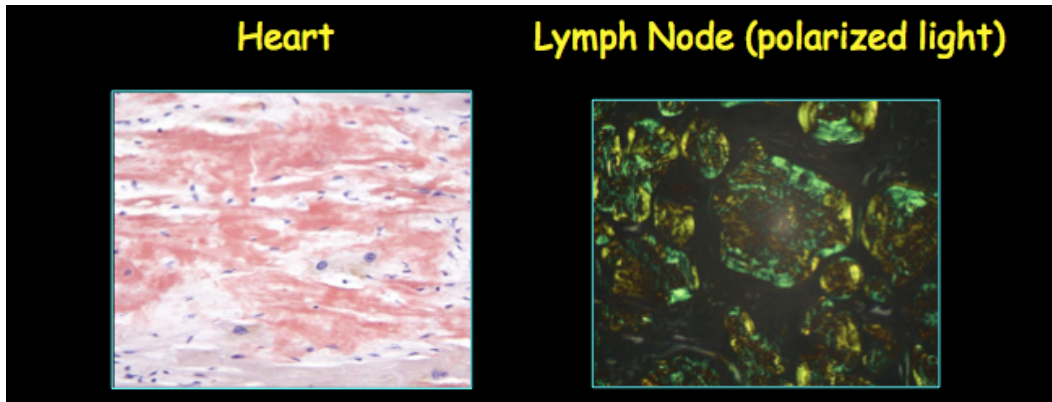
Amyloidosis refers to a variety of disorders that have in common deposition in organs of a mis-folded protein called amyloid. Normally soluble, the misfolding causes the protein to precipitate. The disease manifestations depend on the organs involved—especially the heart and kidneys.

Amyloidosis can involve the sensory and autonomic fibers in peripheral nerves. Peripheral neuropathy in amyloidosis is usually symmetrical. I remember a case of amyloid-associated autonomic failure where the patient wore gloves continuously, in an effort to decrease his distressing “pins and needles” sensations.

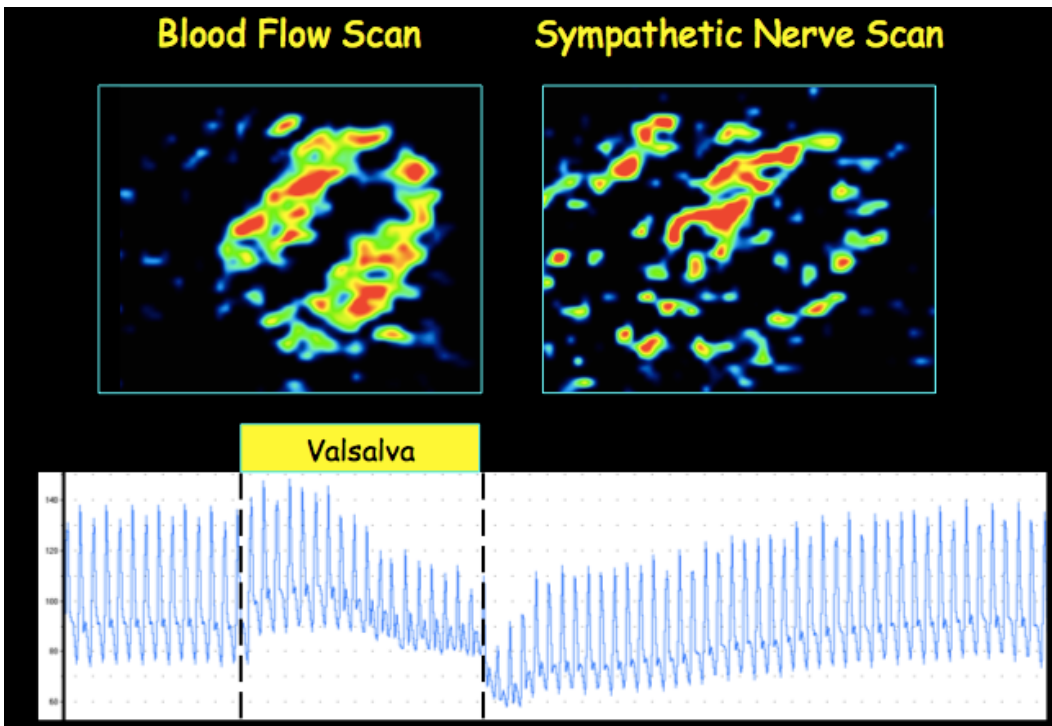
One can diagnose amyloidosis by biopsy of mucus membranes (rectal, buccal) or abdominal fat pad tissue, looking for deposits of amyloid material. Congo red staining, combined with polarized light, demonstrates the amyloid proteins microscopically.

Patients with amyloidosis can have marked reduction in sympathetic noradrenergic nerves, indicated by cardiac sympathetic neuroimaging.

The exact mechanisms of amyloid-related autonomic failure are unknown. There is no known effective treatment of autonomic neuropathy in the setting of amyloidosis.



Congo red staining reveals amyloid deposits in organs such as the heart and lymph nodes.



Laboratory abnormalities in an amyloidosis patient

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome is a condition in which there is autoimmune attack on peripheral nerves. The syndrome often follows by a few days or weeks a respiratory or gastrointestinal viral infection or surgery. The target tissue is the myelin sheath surrounding nerves or the nerve fibers themselves. The longer nerves are affected earlier, explaining initial findings in the feet or hands, with a centripetal progression. The symptoms and signs are of an ascending symmetric weakness or paralysis and altered sensation beginning in the feet and moving upwards in the body. The patient's clinical status declines over the course of hours to days to weeks, with the condition at its worst after a few weeks. In severe cases the patient becomes totally paralyzed and can die from respiratory failure. Eventually the patient recovers, although there can be residual weakness.

Andy Griffith, the beloved sheriff of Mayberry in the hit television series bearing his name, died of a heart attack in 2012. At the time few realized that he had suffered from Guillain-Barré syndrome for many years. The sequence of clinical events in his case was rather typical. He had flu-like symptoms, and when these began to clear, searing pain came on along with inability to feel his legs. He



Andy Griffith, who received a Presidential Medal of Freedom in 2005, suffered from Guillain-Barré syndrome.

collapsed from the pain and subsequently developed spreading muscle weakness and paralysis. He did not develop respiratory failure. He underwent nearly a year of convalescence, and he was left with a permanent limp. For a time he wore plastic leg braces, but discarded them “because they squeaked and the soundman could hear them.”

Treatment of Guillain-Barré syndrome includes, plasma exchange (plasmapheresis) and high-dose intravenous immunoglobulin (IVIG).

Large swings in blood pressure, tachycardia, abnormal heart rhythms, and altered sweating can accompany Guillain-Barré syndrome. These abnormalities suggest involvement of multiple components of the autonomic nervous system, with parasympathetic nervous failure and activation of the sympathetic noradrenergic and adrenergic systems.

Guillain-Barré syndrome patients can develop a form of reversible

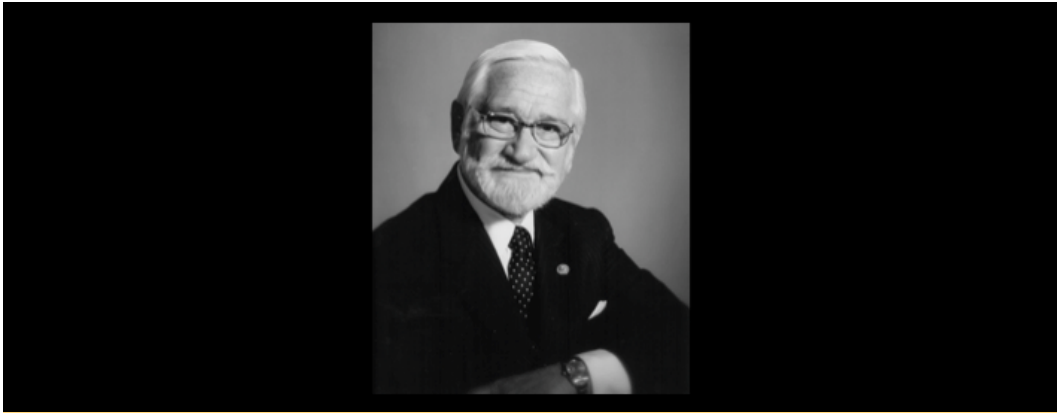
heart failure that may be mediated by catecholamines. The condition resembles *takotsubo* cardiopathy.

The Sabin Affair

Another famous person who may have had Guillain-Barré syndrome was Dr. Albert B. Sabin, the well known developer of the oral polio vaccine.

During World War II Sabin had conducted research on infectious polyneuritis in soldiers. In 1941 he was the first author of a report published in *The American Journal of Pathology*, entitled, “Visceral lesions in infectious polyneuritis (infectious neuronitis, acute polyneuritis with facial diplegia, Guillain-Barré syndrome, Landry's paralysis).”

More than 40 years later, in the early 1980s, and long after having attained international acclaim for developing the oral polio vaccine, Sabin conducted experimental therapeutic trials of an aerosolized measles vaccine in Brazil and Mexico. Not only did the vaccine not work, but he also contracted a syndrome manifested at first by weak and wobbly legs. After studying paralyzing viral diseases for more than a half century, he ironically seemed to have come down with a form of post-viral paralysis.



Albert Sabin, developer of the oral polio vaccine

He was diagnosed with a rare cervical spine disease in which a ligament bordering the spinal canal ossifies. He underwent neurosurgery for this and did have transient relief, but this was followed about two months later by the sudden onset of severe leg pain and ascending paralysis. He lost control of his legs, then his arms, developed pneumonia, and had an episode of respiratory arrest, which an aide noticed; her alerting medical personnel saved his life. He attributed his condition to a side effect of the neurosurgery and his cessation of breathing to obstruction of his endotracheal tube.

The pain and paralysis lasted several months more. A patient at the NIH Clinical Center for rehabilitation therapy, he slowly regained function of his arms and upper body. In a news article he was quoted as saying, “Maybe I'll walk again...I expect to. I'm regaining some powers, fiber by fiber.” In June of that year he gave a half hour talk on viral diseases at the NIH—while standing. By July of 1984 he

could walk briefly without a cane, but with an obvious wobble. To me this sounds like Guillain-Barré syndrome.

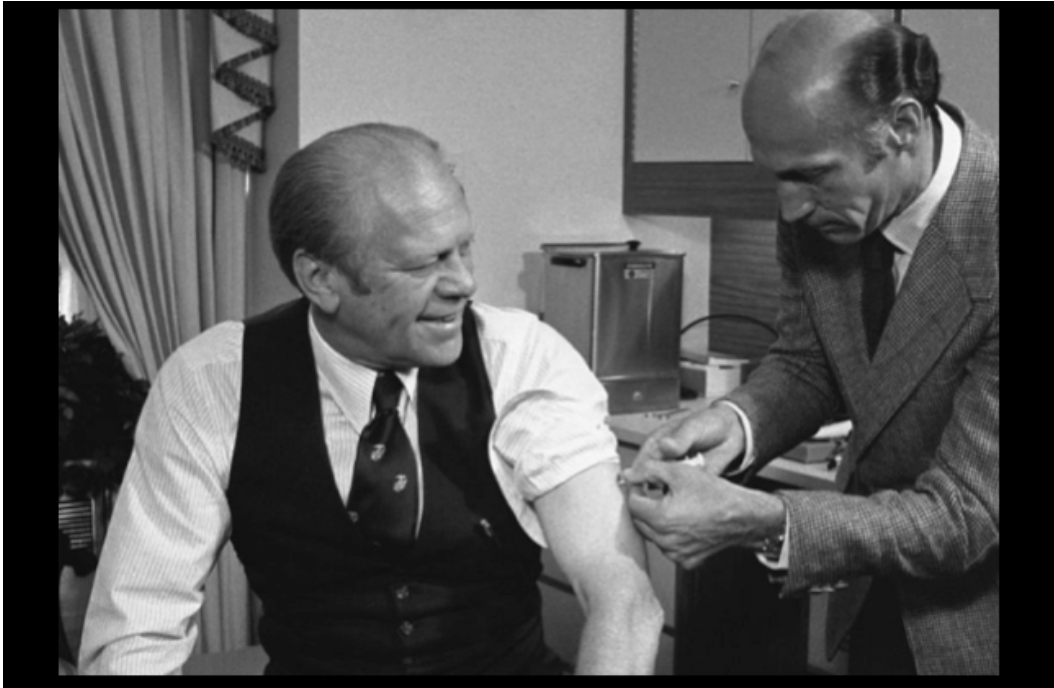
The Swine Flu Affair

In January, 1976 an outbreak of H1N1 “swine flu” virus broke out among Army recruits in Fort Dix, NJ. Because of similarity of the viral strain to that involved in the influenza pandemic in 1918, a massive immunization campaign began. More than 40 million Americans received the vaccination.

When then US President Gerald Ford flew Albert B. Sabin to the White House to help publicize the swine flu vaccination program, Sabin gave the blunt opinion, “I said the whole program was unfounded... There was no basis for vaccinating everybody.” The campaign went ahead anyway.

There were disastrous consequences. About 2,000 people were left permanently paralyzed. About 500 lawsuits against the US Government (corresponding to about \$4 billion) were filed related to Guillain-Barré syndrome as a result of the vaccine. A few months later the US Government stopped the swine flu immunization campaign, because of the cases of Guillain-Barré syndrome.

Since about 40 million people received the vaccine, the risk of Guillain-Barré syndrome, while increased, was extremely small. In



President Gerald Ford receives the swine flu vaccination.

2003 the US Institute of Medicine concluded that there was evidence for a causal relationship between the 1976 swine flu vaccination campaign and Guillain-Barré syndrome in adults.

BAROREFLEX FAILURE

In acute baroreflex failure, the brain does not respond appropriately to information from the cardiovascular system, and the sympathetic noradrenergic system is activated inappropriately.

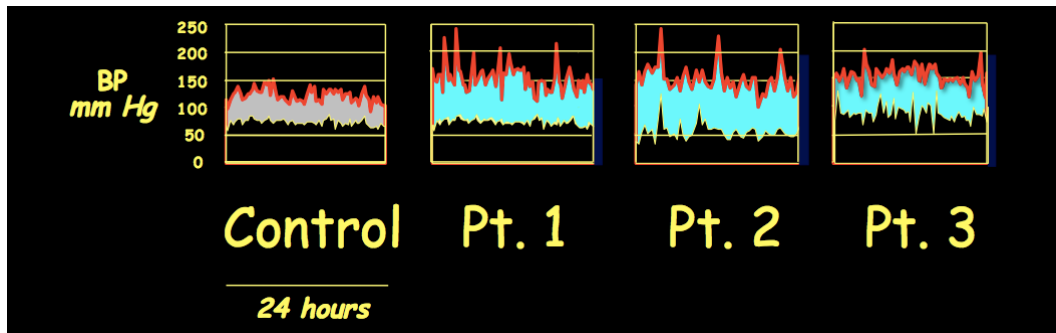
Failure of the arterial baroreflex can produce a condition that looks like POTS.

In baroreflex-cardiovascular failure, the heart rate does not increase appropriately when the person stands up or is tilted. This helps distinguish baroreflex failure from POTS as a cause of chronic orthostatic intolerance.

Orthostatic intolerance in baroreflex failure is associated with large swings in blood pressure, because of the inability of the baroreflexes to keep the blood pressure in check. There are episodes of extreme high blood pressure and fast pulse rate. Because of this failure, relatively minor stimuli can produce large increases in the activity of the sympathetic noradrenergic system in this condition.

Arterial baroreflex failure can result from tumors or neurosurgery that involve the dorsal medulla. Baroreflex failure also is a common correlate of congestive heart failure.

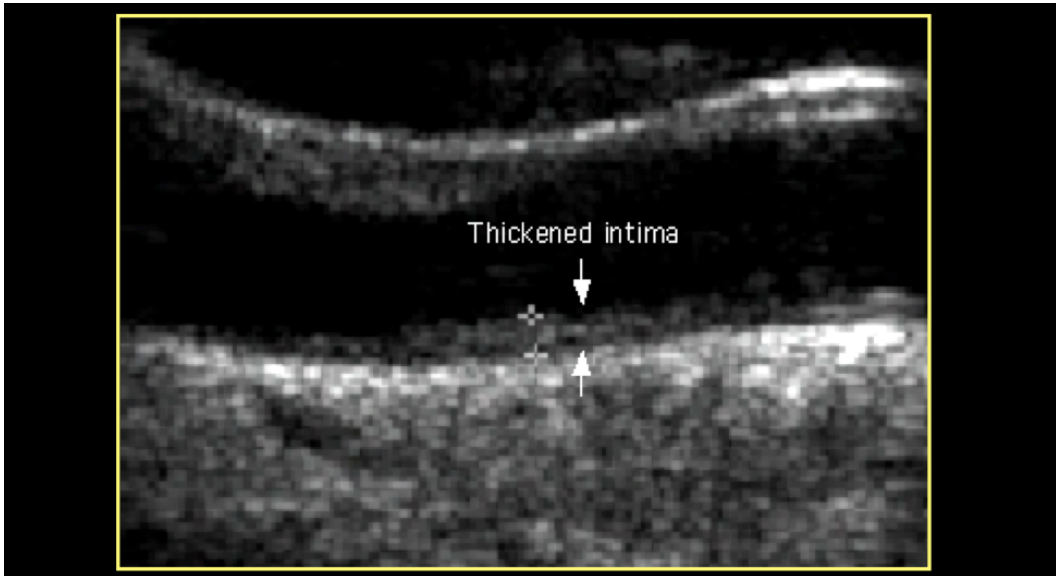
Several years ago Dr. Yehonatan Sharabi, then a Clinical Fellow in our Section, noted that a group of patients with labile blood pressure had a remote history of neck radiation therapy, such as to treat a lymphoma. The disease itself was gone. He guessed—correctly—that baroreflex failure linked neck irradiation in the distant past with cardiovascular instability years later.



Excessive blood pressure variability documented by ambulatory blood pressure monitoring in patients with arterial baroreflex failure

Radiation therapy tends to accelerate hardening of the arteries (arteriosclerosis) in the irradiated area. The baroreceptors are concentrated in the carotid sinus, where the common carotid artery splits in the neck into the internal carotid artery, which supplies blood to the brain, and the external carotid artery, which supplies blood to the face and scalp. The baroreceptors are distortion receptors. If they became encased in a rigidified carotid sinus, such as due to arteriosclerosis after neck irradiation, then baroreflex failure could result. Because of the “debuffering” the blood pressure is allowed to increase and decrease excessively.

Baroreflex failure is often very difficult to treat. Some patients have improvement with clonidine.



Atherosclerotic intimal wall thickening in a patient with arterial baroreflex failure years after neck irradiation

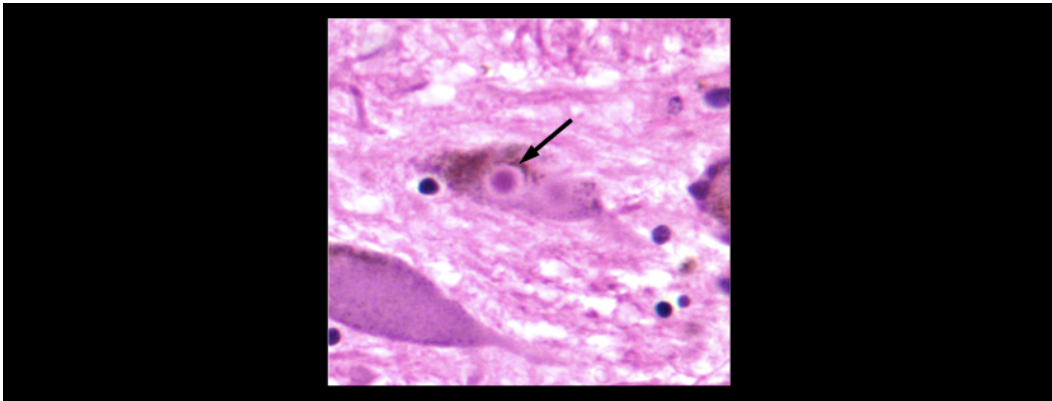
AUTONOMIC SYNUCLEINOPATHIES

Neurologists have long recognized three forms of primary chronic autonomic failure—pure autonomic failure (PAF), multiple system atrophy (MSA), and autonomic failure in the setting of Parkinson’s disease (PD).

Now it is known that all three diseases come under the umbrella of “synucleinopathies,” meaning that they all involve abnormal deposits of a protein, alpha-synuclein.

The alpha-synuclein story is relatively new. In 1997 an international team of researchers reported the first identification of a genetic cause of PD—mutation of the gene encoding alpha-synuclein—in a rare Greek-Italian-American family in which PD was transmitted as an autosomal dominant trait, meaning that one-half of the family members, whether men or women, had PD and one-half didn’t.

This was an important discovery, but since only one family was involved, it was unclear whether the new information would apply to PD as a whole. In the same year, however, it was found that Lewy bodies, a pathologic hallmark of PD, contain abundant precipitated alpha-synuclein. That is, even sporadic PD was found to involve an abnormality of alpha-synuclein.

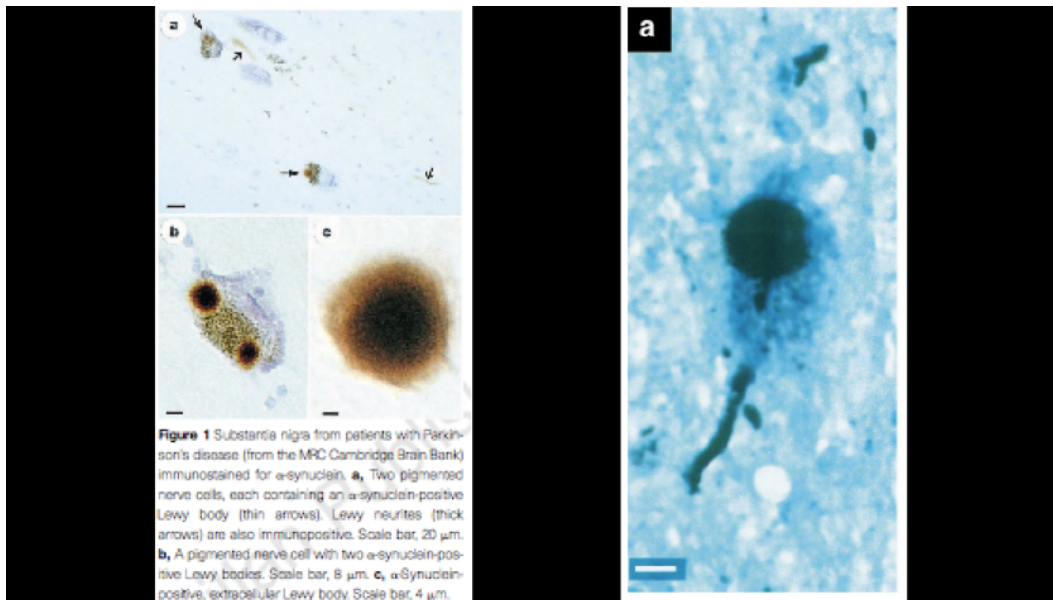


A Lewy body in the brainstem of a patient with pure autonomic failure.

Multiple system atrophy (MSA) was also found to involve alpha-synuclein deposits. In MSA, the deposits are in glial cells, which are helper cells that are not neurons. The deposits of alpha-synuclein were in the cytoplasm of the glial cells, in the form of glial cytoplasmic inclusions (GCIs). MSA of both the parkinsonian and cerebellar types are characterized by GCIs.

Then it was found that PAF, the third form of primary chronic autonomic failure, also involves Lewy bodies, both in the brainstem and in sympathetic ganglia.

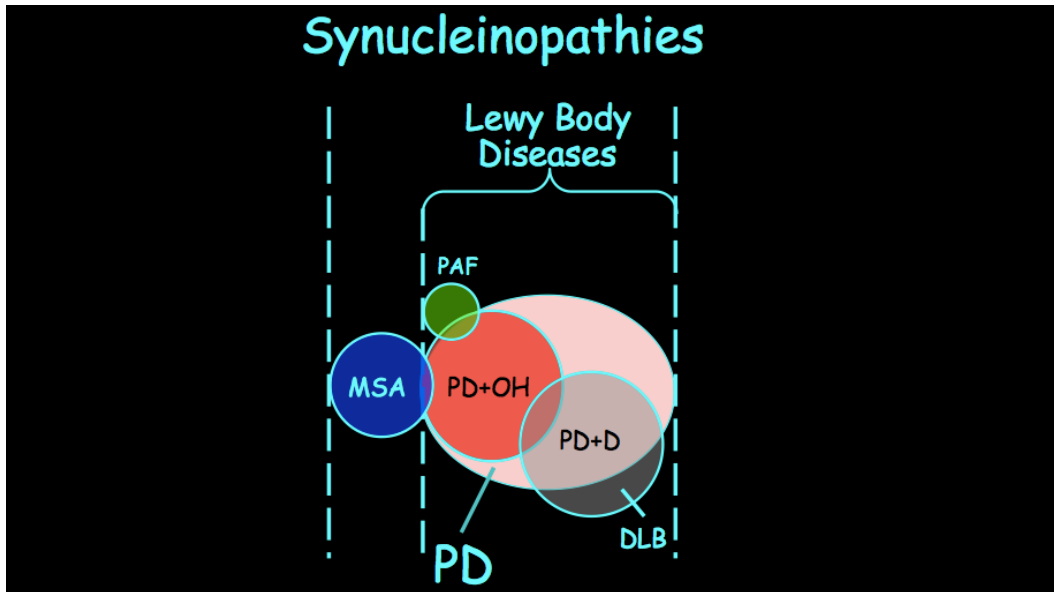
The idea evolved rapidly that the primary chronic autonomic failure syndromes are in a family of synucleinopathies. Together they are



Lewy bodies contain abundant precipitates of alpha-synuclein.

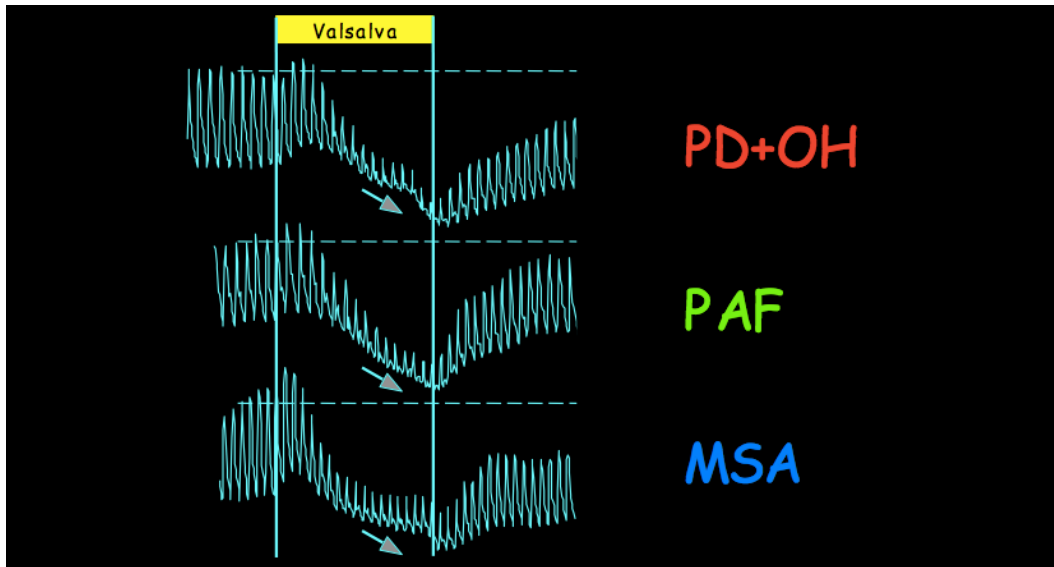
called autonomic synucleinopathies.

About 30-40% of patients with Parkinson's disease have orthostatic hypotension, a fall in blood pressure every time they stand up. This subgroup has been designated "PD+OH." A substantial proportion of PD patients have dementia—PD+D, which overlaps with a condition called dementia with Lewy bodies (DLB), or Lewy body dementia. Most PD patients and at least some PAF patients eventually develop dementia.



Multiple system atrophy (MSA), pure autonomic failure (PAF), Parkinson's disease (PD), and dementia with Lewy bodies (DLB) are forms of autonomic synucleinopathy.

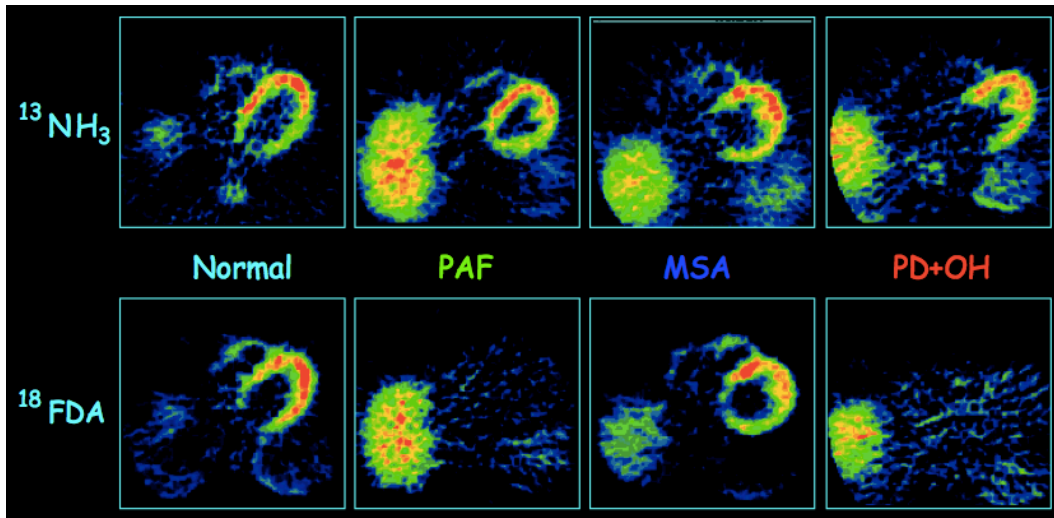
MSA, PAF, and PD+OH patients typically have failure of regulation of the sympathetic noradrenergic system by the arterial baroreflex. When they perform the Valsalva maneuver, they have abnormal beat-to-beat blood pressure responses in Phases II and IV. In a patient with orthostatic hypotension, finding these abnormalities helps establish a diagnosis of sympathetic neurocirculatory failure but is of no value in the differential diagnosis of the three forms of primary chronic autonomic failure.



Parkinson's disease with orthostatic hypotension (PD+OH), pure autonomic failure (PAF), and multiple system atrophy (MSA) involve abnormal beat-to-beat blood pressure responses to the Valsalva maneuver.

MSA is sub-classified into parkinsonian and cerebellar forms (MSA-P and MSA-C).

MSA-P can be very difficult to separate from PD+OH by clinical symptoms or signs. In general, MSA patients do not have much improvement in their movement disorder when they receive levodopa treatment; however, some do. MSA progresses at a faster rate on average than does PD+OH. Virtually all MSA patients have OH,

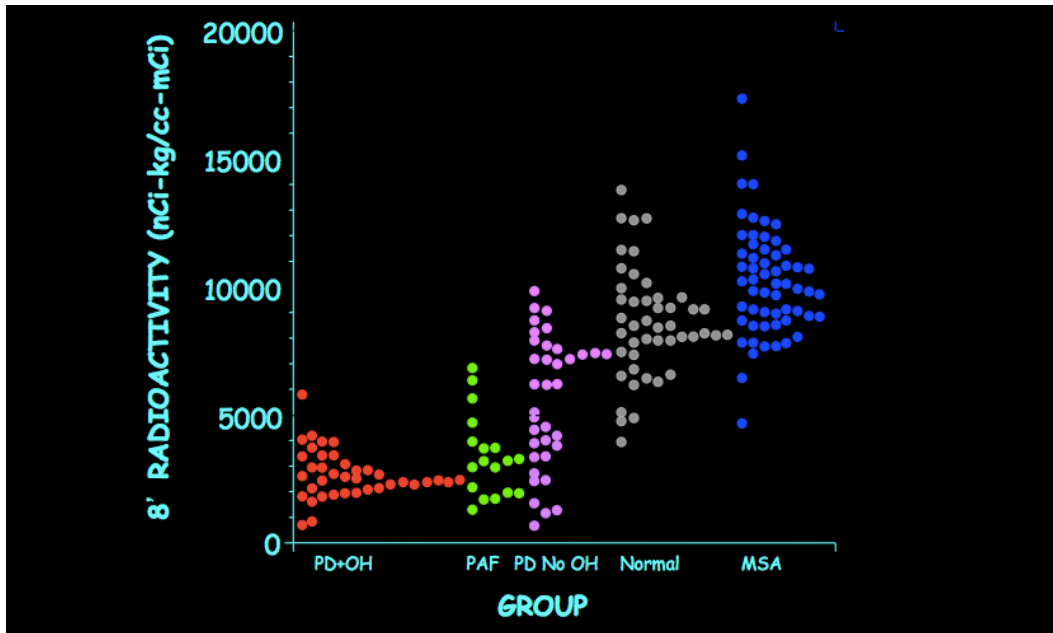


PAF and PD+OH patients have evidence for loss of cardiac sympathetic nerves, and while most MSA patients have evidence for intact cardiac sympathetic innervation.

while only a minority of PD patients have OH. Urinary incontinence is common in both MSA-P and PD+OH, but urinary retention is more closely associated with MSA-P, while urinary frequency and urgency is common in PD.

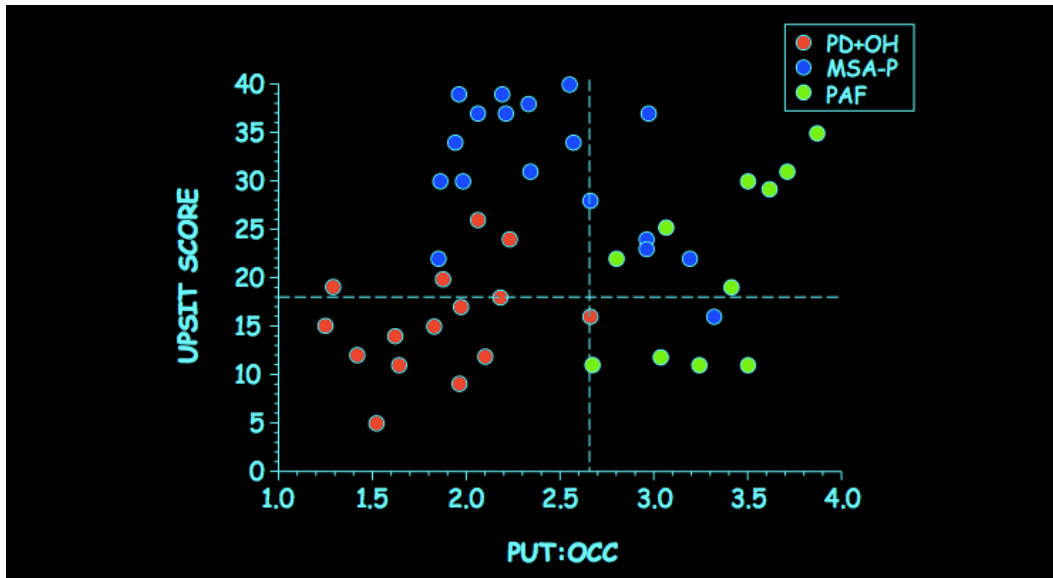
PD is much more prevalent than is MSA. This means that a patient with parkinsonism and OH could have either disease.

A powerful way to distinguish MSA-P from PD+OH is cardiac sympathetic neuroimaging, such as by ^{123}I -MIBG SPECT scanning



All PD+OH patients (in red) have evidence for cardiac sympathetic denervation, whereas most MSA patients (in blue) have evidence for intact cardiac sympathetic innervation.

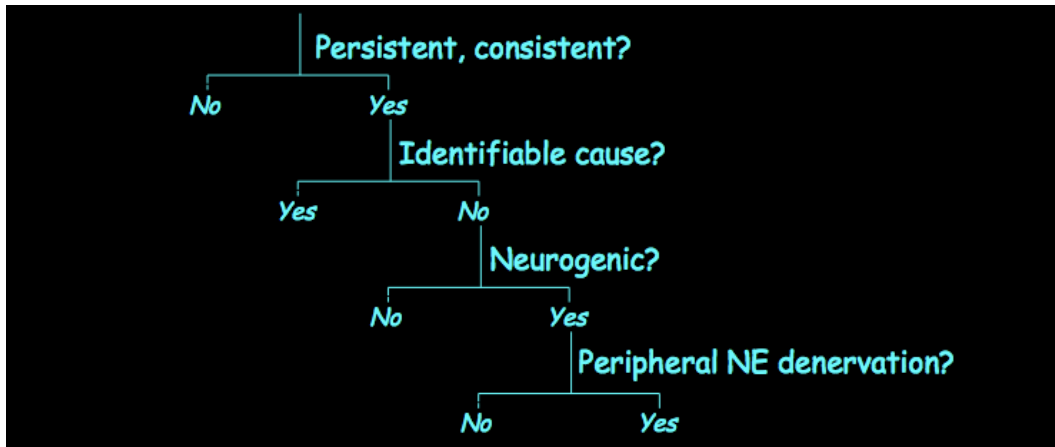
or ^{18}F -dopamine PET scanning. All PD+OH patients have evidence for a loss of sympathetic noradrenergic nerves in the heart, whereas most MSA-P patients have intact sympathetic noradrenergic innervation. A minority of MSA patients have evidence for a loss of cardiac sympathetic nerves; however, in a patient with MSA-P vs. PD+OH, the finding of normal cardiac sympathetic innervation excludes PD+OH.



Most PD+OH patients have anosmia according to the UPSIT, whereas most MSA-P patients do not.

Another valuable clinical laboratory test in the differential diagnosis of PD+OH vs. MSA-P is assessment of the sense of smell, such as by the University of Pennsylvania Smell Identification Test (UPSIT). Most patients with PD+OH are anosmic—the UPSIT score is 18 or less out of 40. In contrast, many MSA-P patients have normal or only slightly to moderately decreased sense of smell. The finding of normal sense of smell on the UPSIT favors a diagnosis of MSA-P over PD+OH.

In the evaluation of a patient with possible primary chronic autonomic

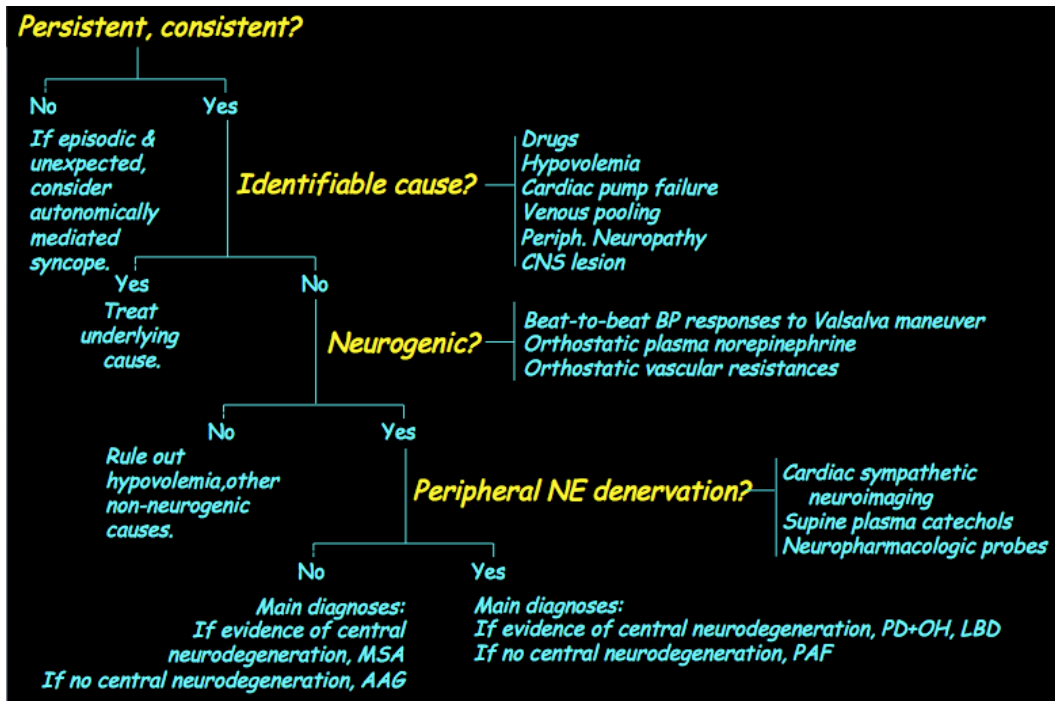


Simple 4-step algorithm for workup of orthostatic hypotension

failure manifesting with orthostatic hypotension, a 4-step algorithm has been proposed.

First, in contrast with conditions such as postural tachycardia syndrome and autonomically mediated syncope, orthostatic hypotension from primary chronic autonomic failure is a persistent, consistent finding. The patient may not always have symptoms of low blood pressure while standing, but the blood pressure always falls. By consensus, the orthostatic decrease in systolic blood pressure is greater than 20 mmHg between lying down for several minutes and standing up for at least 3 minutes.

Second, in order to diagnosis primary chronic autonomic failure,

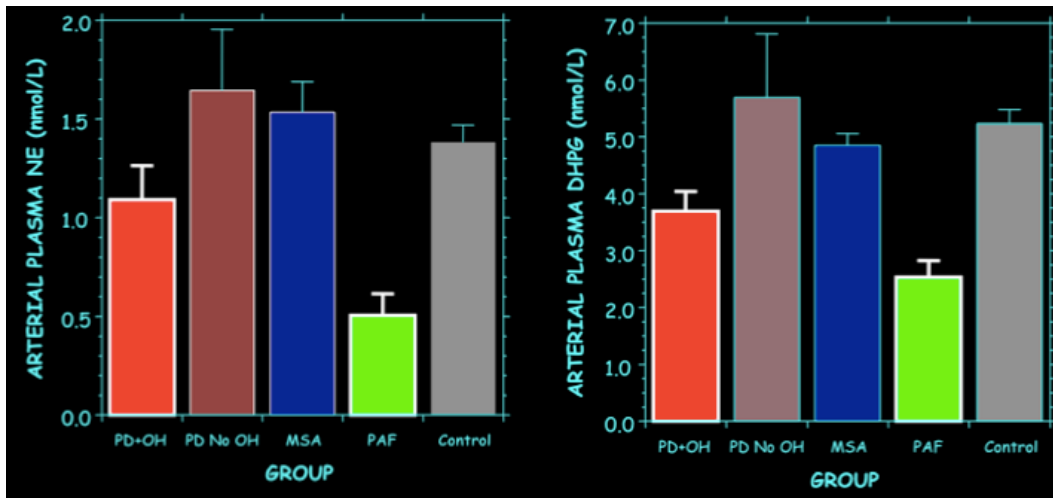


Detailed algorithm for the workup of orthostatic hypotension

secondary causes such as drugs and diabetes must be excluded.

Third, the orthostatic hypotension should be confirmed to be neurogenic. One way to do this is by assessing the beat-to-beat blood pressure responses to the Valsalva maneuver.

Fourth, one should test for loss of sympathetic noradrenergic nerves. This may be done by cardiac sympathetic neuroimaging, assaying plasma catechols, using neuropharmacologic probes, or examining



Among patients with orthostatic hypotension, PD patients have somewhat decreased and PAF patients more clearly decreased plasma norepinephrine (NE) and dihydroxyphenylglycol (DHPG) levels.

skin biopsies for loss of innervation in *arrector pili* muscle or in blood vessel walls.

Sympathetic noradrenergic innervation is generally intact in MSA and is decreased or absent in PD+OH and PAF.

Multiple System Atrophy (MSA)

Synopsis:

Mid-aged or elderly of either sex and any race.

Not inherited or infectious.

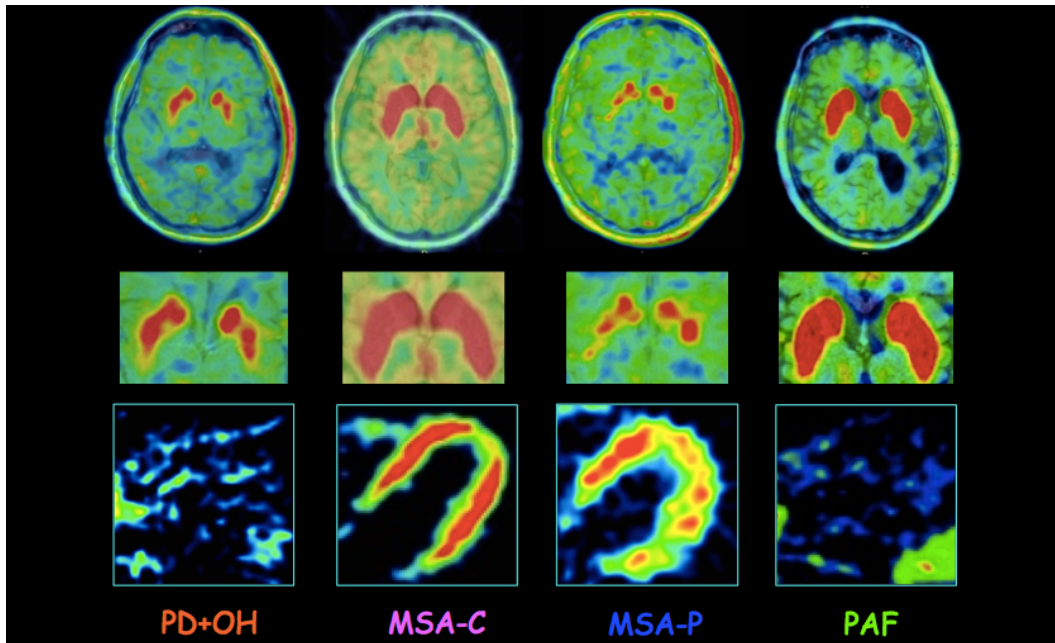
Chronic, persistent autonomic failure.

Signs of brain disease, such as slurred speech, rigidity, tremor, poor coordination.

Relentless progression over years.

Multiple system atrophy (“MSA”) is a disease that involves progressive degeneration of multiple portions of the central nervous system, including portions that regulate the autonomic nervous system. Several unconscious “vegetative” functions fail, such as digestion, urination, speech and swallowing mechanisms, and cardiovascular reflexes. Unlike pure autonomic failure, MSA is unfortunately a disease that is progressive and eventually lethal. On average, patients survive for about a half dozen years after the diagnosis is made. MSA differs from multiple sclerosis, which is characterized clinically by remissions and exacerbations and by relatively few changes in functions of the autonomic nervous system.

No one knows what causes MSA. It is not inherited, and no known environmental toxin causes it. According to one view, MSA results



The cerebellar and parkinsonian forms of MSA usually involve intact cardiac sympathetic innervation. MSA-P is associated with evidence for loss of putamen dopaminergic innervation.

from a form of auto-immune process, where the patient's immune system attacks and destroys particular brain cells. Brain tissue from MSA patients shows abnormal accumulations of alpha-synuclein in glial cells—helper cells that are not neurons. Whether these accumulations cause MSA, and the mechanisms by which the accumulations form, remain unknown.

MSA has different forms, which result in different symptoms and

signs. In the parkinsonian form of MSA (MSA-P) the patient has symptoms and signs of Parkinson's disease, such as stooped posture, muscular rigidity, and slow initiation of movement. Unlike in Parkinson's disease, these problems usually do not respond well to treatment with Sinemet™, the most commonly used drug for Parkinson's disease, and there usually is no “pill roll” resting tremor.

In the cerebellar form of MSA (MSA-C) the patient has symptoms and signs of failure of the cerebellum, which is a part of the brain that plays an important role in coordinated movements, coherent speech, balance, and accurate gait. If the patient has a tremor, it worsens with intentional movements. The typical patient also has slurred speech and a wide-based, “drunken sailor” type gait.

MSA always involves one or more symptoms or signs of failure of the autonomic nervous system. Failure of the parasympathetic nervous system produces urinary retention and incontinence, constipation, and erectile failure in men. Failure of the sympathetic noradrenergic system produces a fall in blood pressure when the patient stands up (orthostatic hypotension) or after a meal (post-prandial hypotension), resulting in symptoms such as dizziness, weakness, or faintness upon standing or after eating.

MSA with a fall in blood pressure standing has been called the Shy-Drager syndrome, but this term is no longer used.

Investigators used to equate MSA with the Shy-Drager syndrome, which by definition involves orthostatic hypotension (OH). Others considered MSA to be an umbrella diagnosis that includes the Shy-Drager syndrome when OH figures prominently in the clinical presentation but also includes forms where signs of cerebellar atrophy or parkinsonism stand out. The term, Shy-Drager syndrome, is no longer used as a diagnosis.

Symptoms and signs of other brainstem degeneration in MSA include particular abnormalities in eye movements (as in progressive supranuclear palsy), slurred speech, poorly coordinated swallowing, abnormal breathing (e.g., stridor), and repeated aspiration, where swallowed food goes into the airway. These problems occasionally occur in patients with MSA who do not have orthostatic hypotension or other evidence of failure of the sympathetic nervous system. In MSA it is thought that the autonomic failure reflects loss of the ability to regulate sympathetic and parasympathetic nerve traffic in the nerves, but the nerves themselves are intact. This appears to be a major difference between MSA and Parkinson's disease, in which autonomic failure typically is associated with a loss of nerves of the sympathetic noradrenergic system. Because of the presence of intact sympathetic nerves, patients with MSA have large increases in blood pressure when they receive drugs such as yohimbine that release norepinephrine from sympathetic nerves and have large decreases in blood pressure when they receive drugs such as trimethaphan that decrease release of norepinephrine from sympathetic nerves. The fact

that trimethaphan, which works by blocking transmission of autonomic nerve impulses in the ganglia, decreases blood pressure in patients with MSA means that in MSA the problem is not so much decreased autonomic nerve traffic as failure of the brain to regulate that traffic appropriately.

Patients with MSA appear to have approximately normal nerve traffic in intact sympathetic noradrenergic nerves when they are lying down, and so while they are lying down they usually have normal plasma levels of norepinephrine, the chemical messenger of the sympathetic noradrenergic system. The patients typically have a failure to increase sympathetic nerve traffic when they stand up, and so they have a failure to increase plasma norepinephrine levels normally when they are tilted upright. In contrast, patients with pure autonomic failure, who have a loss of sympathetic nerves, tend to have low plasma norepinephrine levels even when they are lying down.

Another way to distinguish MSA from pure autonomic failure is by sympathetic neuroimaging. In this type of test, the patient receives an injection of a radioactive drug that gets taken up by sympathetic nerves. The sympathetic nerves in organs such as the heart become radioactive, and the nerves can be visualized by scans that detect where the radioactivity is, in a manner similar to commonly used clinical tests such as bone scans or brain scans. Since in MSA the sympathetic nerves are usually present in the organs, scanning after injection of one of these drugs visualizes the sympathetic innervation.

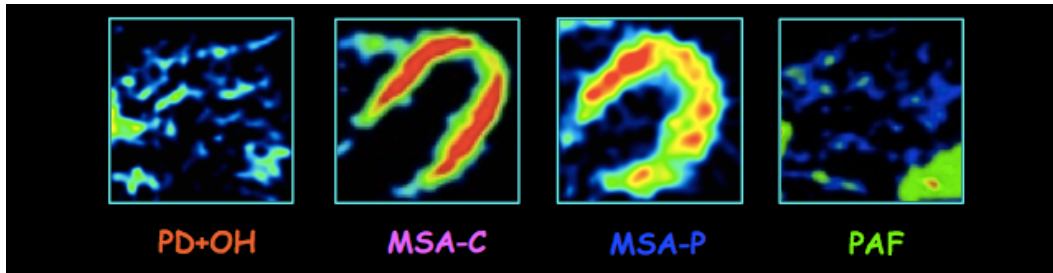
In contrast, in pure autonomic failure (and in Parkinson's disease, discussed elsewhere), where the sympathetic noradrenergic nerves typically are lost, sympathetic neuroimaging fails to visualize the sympathetic innervation of the heart.

The parkinsonian form of MSA can be difficult to distinguish from Parkinson's disease with orthostatic hypotension.

Distinguishing the parkinsonian form of MSA (MSA-P) from Parkinson's disease with autonomic failure can be a difficult diagnostic challenge. One way to distinguish these diseases is by cardiac sympathetic neuroimaging, since most patients with MSA have normal sympathetic innervation of the heart, while all patients with PD+OH have a loss of sympathetic innervation of the heart. In a patient with parkinsonism and OH, the finding of normal results of cardiac sympathetic neuroimaging exclude PD+OH.

Rarely, MSA patients do have a loss of sympathetic nerves in the heart. In this setting it can be very difficult to distinguish the parkinsonian form of MSA from PD+OH. It is even possible that such patients have a kind of hybrid disease.

MSA is a progressive disease for which there is no known effective means to reverse or retard the neurodegeneration. Treatment of MSA is directed at the symptoms and signs, such as orthostatic hypotension, and does not prevent or delay the progressive deterioration of the



MSA patients, whether of the cerebellar or parkinsonian types, usually have normal sympathetic nerves in the heart muscle.

nervous system. There are several ways to treat problems as they arise. For orthostatic hypotension the patient should sleep with the head of the bed elevated on blocks, to minimize orthostatic intolerance after getting out of bed in the morning. The patient should take frequent, small meals and avoid extremes of temperature. Fludrocortisone and a high salt diet may improve orthostatic intolerance, but at the cost of worsening supine hypertension.

Supine hypertension if severe can be alleviated by a calcium channel blocker, an angiotensin II receptor blocker, or nitroglycerine paste or patch. The patient should stay as active physically as possible and have a home exercise program. Physical medicine and rehabilitation efforts have the goal of maximizing mobility and minimizing risk of aspiration.

Because of steadily worsening difficulty with coordination of speech and swallowing mechanisms, patients with MSA have a high risk of

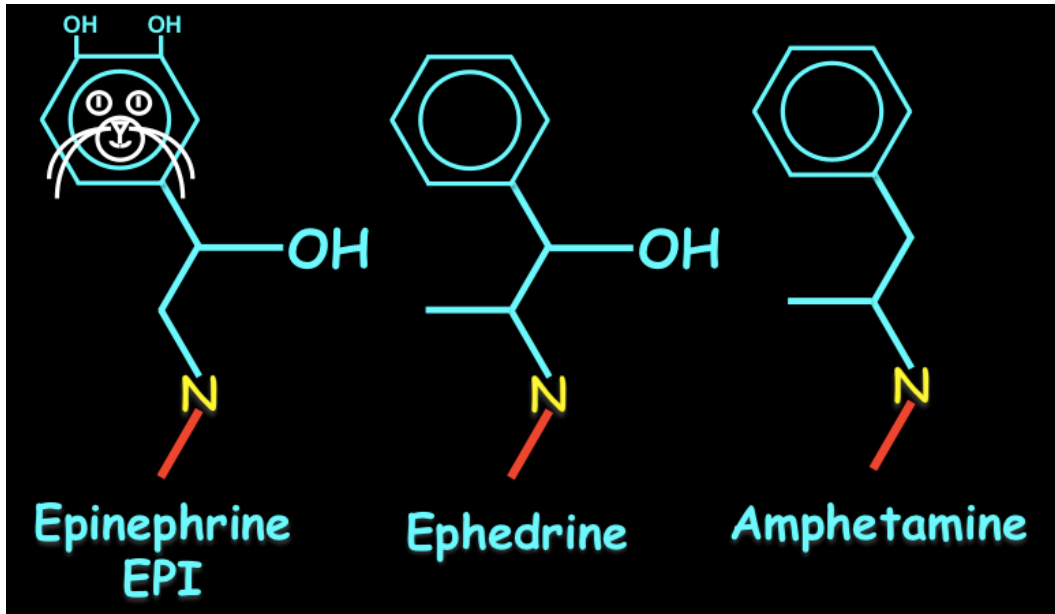
aspiration (inhalation of a foreign body into the airway), aspiration pneumonia, bloodstream infection, or sudden death from stopped breathing.

Ma Huang

I once had a patient with multiple system atrophy (MSA) who first came to medical attention because of a hypertensive crisis after taking *ma huang* tea.

Ma huang is a Chinese medicinal herb from the shrub, *Ephedra sinica*. As the name indicates, the active ingredient in *ma huang* is ephedrine. The patient took *ma huang* tea in the hope this would give him more energy and reduce fatigue. Instead, he developed a paroxysmal headache, and in the emergency room he had extreme hypertension that led to an initial diagnosis of a subarachnoid hemorrhage, which it turned out he did not have.

What he did have was MSA. Patients with MSA have arterial baroreflex failure, resulting in an inability to “buffer” acute changes in blood pressure by compensatory changes in sympathetic noradrenergic system outflows. Ephedrine is a classic sympathomimetic amine that is in the family of amphetamines. Ephedrine augments delivery of norepinephrine to its receptors in the cardiovascular system and therefore increases blood pressure.



Ephedrine resembles epinephrine and amphetamine.

In the setting of baroreflex failure, ephedrine evokes an exaggerated increase in blood pressure.

Because of morbidity and mortality related to ephedra, the US FDA banned the sale of dietary supplements containing ephedra, including *ma huang* tea, in 2004.

Poster Child for the Wrong Disease

Millicent (Milly) Kondracke, the wife of the political commentator Morton Kondracke, suffered for many years with a progressive neurodegenerative disease that was called “Parkinson’s-plus,” because

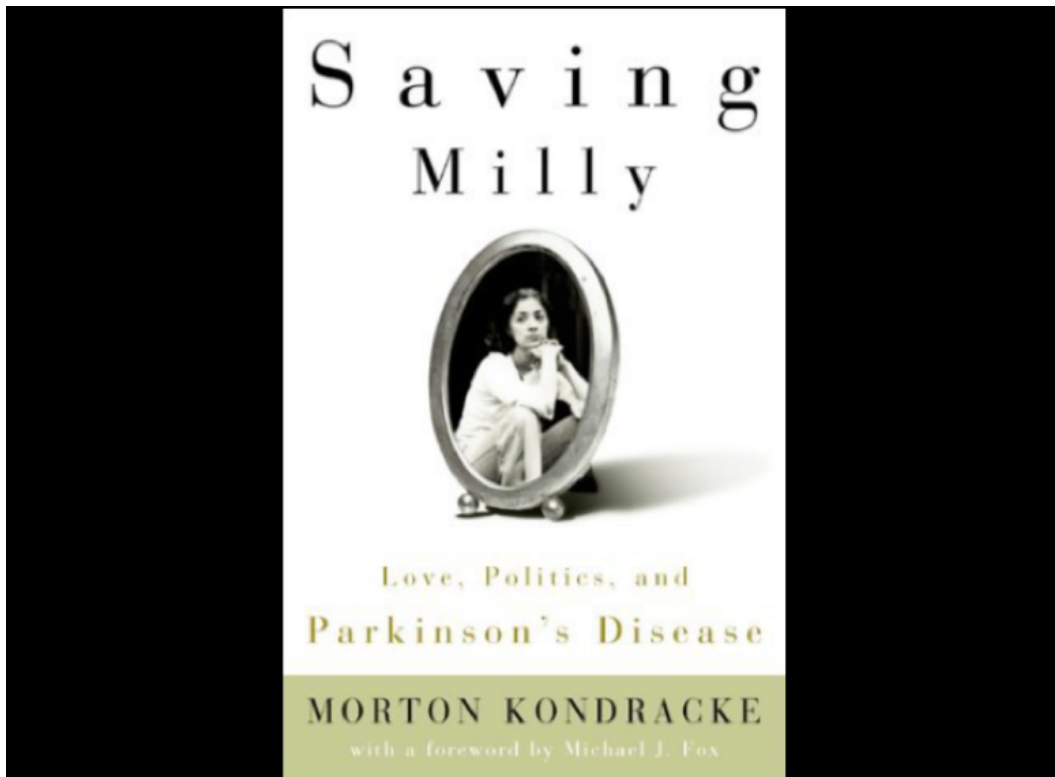
her condition included some features not typically seen in Parkinson's disease (PD). One of the most prominent was slurred speech. Eventually her speech became so garbled that she used a computer to communicate.

When she was evaluated at the NIH Clinical Center, her ^{18}F -dopamine PET scan indicated normal sympathetic noradrenergic innervation of the heart. This convinced me that she had multiple system atrophy (MSA).

Milly became famous as a highly effective spokesperson before Congress and activist for increased funding targeting PD. She was gracious, forthright, eloquent, and courageous. Her husband, Morton, wrote a book about her that became a best-seller and the basis for a made-for-TV movie, "Saving Milly."

After she died, the Parkinson's Action Network named its advocacy award in her honor.

In the ultimate act of philanthropy, she requested that upon her death that her brain be used for research at the NIH. After many months the neuropathologic diagnosis came back from the Armed Forces Institute of Pathology. Her brain had numerous glial cytoplasmic inclusions and no Lewy bodies. She didn't have PD. She had MSA.



Milly Kondracke was thought to have Parkinson disease but actually had multiple system atrophy.

Pure Autonomic Failure (PAF)

Synopsis:

Mid-aged or elderly of either sex and any race.

Chronic, persistent fall in blood pressure during standing up.

No signs of brain disease.

Not inherited or infectious.

Can go one for many years.

Pure autonomic failure (PAF, previously called idiopathic orthostatic hypotension and Bradbury-Eggleston syndrome) is the prototype of primary chronic autonomic failure.

PAF features persistent falls in blood pressure when the patient stands—orthostatic hypotension—in the absence of signs of central nervous system disease and in the absence of other known causes of orthostatic hypotension. The orthostatic hypotension results from sympathetic neurocirculatory failure.

Pure autonomic failure, while chronic and causing disability, is not thought to be lethal.

Patients report progressively worsening dizziness standing up, after a large meal, upon exposure to environmental heat, or after exercise. Because of severe orthostatic hypotension, pure autonomic failure patients often learn to sit or stand with their legs twisted pretzel-like, since this decreases pooling of blood in the legs.

In men, erectile failure is an early symptom. Often the patients have decreased sweating.

In patients with pure autonomic failure, blood pressure responses to

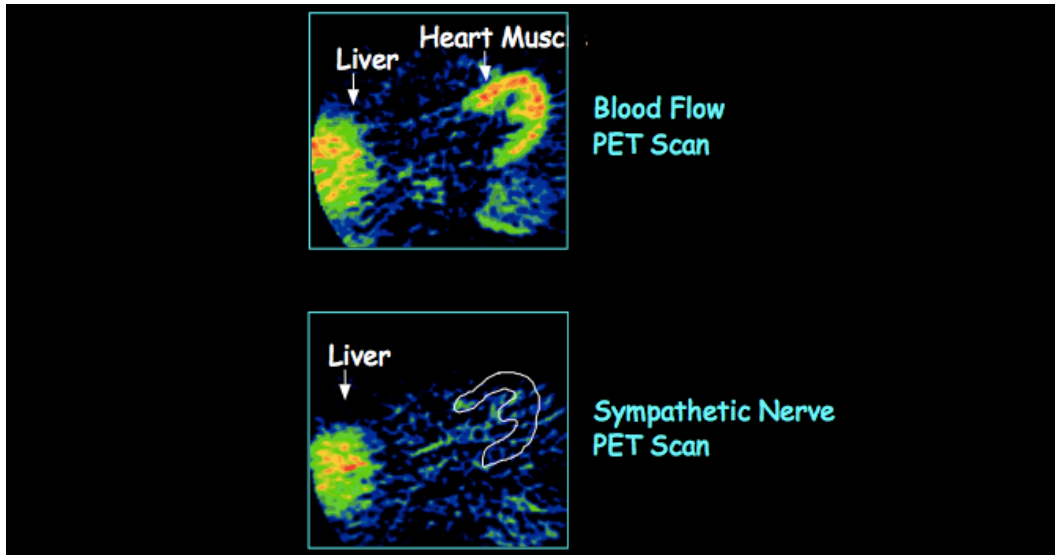
the Valsalva maneuver show the abnormal pattern that indicates sympathetic neurocirculatory failure. The Valsalva maneuver is discussed in the chapter about tests for dysautonomias.

The sympathetic neurocirculatory failure and orthostatic hypotension in pure autonomic failure typically result from loss of sympathetic nerves—in particular, nerves of the sympathetic noradrenergic system.

Drug tests can confirm a diagnosis of pure autonomic failure. Because of the loss of sympathetic nerves, drugs that release norepinephrine from sympathetic nerves, such as yohimbine, tyramine, amphetamine, and ephedrine, produce relatively small increases in blood pressure. In contrast, drugs that directly stimulate norepinephrine receptors, such as midodrine and phenylephrine (Neo-Synephrine™), constrict blood vessels and increase blood pressure.

Because of the phenomenon of “denervation supersensitivity,” in which receptors for norepinephrine increase and other adaptive processes probably occur that exaggerate constriction of blood vessels, patients with pure autonomic failure can have surprisingly large increases in blood pressure in response to the receptor-stimulating drugs.

As a result of loss of sympathetic nerves, plasma norepinephrine levels typically are low in PAF, even with the patient lying down, and because of concurrent baroreflex-sympathoneural failure the levels



Sympathetic neuroimaging tests such as fluorodopamine PET scanning of the chest often produce remarkably graphic results in PAF, with a failure to visualize the heart muscle at all.

fail to increase when the patient stands. PAF patients have low plasma levels of dihydroxyphenylglycol (DHPG), which is a measure of the amount of norepinephrine-containing nerves.

Another way to identify PAF is from sympathetic neuroimaging. In this type of test, the patient receives an injection of a radioactive drug that is taken up by sympathetic nerves. The sympathetic nerves in organs such as the heart become radioactive, and the nerves can be visualized by scans that detect where the radioactivity is, in a manner

similar to commonly used clinical tests such as bone scans or brain scans. Since in PAF the sympathetic nerves usually are absent in the organs, scanning after injection of one of these drugs fails to visualize the sympathetic innervation.

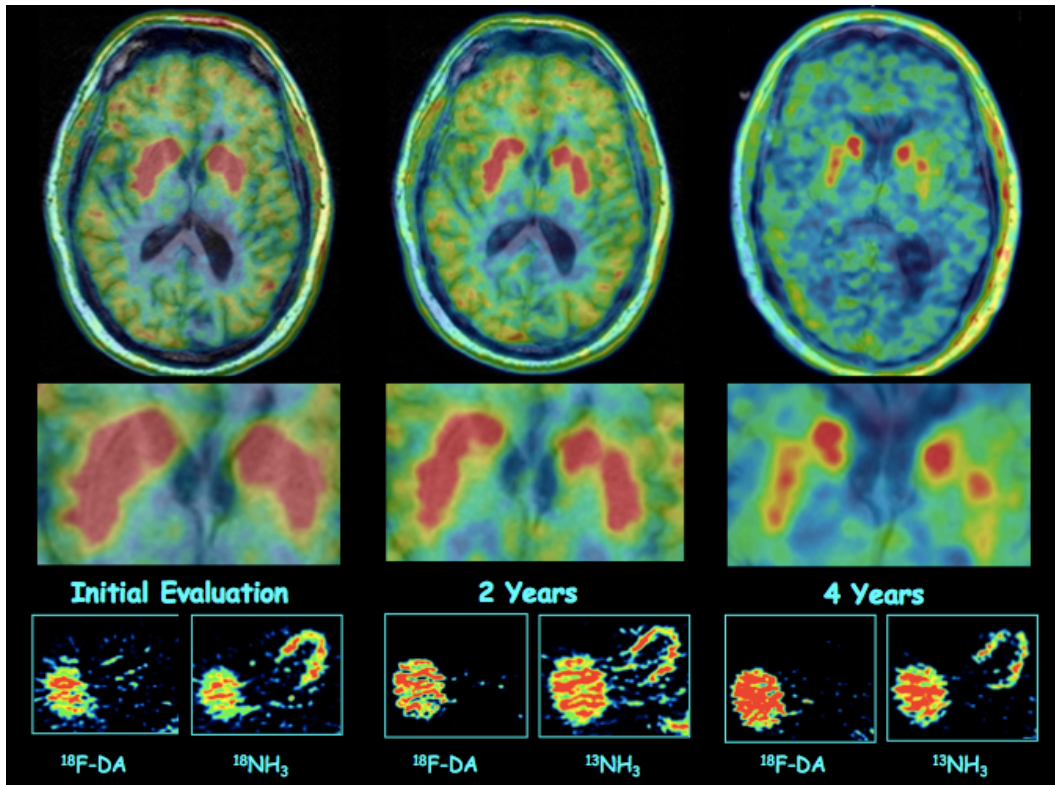
No one knows what causes PAF. It is not inherited, and no known environmental toxin causes it. Studies of tissues from patients with PAF indicate that it is related to Parkinson's disease, even though the patients do not have evidence of parkinsonism or other brain disease.

Treatment of pure autonomic failure is directed mainly at the orthostatic hypotension, which virtually always is severe and disabling.

Fludrocortisone, a high salt diet, and potassium supplementation are the mainstays of treatment.

Clinicians usually recommend elevation of the head of the bed. Body stockings may or may not help. The patient should not take large meals, because this may cause the blood pressure to decrease.

Drugs that release norepinephrine from sympathetic nerves, such as ephedrine, Ritalin™, or yohimbine, may not work well, because of the lack of nerves, whereas drugs that artificially stimulate receptors for norepinephrine, such as midodrine, can be very effective.



Evolution of pure autonomic failure into dementia with Lewy bodies and Parkinson disease. There was initially normal putamen ^{18}F -DOPA-derived radioactivity, but this decreased over the years.

Rarely, patients who have the symptoms, signs, and clinical laboratory abnormalities that characterize PAF have evidence for normal sympathetic innervation of the heart. This can be a clue that the patient has autonomic failure not because of a loss of sympathetic nerves but from interference with transmission of the control signals

to those nerves in the ganglia. Such patients can have an antibody to the nicotinic receptor, a condition that has been called autoimmune autonomic neuropathy, autoimmune autonomic failure, or autoimmune autonomic ganglionopathy. Treatments that work by their effects on the immune system can be effective for this form of dysautonomia.

Pure autonomic failure can be difficult to distinguish from early or mild Parkinson disease. At least in some patients, pure autonomic failure evolves into dementia with Lewy bodies and Parkinson disease with orthostatic hypotension, but the frequency of this happening is a topic of current research.

Death in a Jet's Bathroom

A patient with pure autonomic failure (PAF) was flying internationally and went to the bathroom in the jet during flight. When he didn't come out, eventually the staff broke open the door and found him—dead.

One may speculate about what went wrong. Patients with neurogenic orthostatic hypotension have an inability to tighten blood vessels reflexively to counter effects on blood pressure of decreased venous return to the heart. That is, when the venous return to the heart decreases, the blood pressure decreases. When a person strains at stool, the high pressure in the abdomen decreases venous return to the

heart, and this exacerbates the fall in blood pressure. Eventually there may be a severe enough fall in blood pressure that the patient loses consciousness and falls limp to the floor. But in a jet's bathroom the patient would not be able to do this. If the patient were kept sitting, the blood flow to the brain would become critically low.

A Dive into a Nightstand

Dream enactment behavior occurs commonly in autonomic synucleinopathies. The patient acts out his or her dreams and thrashes about in bed. Polysomnography shows an absence of the normal loss of limb muscle tone during rapid eye movement (REM) sleep, and so the condition is called REM Behavior Disorder, or RBD.

In men with RBD the dream often involves an attempt at active defense. Men with RBD can attack their bed partners and cause substantial physical—and psychological—trauma, all while asleep. At the NIH Clinical Center we had a patient with PAF who reported he had had dream enactment behavior for many years. He had been a troop leader in Vietnam. In his dreams he would be with his soldiers on a paved road, when an enemy plane would fly toward them, strafing the road. He would yell to dive to the side of the road. One night in the Clinical Center he dove headfirst into his bedside chest of drawers. He lacerated his head, but luckily there was no evidence of brain damage from the fall.

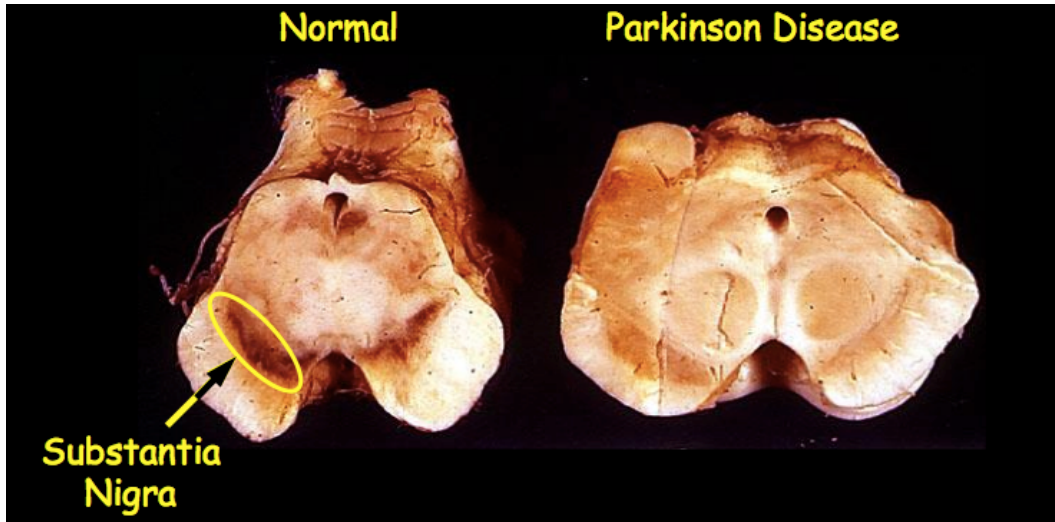
Parkinson's Disease (PD)

Parkinson's disease (or Parkinson disease, PD) is the second most common neurodegenerative disease of the elderly (the first is Alzheimer's disease). PD is well known to be characterized by a movement disorder that includes slowness (bradykinesia), limb rigidity, tremor at rest, and gait imbalance.

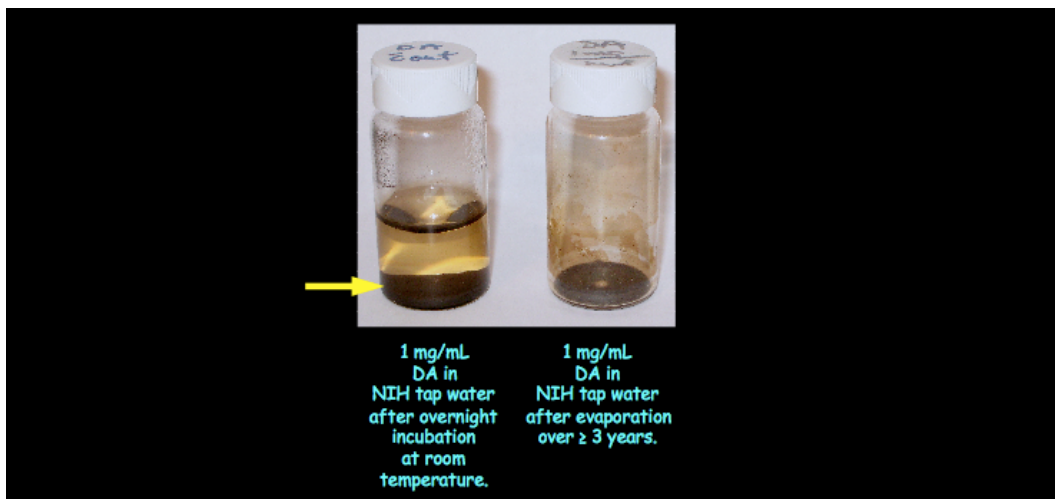
The key pathologic change in the brain that is seen in PD is the loss of black pigmentation in the substantia nigra (from the Latin for “black substance”) in the midbrain of the brainstem. The loss of black pigment probably reflects a decreased number of neurons that contain the catecholamine, dopamine. It is no coincidence that dopamine in solution spontaneously oxidizes and polymerizes to form a black pigment—melanin (from the Greek for “black”).

Nerve fibers from the substantia nigra travel to the striatum (plural striata), a pair of large structures on each side of the brain further up in the central nervous system. The striatum has two parts—the caudate nucleus and the putamen. The putamen is the main damaged site in PD.

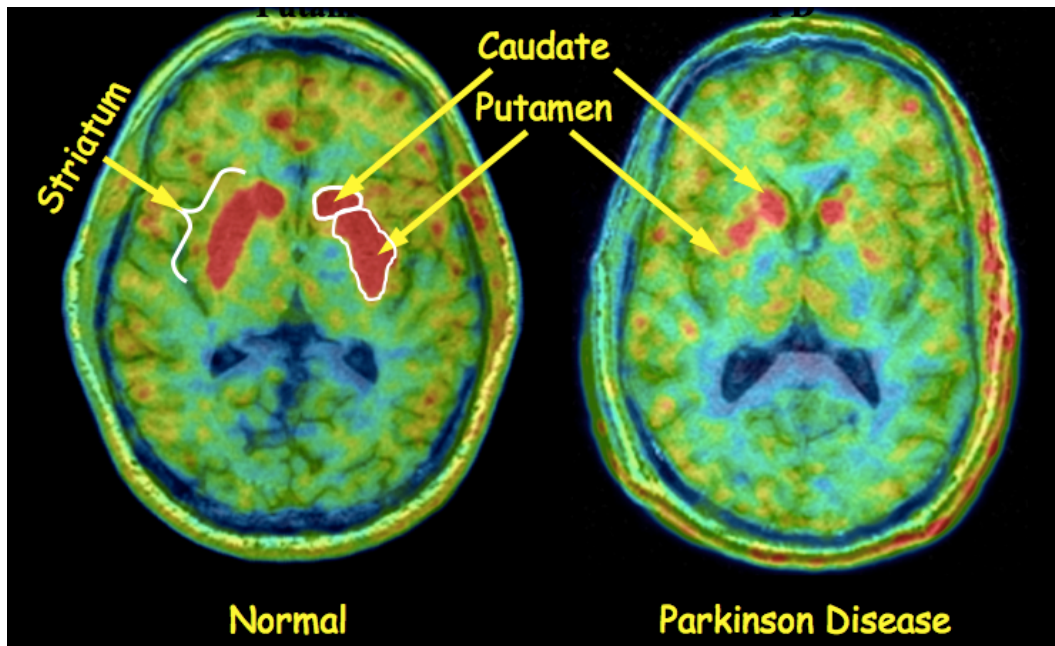
PD was the first neurodegenerative disease for which the underlying neurochemical abnormality was identified—severe depletion of the



Loss of pigment in the substantia nigra is a classic neuropathologic finding in Parkinson disease.



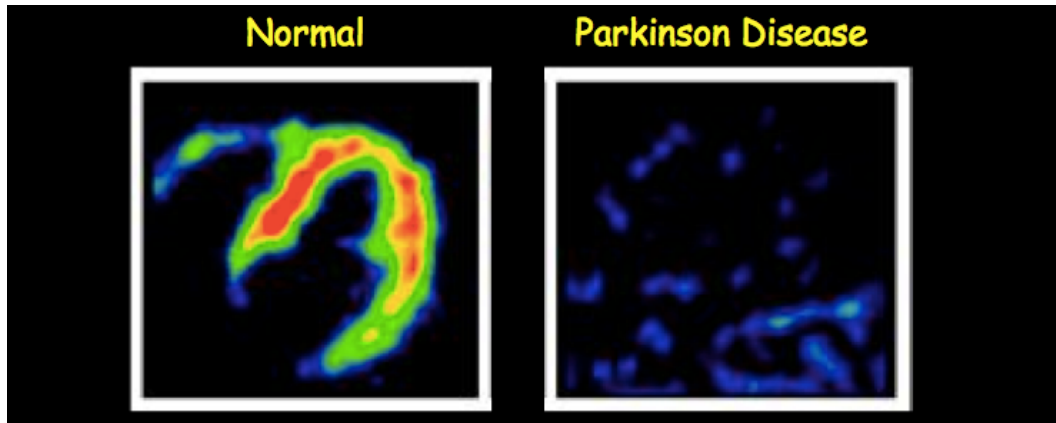
Dopamine in solution spontaneously oxidizes and polymerizes to form a black pigment, melanin.



Loss of dopamine-containing nerve terminals in the striatum, especially in the putamen, is a characteristic feature of PD.

catecholamine dopamine (DA) in the striatum.

Alleviation of dopamine (DA) deficiency by levodopa treatment for PD was revolutionary in the history of medical neuroscience. All current approved treatments of PD work directly or indirectly by countering effects of striatal DA depletion. While often effective in alleviating motor symptoms, no treatment has been proven to slow the loss of nigrostriatal neurons.

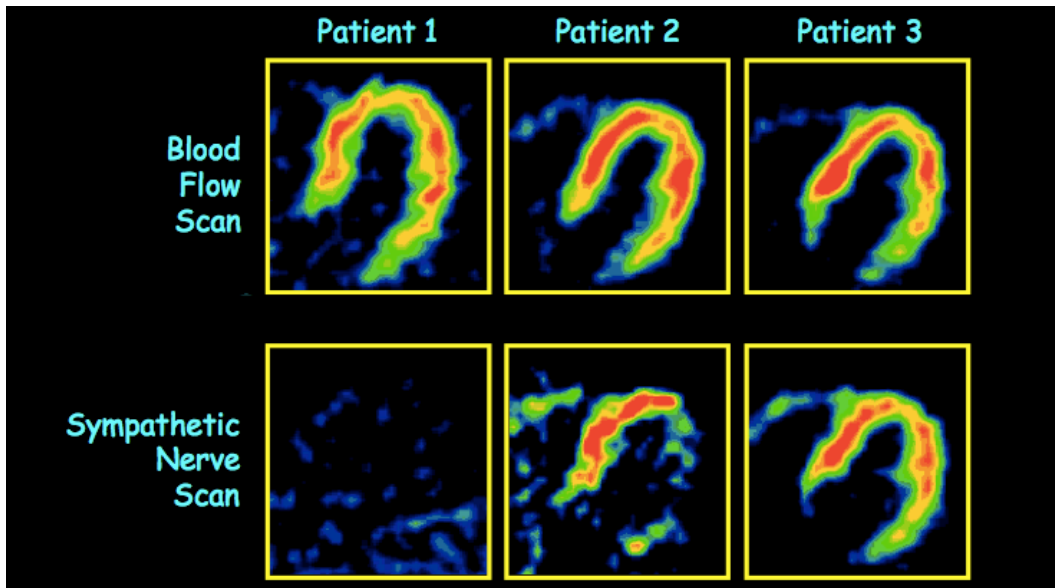


Most PD patients have at least some loss of sympathetic noradrenergic nerves in the heart, revealed by cardiac sympathetic neuroimaging.

Perhaps surprisingly, most patients with Parkinson disease have evidence for at least some loss of sympathetic nerves in the heart.

The discovery of loss of cardiac sympathetic nerves in PD provided clear evidence that PD is more than a brain disease and more than a movement disorder. It is also a disease that involves the sympathetic noradrenergic system and is a form of dysautonomia.

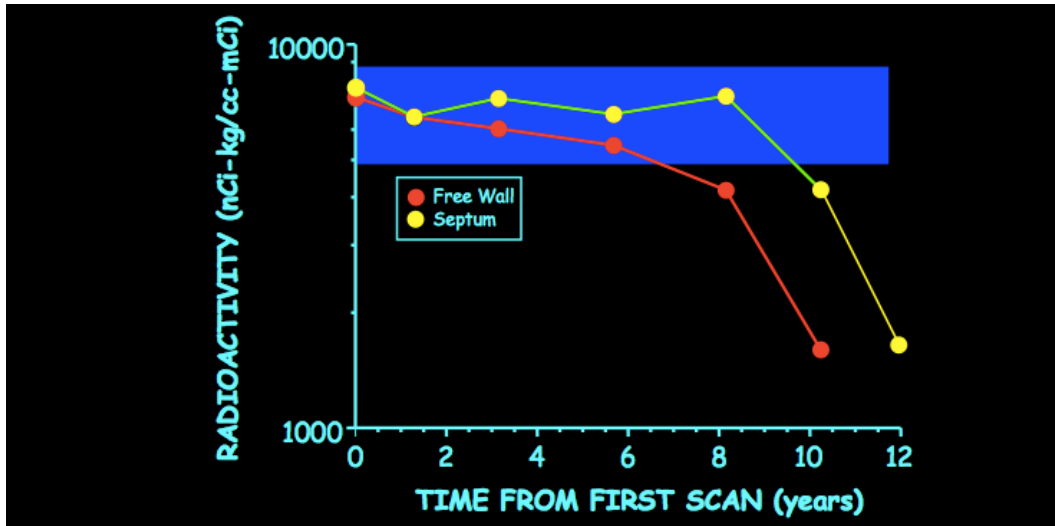
The functional significance of loss of sympathetic nerves in the heart



Most PD patients have a loss of cardiac sympathetic nerves throughout the heart, a substantial minority have localized loss, and a small minority have normal innervation.

in Parkinson's disease remains unknown. One would guess that this might cause or contribute to fatigue or shortness of breath during exercise.

Among PD patients who do not have orthostatic hypotension, about 1/2 have loss of sympathetic nerves throughout the left ventricular myocardium, a few have normal innervation, and a substantial minority have partial loss of sympathetic nerves. The partial loss is in the apex or free wall of the heart.



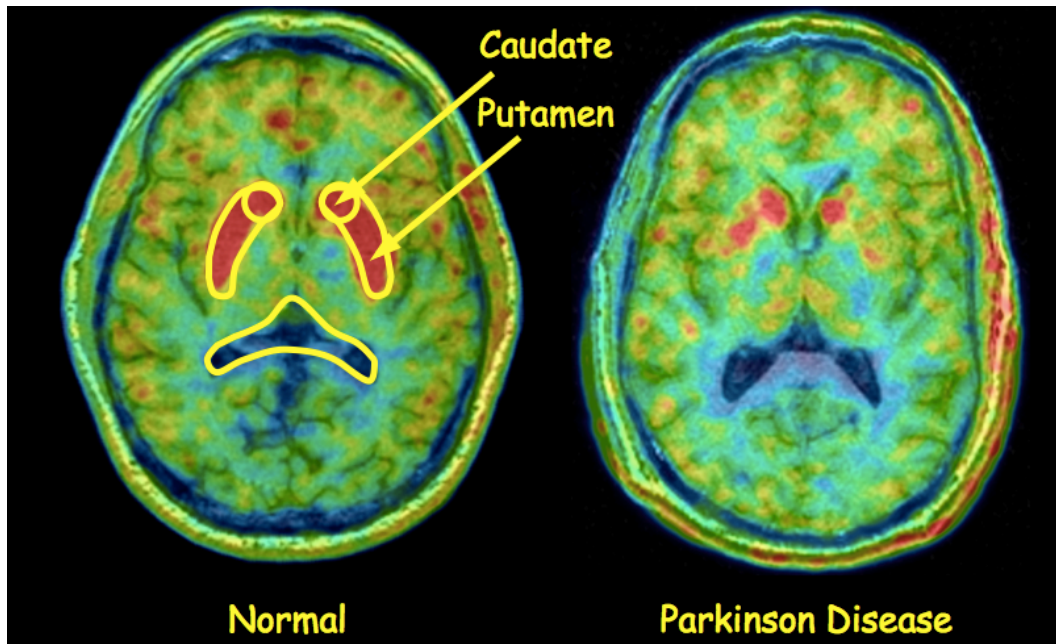
It can take several years for a PD patient to begin to lose cardiac sympathetic nerves, but once it begins the loss progresses rapidly.

In the PD patients who have a partial loss of the sympathetic nerves in the heart, when the patients are followed over years, the loss of sympathetic nerves in the heart progresses.

So far, it seems that all PD patients eventually lose cardiac sympathetic nerves. It may take several years for this to begin, but once it does, the loss progresses rapidly.

The Sad Clown's Eyes

^{18}F -DOPA PET scanning is an excellent way to see if there is a loss



In PD the “eye liner” of the “sad clown’s eyes” seems washed away.

of striatal dopamine terminals. On a ^{18}F -DOPA scan, the striata look like a sad clown’s eyes.

A special type of brain scan can show the abnormality that causes the movement disorder in PD.

The beady eyes themselves correspond to the head of the caudate on each side. The eye liner corresponds to the putamen. The putamen is the main site of damage in PD. In PD the eye liner seems washed away. Usually the loss is worse on one side, the side opposite to the

side of the movement disorder.

Parkinson Disease with Orthostatic Hypotension (PD +OH)

Synopsis:

Elderly of either sex and any race (usually light skin)

Signs of Parkinson's disease, such as slow movements, rigidity, tremor.

Movement problem improves with Sinemet™ (DOPA +carbidopa).

Chronic, persistent fall in blood pressure standing.

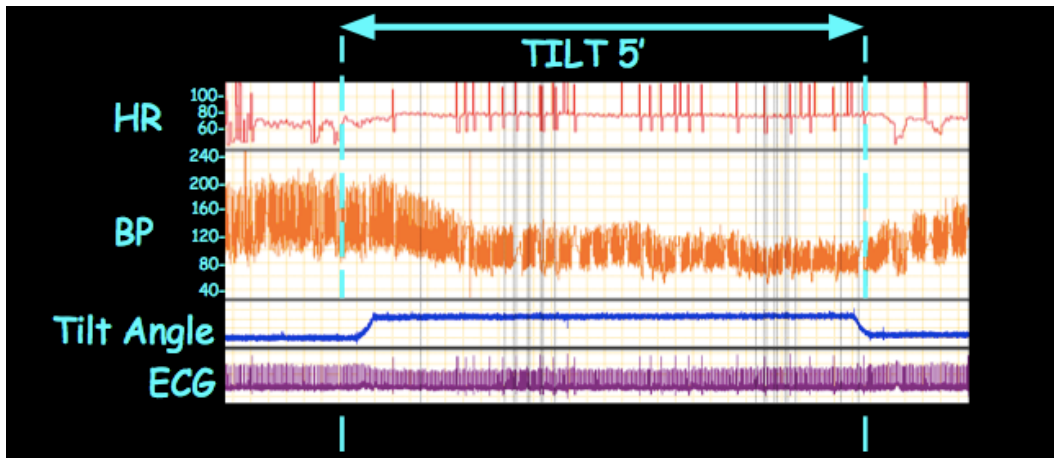
OH can come on before movement problems.

Can be inherited.

Slow progression over years.

Symptoms or signs of autonomic dysfunction occur extremely commonly in PD. These include constipation, urinary frequency and urgency, drooling, erectile failure in men, altered sweating, and orthostatic intolerance due to orthostatic hypotension.

Exactly how these problems, which reflect involvement of different components of the autonomic nervous system, relate to each other is unclear. For instance, the prevalence of constipation and urinary



Orthostatic hypotension during head-up tilt table testing in a patient with PD+OH

frequency and urgency is about the same regardless of the occurrence of orthostatic hypotension.

It has been estimated that 90% of PD patients have problems with the functioning of the autonomic nervous system.

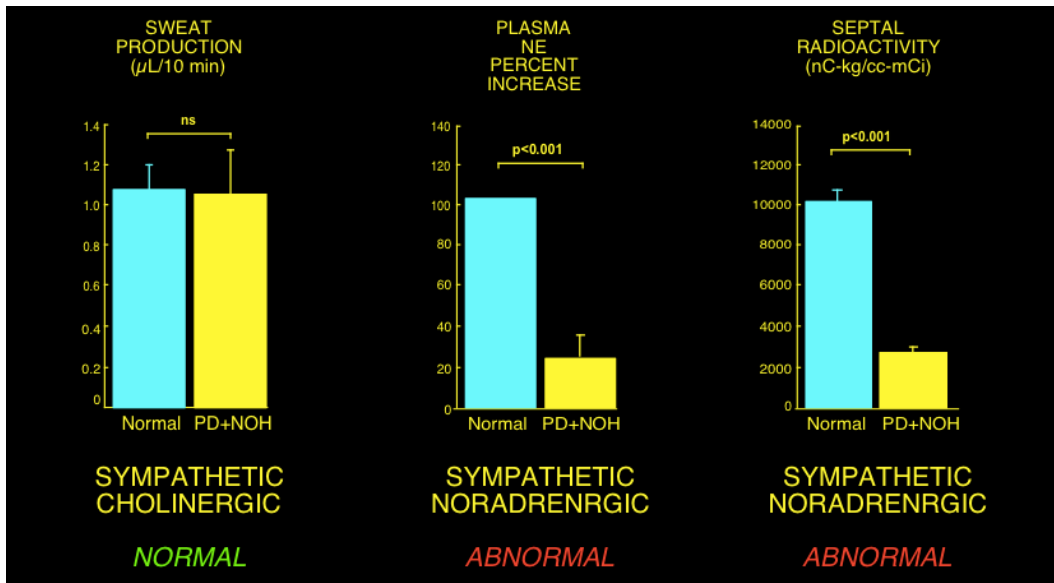
Orthostatic hypotension (OH), a fall in blood pressure when the patient stands up, occurs in 30-40% of patients with Parkinson disease. The frequency of OH is underestimated when clinicians depend on symptoms or signs, because many patients with OH feel nothing wrong when they are upright or have symptoms that are non-specific. The only way to determine accurately whether a patient with PD has OH is to measure the blood pressure after the patient has been lying down for several minutes and then again after the patient has

been upright for at least 3 minutes. To be diagnosed with OH a patient must have a persistent, consistent fall in systolic blood pressure of at least 20 mmHg.

Patients with Parkinson disease and a fall in blood pressure when they stand up have a form of dysautonomia.

Neurologists have presumed that the orthostatic hypotension (OH) attending PD results from treatment with levodopa, or else the patient doesn't really have PD but has a different disease, such as "striatonigral degeneration" or multiple system atrophy. It is by now clear that in PD, OH occurs independently of levodopa treatment. In PD, OH reflects sympathetic neurocirculatory failure and is therefore a form of dysautonomia. The sympathetic neurocirculatory failure appears to result from a combination of loss of sympathetic nerves (especially in the heart and kidneys) and baroreflex failure. Because of the loss of sympathetic nerves there is decreased norepinephrine available for release, and because of the baroreflex failure there is blunting of the reflexive increase in sympathetic noradrenergic system outflows as the blood pressure falls.

One way to document insufficient reflexive sympathetic noradrenergic system (SNS) activation is by measuring plasma levels of norepinephrine (NE), the chemical messenger of the SNS. Normally, plasma NE levels approximately double by 5 minutes after the patient

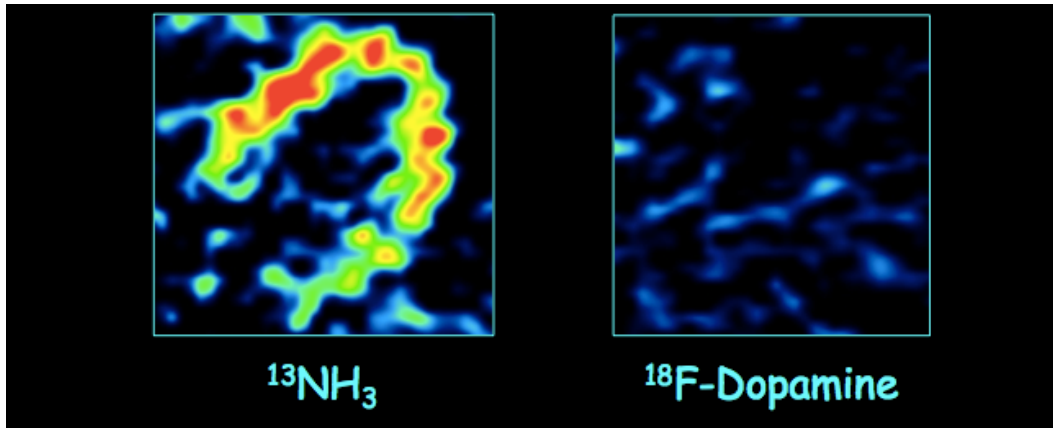


One can document that in PD, OH is neurogenic (NOH) by measuring the percent increase in plasma norepinephrine (NE) during head-up tilt table testing. Cardiac sympathetic neuroimaging can then identify whether the OH is related to loss of noradrenergic nerves.

is tilted upright from lying supine.

All patients with PD and orthostatic hypotension have a loss of sympathetic nerves in the heart.

In this respect PD+OH differs from the parkinsonian form of multiple system atrophy (MSA-P). Most MSA-P patients have neuroimaging

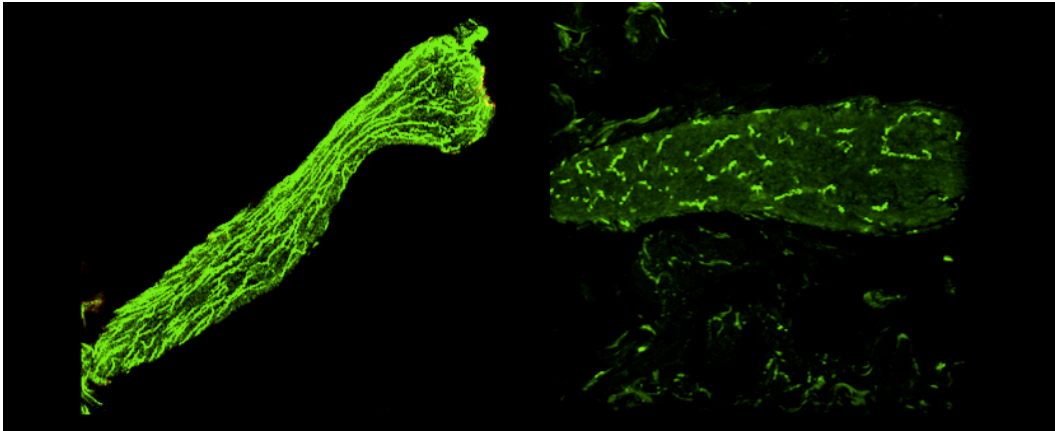


Blood flow imaging by $^{13}\text{NH}_3$ scanning and sympathetic neuroimaging by ^{18}F -dopamine scanning demonstrate loss of cardiac sympathetic nerves in PD+OH.

evidence for normal cardiac sympathetic innervation, although there are exceptions. In the differential diagnosis of PD+OH vs. MSA-P, the finding of normal cardiac sympathetic neuroimaging excludes PD+OH.

In contrast, sweat production, which is mainly a function of the sympathetic cholinergic system, can be normal in PD+OH, and the majority of PD+OH patients have normal QSART results.

Patients with Parkinson disease often have constipation and urinary urgency, frequency, and incontinence. These might reflect a form of failure of the parasympathetic nervous system; however, whether this



Skin biopsy showing normal sympathetic noradrenergic innervation of arrector pili muscle (left) and markedly decreased, fragmented innervation in a patient with PD+OH (Images courtesy of R. Freeman, C. Gibbons, and N. Wang).

is the case remains unknown. Decreased traffic in the vagus nerve, the nerve of the parasympathetic nervous system that supplies the heart, appears to cause the constant pulse rate seen in most patients with PD+OH. This could reflect a loss of parasympathetic nerves or a problem in intact nerves.

Another way to visualize decreased sympathetic noradrenergic innervation in PD+OH is by analyzing skin biopsy tissue. Each hair follicle has a muscle, *arrector pili* muscle, which is responsible for the hair bristling such as during cold exposure. The *arrector pili* muscle receives mainly sympathetic noradrenergic innervation. The finding of decreased nerve fibers in *arrector pili* muscle fits with loss of

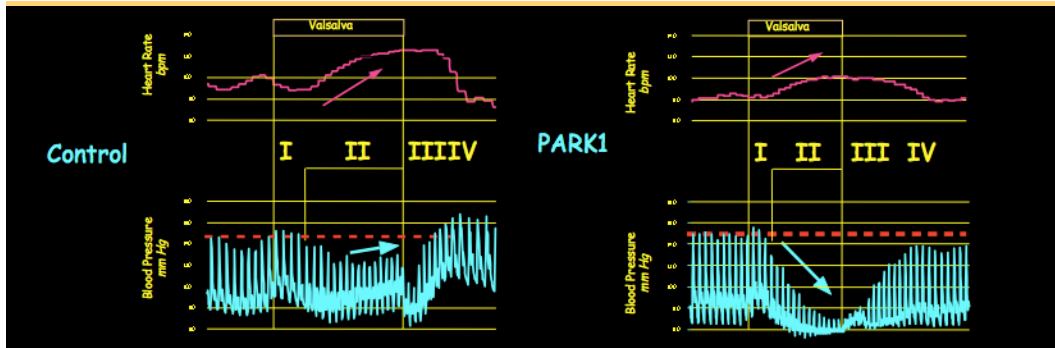
sympathetic noradrenergic innervation.

The long-term outlook in PD+OH is worse than in PD without OH. Patients with PD+OH are on average about a decade older than patients without OH when the movement disorder first becomes apparent; however, PD+OH patients have shorter survival than do PD No OH patients after adjustment for age.

Treatments used for PD+OH include fludrocortisone and a high salt diet, midodrine, frequent small meals and avoidance of large meals, and elevation of the head of the bed on blocks at night. Treatments that depend on release of norepinephrine (NE) from sympathetic nerves, such as ephedrine, d-amphetamine, methylphenidate, and yohimbine, may not work well in PD+OH, because of the loss of the nerves. Recently, L-dihydroxyphenylserine (L-DOPS, Northera™), a NE precursor, was approved by the US FDA for symptomatic OH. This drug may be effective in treating PD+OH, especially because of denervation supersensitivity and baroreflex failure in PD+OH. Theoretically, the carbidopa in Sinemet™ used to treat PD would inhibit conversion of L-DOPS to NE, but practically the carbidopa dose required to produce this effect is far more than is found in Sinemet™.

The Contursi and Iowa Kindreds

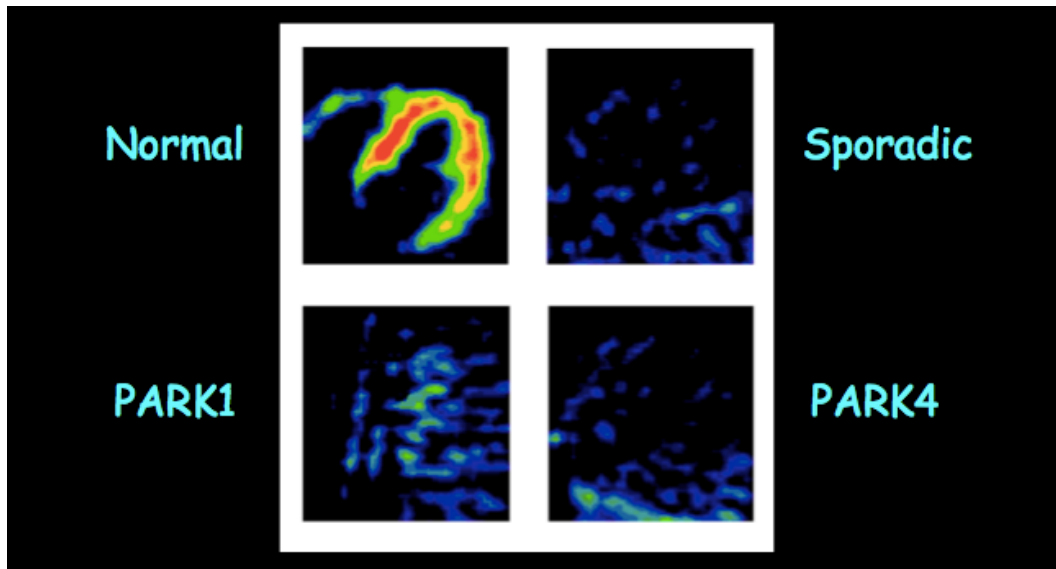
In 1997 the first clear evidence for a genetic cause of PD was reported



Abnormal pattern of beat-to-beat blood pressure in a patient with familial PD from mutation of the gene encoding alpha-synuclein.

—mutation of the gene encoding the protein, alpha-synuclein. In a large Greek-Italian-American kindred called the Contursi kindred, PD is transmitted as an autosomal dominant trait (half the family members developing PD). A53T mutation of the alpha-synuclein gene was found to be causative in this family. This rare form of familial PD is called PARK1. Exactly why and how the “typo in the genetic encyclopedia” results in loss of nigrostriatal dopamine neurons remain unsettled.

We had the opportunity to carry out autonomic function testing in a PARK1 patient. He had clear evidence of orthostatic hypotension. Until the evaluation he had never had his blood pressure measured while lying down and then while upright.



The finding of cardiac sympathetic denervation in PARK1 and PARK4, as in sporadic PD, demonstrates that alpha-synucleinopathy can cause loss of sympathetic noradrenergic neurons.

His pattern of beat-to-beat blood pressure associated with performance of the Valsalva indicated sympathetic neurocirculatory failure. During Phase II the blood pressure declined progressively, and in Phase IV there was no pressure overshoot. Since his heart rate increase was blunted for the amount of fall in blood pressure during Phase II, he also had baroreflex-cardiovagal failure.

Cardiac sympathetic neuroimaging in this patient showed markedly decreased ^{18}F -dopamine-derived radioactivity throughout the left

ventricular myocardium, indicating that his neurogenic orthostatic hypotension was the result of both baroreflex failure and loss of sympathetic noradrenergic neurons.

Another form of familial PD was reported in a kindred called the Iowa kindred. Here the causative abnormality is triplication of the normal alpha-synuclein gene. This form of dominantly inherited PD is called PARK4.

PARK4 patients also have physiological evidence of baroreflex-sympathoneural failure and neuroimaging evidence of cardiac sympathetic denervation.

The findings in PARK1 and PARK4 helped establish that alpha-synucleinopathy can cause not only loss of striatal dopaminergic innervation but can also cause loss of cardiac sympathetic noradrenergic nerves, neurogenic orthostatic hypotension, and baroreflex failure.

The Fainting Attorney General

In March of 1995, Janet Reno, then 57 years old and two years into her term as the first female US Attorney General, began to notice a tremor in her left hand during her walks around the Capitol in the early morning hours. She was diagnosed with PD.

About two years after the motor onset of PD, she fainted in a hot, crowded room during an international conference at the El Camino Real Hotel in Mexico City. The fainting was attributed to gallstones and fatigue. Her doctor, the director of the Parkinson's Disease and Movement Disorder Clinic at the University of Miami, gave the opinion that fainting is not usually associated with PD.

In 1998 she fainted at about 8:30 AM at Full Gospel AME Church in suburban Clinton, MD, also on a hot day. A medical spokesman at the Georgetown University Medical Center stated, "This is just a fainting spell. Her condition is good."

In a patient with chronic autonomic failure, attending a church service on a hot Sunday morning could be a real autonomic stress test, with fainting evoked by severely decreased blood pressure. First, the patient would likely to be standing still for prolonged periods, resulting in blood pooling in the abdomen, pelvis, and legs. Second, in autonomic failure syndromes, orthostatic hypotension is usually worse in the morning than later in the day. Third, singing increases the pressure in the chest and abdomen and decreases venous return to the heart. Fourth, exposure to environmental heat relaxes blood vessels. Fifth, if a church breakfast preceded the service, blood could be shunted toward the gut after the meal (post-prandial hypotension). Sixth, if the worshipper felt distressed during the service, high circulating adrenaline levels would relax blood vessels in the skeletal muscle, decreasing total peripheral resistance to blood flow.

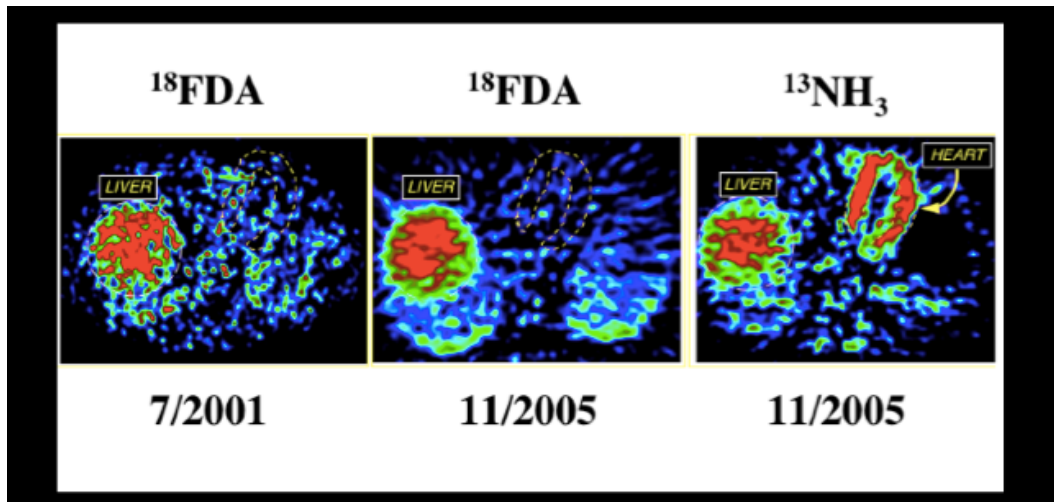
In 2002, at 63 years old, she fainted again while giving a talk at the University of Rochester during her primary campaign for Governor of Florida. An examining physician stated, “We discovered no link between the incident and her previously reported Parkinson's disease.”

I'm not so sure about the claimed lack of a link between fainting and PD, because of the possibility of PD+OH.

In PD When does Autonomic Failure Occur?

About 90% of PD patients have symptoms or signs of some form of autonomic failure, and about 30-40% have neurogenic orthostatic hypotension. The findings in an important case we reported several years ago demonstrate that cardiac sympathetic denervation can precede the movement disorder by several years. This case is discussed in more detail later in this section.

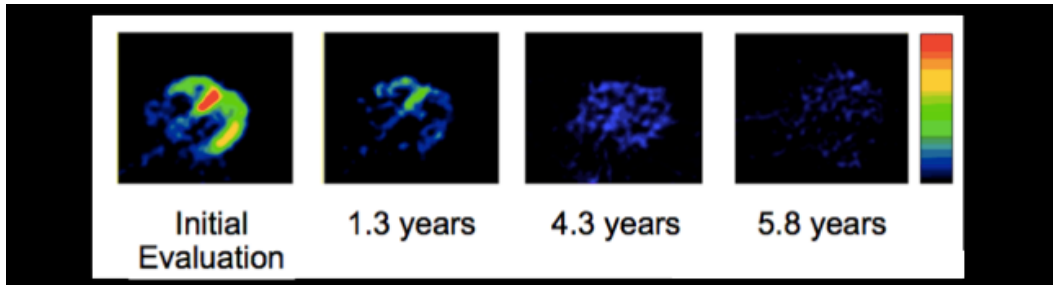
On the other hand, patients who already have symptomatic PD can have normal or only localized loss of cardiac sympathetic innervation. For instance, several years ago we evaluated a PD patient who did not have orthostatic hypotension and found that she had decreased ¹⁸F-dopamine-derived radioactivity in the left ventricular free wall and apex of the heart, but there was normal radioactivity in the septum. Over the course of just a few years the loss of innervation progressed to completion.



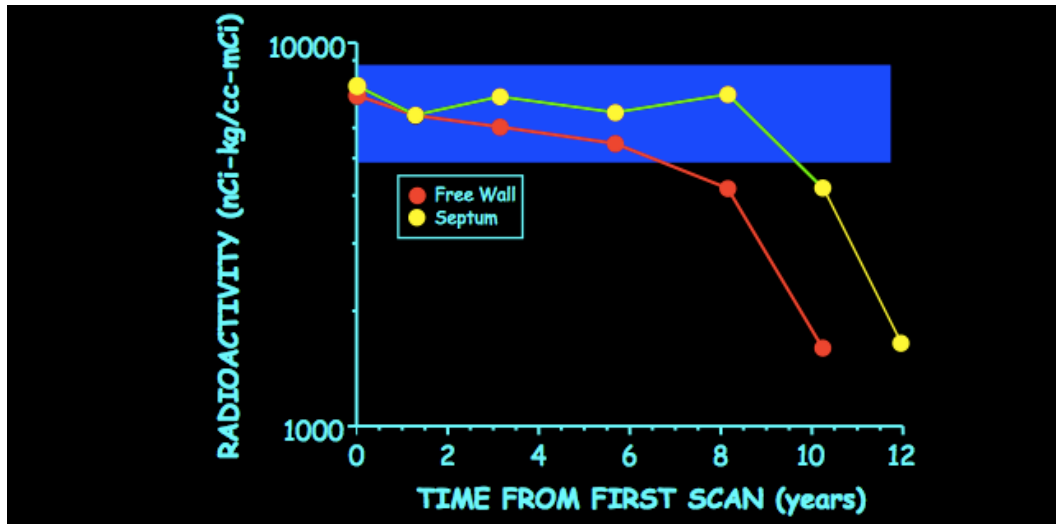
This PD patient had evidence of cardiac sympathetic denervation about 4 years before the motor onset of PD.

In another patient, who already had PD, cardiac sympathetic innervation seemed normal over about 8 years of follow-up. Then the patient had partial denervation in the free wall. This was followed soon after by diffuse denervation, with loss of innervation in the inter-ventricular septum.

Therefore, in PD without orthostatic hypotension, the loss of cardiac sympathetic noradrenergic nerves seems to occur independently of the movement disorder. In some patients cardiac sympathetic denervation can be a biomarker predicting later development of PD, but in others cardiac sympathetic denervation is a late finding.



This PD patient had partial cardiac denervation when first seen. The denervation progressed rapidly.



This PD patient had normal cardiac sympathetic innervation for several years, followed by a rapid loss, which was first noted in the left ventricular free wall.

Androids

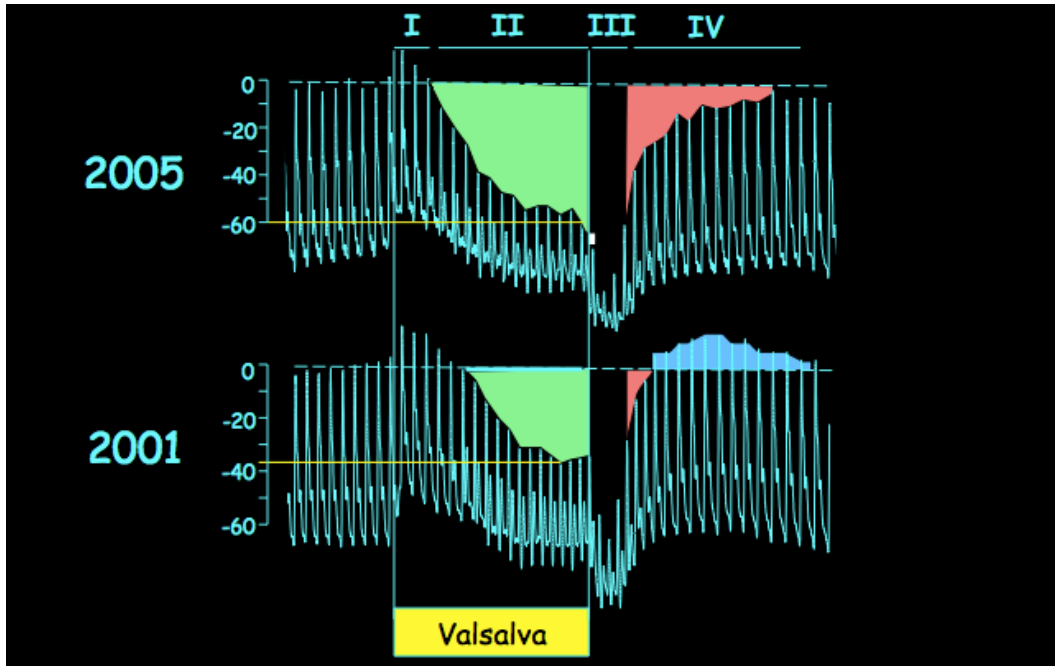
Several years ago, a patient had undergone a workup for a possible pheochromocytoma, a tumor that produces and releases catecholamines, because of variable, high blood pressure. The workup at the NIH Clinical Center was negative, and he received a diagnosis of “pseudopheochromocytoma.” As part of the testing the patient had a fluorodopamine PET scan.

About 4 years later, the patient returned to be in a study about pseudopheochromocytoma. He reported the gradual onset over a few months of slow movement, limb rigidity, a shuffling gait, and decreased facial expression. He said he felt like a robot. He indeed did remind me of an android.

Cardiac sympathetic neuroimaging showed a loss of sympathetic noradrenergic nerves, as is typical of PD. In the interim the patient had also developed baroreflex-cardiovagal and baroreflex-sympathoneural failure, and the beat-to-beat blood pressure response to the Valsalva maneuver now showed a progressive decrease in pressure in Phase II and no overshoot of pressure in Phase IV.

In retrospect, the fluorodopamine PET scan from 4 years previously had shown a loss of sympathetic innervation throughout the left ventricular myocardium.

The report of this case was the first to note that cardiac sympathetic



Beat-to-beat blood pressure responses to the Valsalva maneuver in a patient before and after development of motor signs of PD.

denervation can precede the motor onset of PD.

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB), or Lewy body dementia (LBD), is a form of alpha-synucleinopathy in which dementia is a key part of the clinical picture. DLB is the second most common form of dementia (the first being Alzheimer's disease).



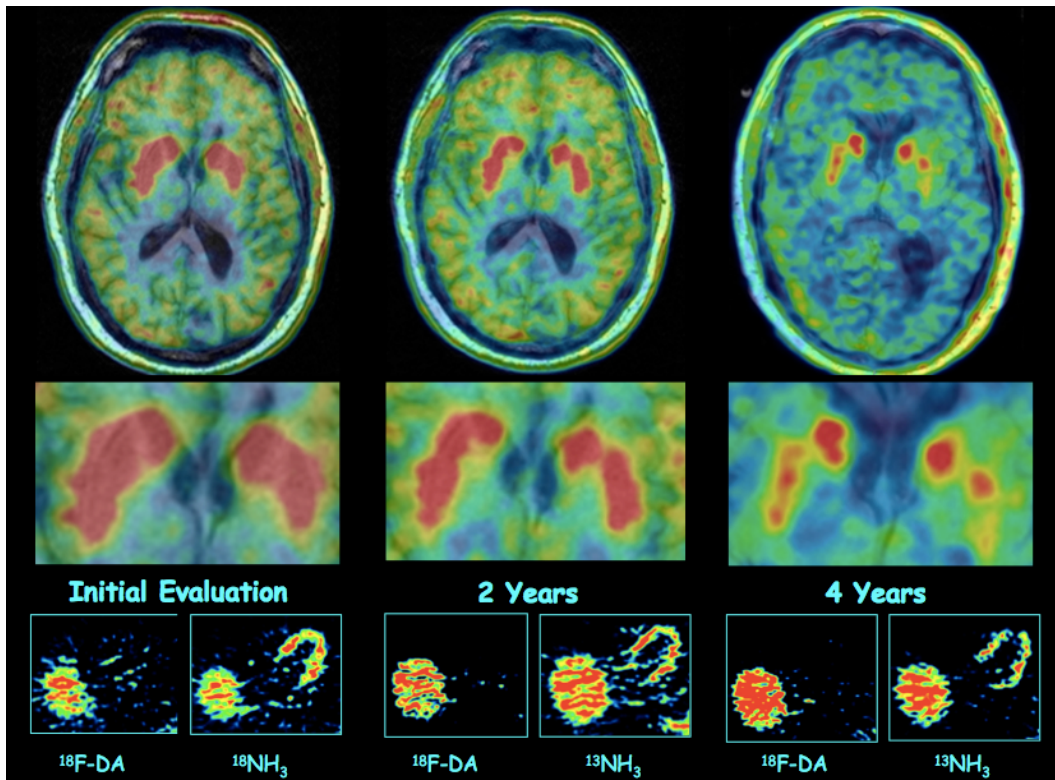
Estelle Getty, Robin Williams, and Casey Kasem were celebrities with Lewy Body Dementia.

Two clinical characteristics may help separate DLB from Alzheimer's disease. The first is visual hallucinations, which occur commonly in DLB. The second is the clinical course. Alzheimer's disease involves a steady, progressive decline. In DLB the patients have fluctuating mental status.

Parkinson's disease with dementia (PD+D) and Alzheimer's disease are both difficult to separate from DLB. By consensus, in PD+D, the dementia develops in the setting of PD.

Clinical laboratory test that can help distinguish DLB from Alzheimer's disease include neuroimaging tests of catecholamine systems. The finding of decreased putamen ^{18}F -DOPA-derived radioactivity would fit better with DLB than with Alzheimer's disease.

DLB, as all forms of synucleinopathy, often involves a loss of



In this patient with pure autonomic failure there was a progressive loss of putamen $^{18}\text{F-DOPA}$ -derived radioactivity accompanied by development of visual hallucinations and then dementia, diagnostic of Lewy body dementia.

myocardial noradrenergic nerves. Results of cardiac sympathetic neuroimaging may therefore be abnormal in DLB, whereas this is not typically the case in Alzheimer's disease.

A common finding in DLB is visual hallucinations. The patients may

report their mind “playing games” with them. A patient with PD, orthostatic hypotension, and incipient LBD put it this way when he was asked, “Have you had an experience where you thought were seeing something that really wasn’t there or thought you were hearing something that really wasn’t there?”

“I haven’t had any hallucinations—I wouldn’t admit to that anyway. I do find my brain to be more creative than it used to be, in filling in the blanks, so to speak. Sometimes you’ll see an image, particularly in the distance, not terribly clear, and you think its one thing, it turns out to be another, but while you’re thinking it’s one thing your brain is making it look like that one thing. That phenomenon seems more pronounced to me. I’ve noticed my peripheral vision sometimes creates illusions, like when I’m driving it seems there’s something or someone peripherally when there isn’t...but no hallucinations.”

Pathologically, DLB is characterized by Lewy bodies distributed widely in the brain. “Diffuse Lewy body disease” is a pathologic diagnosis, whereas DLB is a clinical diagnosis.

The Thomas Graboys Case

Dr. Thomas Graboys was one of the cardiology “dream team” that evaluated Reggie Lewis and recommended that Lewis not return to professional basketball.



Dr. Thomas Graboys

Graboys wrote a book, entitled, “Life in the Balance.” In it he related that on the morning of his second marriage, he fainted, and he called a cardiologist about it. Before this Graboys, an avid tennis player, had noted episodic lightheadedness or faintness while playing. He also thought he was losing his mental edge. The cardiologist dismissed the problem as mere fainting. Graboys didn’t tell his wife about this until later. This was a major trauma in their marriage.

It turned out that, just as in Reggie Lewis’s case, Graboys’s condition was not mere fainting. His episodic lightheadedness and loss of mental edge were actually early symptoms of Parkinson disease with orthostatic hypotension and Lewy body dementia.

Graboys was a founding co-president of International Physicians for the Prevention of Nuclear War, which received a Nobel Peace Prize in 1985. He had to retire from his cardiology practice in 2005, and he died January 5, 2015.

Engines that are Slow to Start

Later you will learn about the “getaway car analogy” for the mechanism of PD. I’d like to introduce the analogy here and end this section with a remarkable quote from Thomas Graboys.

The getaway car analogy helps provide answers to four key questions about the pathogenesis of PD. (1) Only a very small fraction of neurons are catecholaminergic. What renders them susceptible to loss in PD? (2) How do generalized abnormalities causing Parkinsonism, such as gene mutations and environmental exposures, lead to relatively specific loss of catecholamine neurons? (3) Why does alpha-synuclein tend to precipitate in the cytoplasm of catecholamine neurons, in Lewy bodies that are a pathologic hallmark of PD? And (4) Why is PD a disease of the elderly?

To answer these questions I use the analogy of a bank robber’s getaway car. The getaway car is kept in “idle.” This has obvious advantages because of the ability to shift into gear rapidly and get away, but there is a cost—cumulative wear and tear. Eventually the idling engine would fail, especially if there were design and manufacturing flaws. If one conducted a “post-mortem” on the engine one would find deposits—gunk—regardless of the specific design or manufacturing flaw.

Catecholamine neurons are like the idling engine of a getaway car. Vesicular catecholamines leak continuously into the cytoplasm, where they are “combusted” by spontaneous and enzyme-catalyzed oxidation. Having leaky vesicles and active but imperfect recycling back into the vesicles enables rapid initiation of movement and prolonged performance without exhausting releasable stores; but there is a cost. Cytosolic catecholamines are toxic, including via formation of catecholaldehydes such as 3,4-dihydroxyphenylacetaldehyde (DOPAL), catalyzed by monoamine oxidase. Just as the getaway car engine depends on fuel recovery to limit combustion and on a catalytic converter to detoxify immediate toxic byproducts of combustion, dopamine neurons depend on vesicular sequestration to limit DOPAL production and on aldehyde dehydrogenase (ALDH) to detoxify DOPAL (enzymes literally are catalytic converters).

Consistent with the “catecholaldehyde hypothesis,” recently obtained evidence shows that the putamen of PD patients contains a buildup of DOPAL, decreased vesicular sequestration of cytosolic catecholamines, and decreased ALDH activity. Moreover, DOPAL potently oligomerizes and precipitates alpha-synuclein, which in turn appears to interfere with vesicular uptake, and lipid peroxidation products, a general feature of neuronal damage, inhibit ALDH. The catecholaldehyde hypothesis therefore predicts the aging-related, selective loss of catecholaminergic neurons that characterizes PD.

As noted above, Dr. Thomas Graboys was one of the cardiology

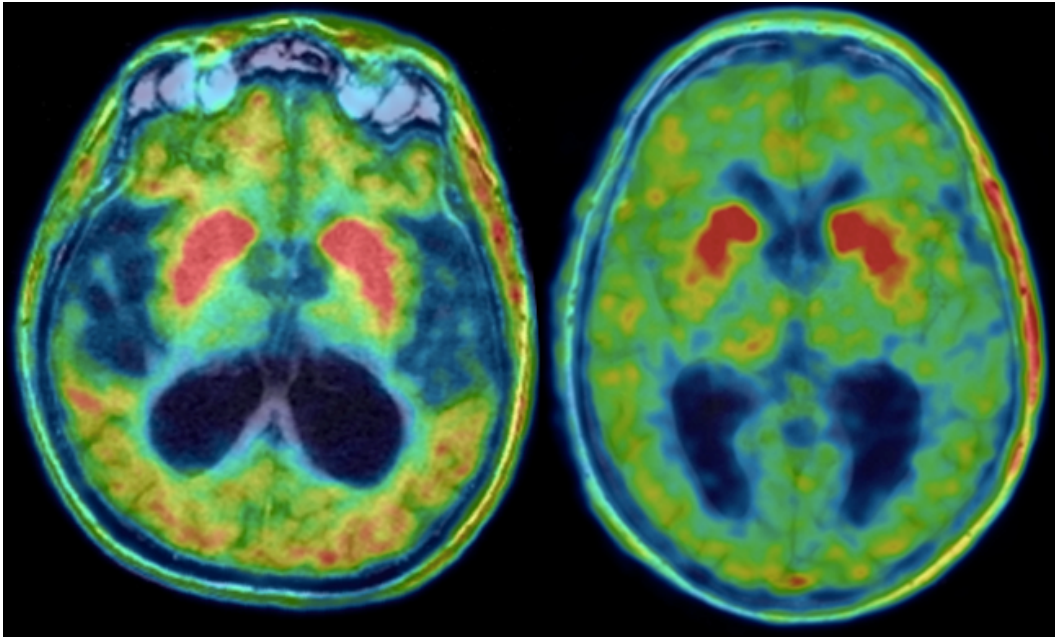
“dream team” that evaluated Reggie Lewis. Both Graboys and Lewis had fainted and been told that this was a benign condition. In Lewis’s case, the fainting was not benign but was a sign of a serious cardiologic condition that killed him. In Graboys’s case, the fainting was not benign but was an early sign of the triad of Parkinson disease, orthostatic hypotension, and dementia with Lewy bodies.

In his autobiographical book, *Life in the Balance*, Graboys wrote about the effects of his disease:

As a young intern and resident, and later as an attending cardiologist, I was accustomed to being summoned suddenly in the middle of the night. I could launch myself out of bed, get dressed, and perform at my intellectual peak within moments. I could make life-and-death decisions within seconds of a night-time phone call. Today, I wait for thousands of tiny cellular engines to start themselves so I can rise from the bed and begin another day...

One cannot imagine a more poignant confirmation of the applicability of the getaway car analogy to the pathogenesis of Lewy body diseases.

Nature Abhors a Vacuum



Enlargement of the cerebral ventricles and brain atrophy seem to be associated with dementia in autonomic synucleinopathies.

In patients who initially have pure autonomic failure (PAF), the disease can progress to Parkinson disease with orthostatic hypotension and to dementia with Lewy bodies (DLB).

One manifestation of the development of dementia in the setting of an alpha-synucleinopathy is shrinkage of the brain and replacement of the brain tissue with fluid. The ventricles become enlarged. In the body, nature abhors a vacuum, and cerebrospinal fluid in enlarged cerebral ventricles replaces lost brain tissue. Sometimes the extent of

enlargement of the ventricles is so massive in PD+OH that the clinician considers a diagnosis of normal pressure hydrocephalus.

In our experience so far, almost every PD+OH patient has had ventricular enlargement or cortical atrophy upon MRI scanning.

ACQUIRED AUTONOMIC FAILURE

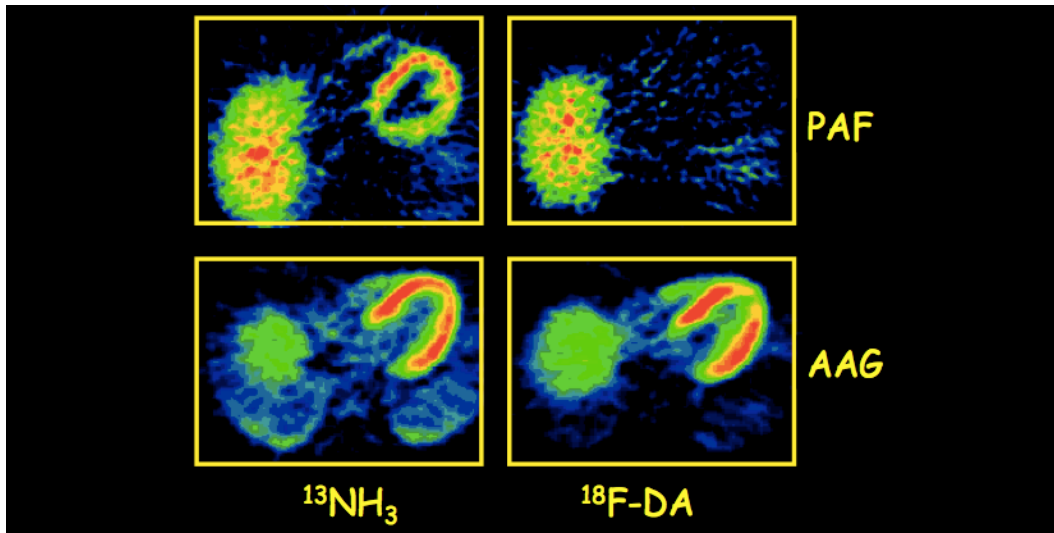
There probably are several forms of acquired autonomic failure. The section on baroreflex failure discusses arterial baroreflex failure as a late sequela of neck irradiation. Cancer chemotherapy can produce autonomic failure that in some situations can limit the treatment.

Probably the clearest evidence for acquired autonomic failure is from autoimmune autonomic ganglionopathy (AAG).

There is a rather prevalent view among patients and support groups that dysautonomias such as POTS have an autoimmune basis, and research along these lines is ongoing. Some clinicians have tried intravenous immunoglobulin (IVIG) to treat patients who have acute or subacute onset of POTS or autonomically mediated syncope. As of this writing, however, the only form of dysautonomia in which strong evidence for an autoimmune mechanism has been obtained is AAG.

Autoimmune Autonomic Ganglionopathy (AAG)

Autoimmune autonomic ganglionopathy (AAG) is a rare form of acquired autonomic failure in which there is decreased activity of all the components of the autonomic nervous system—pandysautonomia. The pandysautonomia results from circulating antibodies to the



Cardiac sympathetic neuroimaging distinguishes autoimmune autonomic ganglionopathy (AAG) from pure autonomic failure (PAF).

neuronal form of the nicotinic acetylcholine receptor (nAChR). The antibodies interfere with ganglionic neurotransmission, and so post-ganglionic nerve traffic is decreased in the parasympathetic nervous system and the sympathetic noradrenergic and cholinergic systems.

AAG manifests with symptoms and signs of decreased post-ganglionic neurotransmission. Because of parasympathetic cholinergic failure, the patient has decreased salivation, lacrimation, gastrointestinal movements, and bladder tone. Because of sympathetic cholinergic failure, the patient has decreased sweating. Because of sympathetic noradrenergic system failure, the patient has

neurogenic orthostatic hypotension.

Since the lesion in AAG is at the level of the neuronal nicotinic receptor, there is no reason to suspect that the neurogenic orthostatic hypotension reflects loss of post-ganglionic sympathetic noradrenergic nerves. On the other hand, interference with ganglionic neurotransmission would result in decreased post-ganglionic sympathetic nerve traffic. This explains the combination of low plasma norepinephrine levels with normal cardiac sympathetic neuroimaging results in AAG.

Plasma levels of DHPG, the main neuronal metabolite of norepinephrine, provide a better index of sympathetic noradrenergic innervation than do levels of norepinephrine itself. In PAF, DHPG levels are lower than expected for norepinephrine levels. In AAG, the opposite is the case, and plasma norepinephrine levels are lower than expected for DHPG levels. Presumably this is because of decreased stores of norepinephrine in PAF and decreased exocytotic release from generally intact post-ganglionic sympathetic nerves in AAG.

Management of AAG usually focuses on anti-autoimmune therapies with plasma exchanges (to remove the circulating antibody to the neuronal nicotinic receptor), steroids, rituximab (which is toxic to antibody-producing B cells), and Cellcept.

The Old Lady Who Couldn't Spit

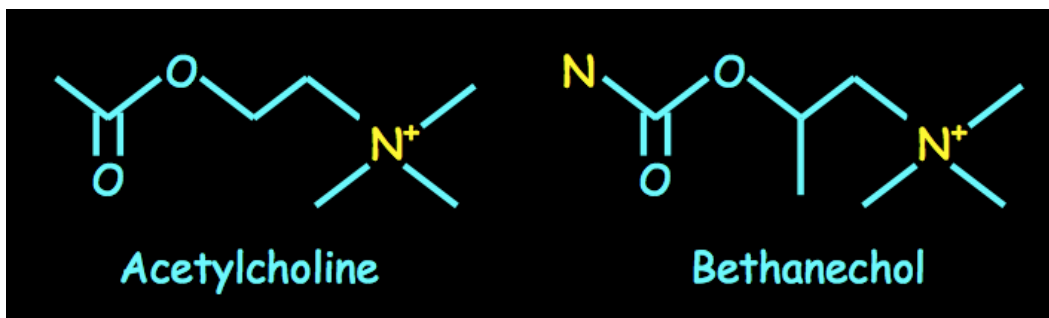
Several years ago an elderly African-American resident of the District of Columbia was evaluated at the NIH Clinical Center for severe orthostatic hypotension. Although she had orthostatic intolerance, this was not her chief complaint. Her chief complaint was that she couldn't make spit.

Her mouth was so dry, she couldn't masticate food. She was also severely constipated. The combination of not being able to salivate and having severe constipation had resulted in her becoming malnourished. When first seen, she looked cachexic, like a concentration camp survivor or a patient with end-stage cancer.

She had characteristic abnormalities of beat-to-beat blood pressure associated with the Valsalva maneuver, indicating that her orthostatic hypotension was not from dehydration but from a neurogenic cause. She also had an extremely low plasma norepinephrine level. Initially we thought she had pure autonomic failure (PAF) and predicted that her ^{18}F -dopamine PET scan would show loss of sympathetic innervation of the heart.

Instead, her ^{18}F -dopamine PET scan was normal. Moreover, under the study protocol she received a ganglion blocker, and this produced hardly any effects at all.

At about that time Dr. Steven Vernino had published a study about



Bethanechol resembles acetylcholine structurally.

autoimmune autonomic neuropathy associated with a circulating antibody to the neuronal nicotinic receptor, which mediates ganglionic neurotransmission. No patient with PAF had such an antibody; we suspected our patient might, and we sent Dr. Vernino a sample, which was positive. Together we published the first case of what has come to be known as autoimmune autonomic ganglionopathy (AAG).

To treat the patient's chief symptom, dry mouth, we prescribed bethanechol (Urecholine™), which is a muscarinic cholinergic agonist. Bethanechol resembles acetylcholine structurally, but bethanechol is not broken down by acetylcholinesterase. Bethanechol treatment produced a very gratifying result in our patient—she had a return of her ability to make saliva, alleviating her chief complaint.