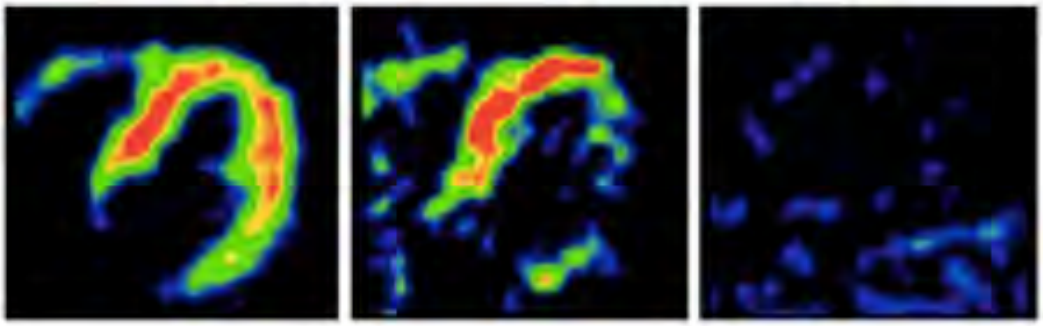
Principles of Autonomic Medicine



David S. Goldstein, MD PhD

TABLE OF CONTENTS PAGE #

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CVRx (carotid sinus stimulator, p. 574)

DEDICATION

I dedicate this book to my family, for their support and understanding; my colleagues and friends at the NIH, for their devotion to our research mission and to me; and especially to the many patients who have put their trust in me and provided me with sparkles of insight about how the body's "automatic" systems function in health and disease.

I've benefitted from a rich network of NIH colleagues, whom I have cherished for their sharing time with me in a common quest for truth and meaning. Some of these, in alphabetical order, are: Ines Armando, John Bacher, George Bagdy, Krys Bankiewicz, Oladi Bentho, Alan Breier, Simon Bruce, Huaibin Cai, Richard Cannon, Peter Chang, Jamie Cherup, George Chrousos, Glen Cook, Adele Cooney, Vic Convertino, Abraham Corrales, Nadir Dakak, Raghu Dendi, Ray Dionne, Yu-Fe Duan, Debra Ehrlich, Lee Eiden, Graeme Eisenhofer, Basil Eldadah, Igor Elman, Giora Feuerstein, John Finberg, Joan Folio, Steve Frank, Koki Fukuhara, Moshe Garty, Janna Gelsomino, John Gill, Anna Golczynska, Phil Gold, Ehud Grossman, Judy Harvey-White, Peter Herscovitch, Aaron Hoffman, Courtney Holmes, Doug Hooper, David Hovevey-Sion, Thanh Huynh, Richard Imrich, Risa Isonaka, Yunden Jinsmaa, Jan Johannessen, Steve Kaler, Barbara Karp, Minoru Kawamura, Harry Keiser, Joong-Seok Kim, Ken Kirk, Irv Kopin, Richard Kvetnansky, Ray Lake, Itzhak Lamensdorf, Guillaume Lamotte, Jacques Lenders, Paul Levinson, Shengting Li, Oscar Linares, Roshanak Mansouri, Reversa Mills, Jeff

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I've also learned from discussions and collaborations with many colleagues at institutions outside the NIH. Some of these people, also in alphabetical order, are: Frank Abboud, Jeffrey Ardell, Felicia Axelrod, Edurado Benarroch, Italo Biaggioni, Hugh Calkins, Jason Carter, Mark Chapleau, Bill Cheshire, Yu-Shin Ding, Vincenzo Donadio, Jonathan Doorn, Murray Esler, David Fink, Roy Freeman, Peter Friberg, Alfred Geller, Chris Gibbons, Giris Jacob, Samay Jain, Daniela Jezova, Jens Jordan, Meyer Katzper, Horacio Kaufmann, Ramesh Khurana, Amos Korczyn, Ben Levine, Kelly Lohr, Phillip Low, Chris Mathias, Allyn Mark, Deborah Mash, Richard McCarty, Gary Miller, Lucy Norcliffe-Kaufmann, Dan O'Connor, Satoshi Orimo, Mark Pekker, Murray Raskind, David Robertson, Alberto Palma, Elaine Peskind, Satish Raj, Srinivasa Raja, Ali Salahpour, Paola Sandroni, Ron Schondorf, Kalyanam Shivkumar, Jay Shulkin, Wolfgang Singer, Kathy Swoboda, Gert. van Dijk, Alessandro Stefani, Julian Stewart, George Stoica, Jens Tank, Laura Vecchio, Steve Vernino, Debra Weese-Mayer, Jill Wecht, Wouter Wieling, and Jing Zhang,

Dr. Irwin J. ("Irv") Kopin was my boss and mentor for many

Fig. 1: Irv Kopin and Courtney Holmes. *In their own ways, Irv and Courtney were founders of autonomic medicine.*

years, and I honor his memory here. Irv was an example of intellectual rigor, productivity, perspective, and integrity, an inspiration throughout my career at the NIH.

Courtney Holmes ran our Section's catecholamine neurochemistry lab for 28 years. Thanks to her attention to detail, work ethic, and monumental expertise, she pointed me unerringly to the truth. If there were a catecholamine Hall of Fame, Courtney surely would be in it.

Finally, I thank the many patients who have volunteered to participate in research protocols for which I have been the Principal Investigator at the NIH. I remember with awe and appreciation those who requested they be autopsied to enhance understanding of their disease—an ultimate act of philanthropy. I feel honored and humbled and would name them here but for respect of privacy and confidentiality.

INTRODUCTION

Why Did I Write this Book?

Principles of Autonomic Medicine is designed to be a resource that patients, students, and clinicians can share.

A SHARED RESOURCE

Writing a shared resource like this isn't easy. Across the readerships there are obvious differences in education, competencies, vocabulary, needs, and expectations. I've tried to meet these challenges as follows.

The text highlighted in blue is for lay people, patients, and caregivers.

At the end of the book is a large glossary, but you can find out the meanings of words or phrases instantly by "popups" in the pdf file of the book. Hovering over words or phrases pops up balloons that show the definitions in the glossary. You can try that here: try hovering over the phrase, autonomic nervous system, and see what happens.

I also wrote this book to teach trainees in autonomic disorders. There are a growing number of autonomics fellowships accredited by the United Council for Neurological Subspecialties (UCNS). I want to help autonomics fellows pass the UCNS certifying examination.

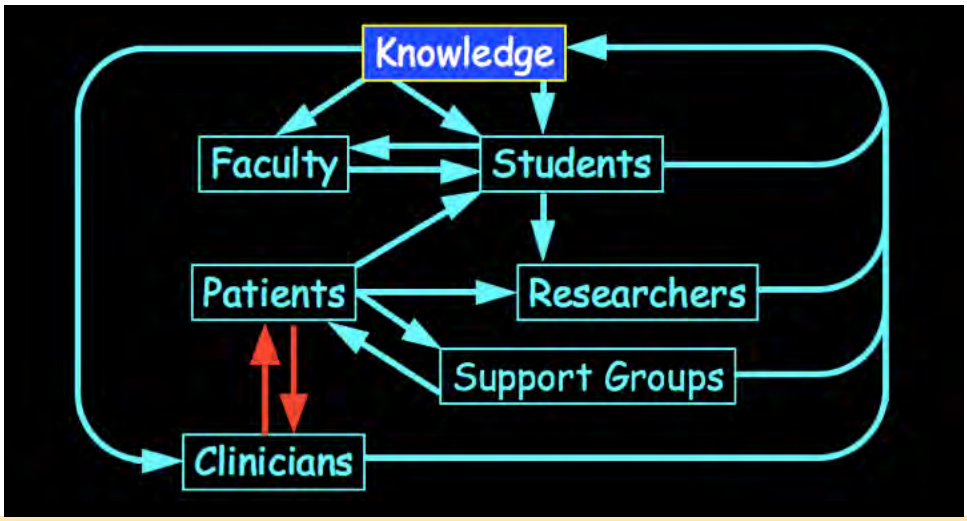


Fig. 2: The medical knowledge network. *To help students and trainees grasp the scientific concepts, I've drawn many figures and diagrams. The figure legends in italics provide a kind of parallel text. This one illustrates the many interactions among groups of people in the advancement of medical knowledge.*

For clinicians there are descriptions of several autonomic function tests, emphasizing that the most informative such test is an intelligently obtained medical history. I've also included concepts underlying several treatments, emphasizing that management of autonomic disorders should be tailored to the individual condition and patient; that reassurance, accurate information, and empathy often are at least as effective as drugs; and that education is itself a form of treatment.

For clinicians who are academicians I'm proposing a few ideas that seem to me to have potential for enhancing understanding of autonomic and catecholamine-related disorders, such as homeostats as metaphors, allostatic load, catecholamine autotoxicity, and cybernetic medicine.

I consider this book to be more of a teaching aid than a rigorous academic treatise. There are some literature citations, which you can access by clicking on hyperlinks in the text that look like this: https://www.ncbi.nlm.nih.gov/pubmed/31807952.

I hope this shared resource is a first step toward "flipping" the classroom and the clinic in autonomic medicine, giving students more power and responsibility in their education and giving patients more power and responsibility in their clinical management.

I sense a disconnect between the public health burden of dysautonomias, which is growing rapidly, and the available cadre of autonomics specialists who are comfortable with and competent at managing the patients. This book is part of an effort to resolve this discrepancy.

What is Different about this Book?

I think you can see from what you've already read that this book is different from others you've come across.

One reason this book is different is that it is a monograph. A single-authored medical book has advantages and disadvantages. A strong advantage is consistency in the presentation. Over the years I've developed a particular approach to clinical evaluations and a system of research and style of teaching about autonomic and catecholamine-related disorders. Students may acquire the material better if it is presented consistently across chapters.

There are also disadvantages. This is a rather personal account. The presentation is eclectic, not encyclopedic. Many topics are covered cursorily. Some potentially relevant topics aren't covered at all.

The discipline of autonomic medicine is immense and expanding. No one has sufficiently comprehensive knowledge of the subject matter. Like everyone else, I think that what I see is all there is. I over-emphasize what I've observed or published. To pique interest, sometimes I include viewpoints for which the supporting data are incomplete or simply not there. I try to point out when I've done this.

I've exploited the electronic and internet-based format in a few ways. First, by hovering over a particular word or phrase in the PDF file of the book, a popup should appear that shows the meaning listed in the glossary. This helps avoid the disruption of having to go to the glossary to understand what you're reading. Second, clicking on a particular heading or subheading in the Table of Contents should take you immediately to the section with that heading. Third, in conjunction with composing version 4.0, as an initiative of the American Autonomic Society I'm supervising the assembly of numerous short videos that correspond to particular topics in the book. Using the videos as "Lego bricks of knowledge" should enable construction of future courses that are tailored to topics appropriate for the curriculum and students.

THREE A'S OF STICKY TEACHING

In writing this book I've used three ways to make the teaching

points "sticky." By "sticky" I mean memorable. The points stick in your head. For stickiness I've depended on what I call the three A's of sticky teaching: art, analogy, and anecdote.

I've exploited a talent for drawing and cartooning to convey concepts that would be difficult to grasp from the text alone. Many figures in this book are concept diagrams. I use the figure legends to convey the key teaching points.

Eternal vigilance is the price of "stickiness."

It's not easy balancing scientific correctness vs. stickiness. Concept diagrams, analogies, and anecdotes can be incomplete, overly simplistic, biased, or just plain wrong.

I've tried to spice up the book with sprinkles of wit. This sort of whimsy may not be to everyone's taste. Topic headings in this book include "A Little Pain Can't Hurt" and "A Waist is a Terrible Thing to Mind." At times (like now) I'll be pointing out that what you just read was funny. My sense of humor has been described as "wry" and my writing style, well, "interesting."

Diss-auto-NO-mias and Cat-a-COLA-means

This book is founded on two pillars—dysautonomias and catecholamines. The reason for the overlap between dysautonomias and catecholamines is that key parts of the autonomic nervous system use catecholamines as their chemical

messengers.

Dysautonomias are a particular class of medical disorders. Catecholamines are body chemicals that often are related to those disorders. Unfortunately, both the disorders and the chemicals have names that are hard to pronounce. The disorders are dysautonomias, pronounced diss-auto-NO-mias. The chemicals are catecholamines, pronounced cat-a-COAL-a-means.

By measuring levels of the messengers, we can learn about how those parts of the nervous system work in health and disease. From identifying specific abnormalities or vulnerabilities of catecholamine-related systems, we can understand the mechanisms and might even come up with new therapeutic or preventive strategies for particular disorders.

There are a large number of conditions in which altered functions of one or more components of the autonomic nervous system adversely affect health. As a group they are called dysautonomias.

By way of introduction, the catecholamine chemical family has three members—dopamine, norepinephrine, and adrenaline (synonymous with epinephrine—I'll explain later why I use "adrenaline" in this book). All three catecholamines are vitally important in the body, but in different ways.

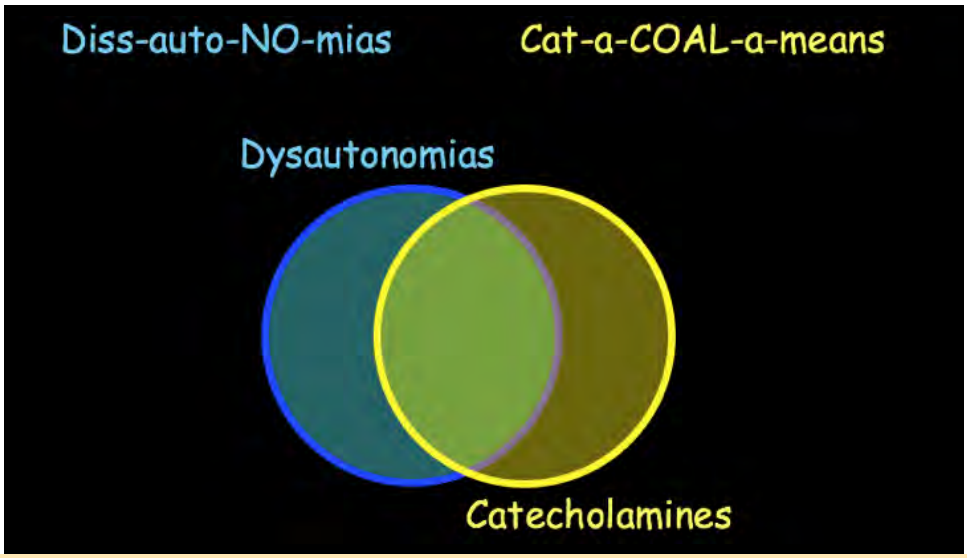


Fig. 3: Diss-auto-NO-mias and Cat-a-COAL-a-means.
Dysautonomias and catecholamine-related disorders overlap.

WHY ARE DYSAUTONOMIAS HARD?

Dysautonomias are a difficult subject—for patients, doctors, students, and researchers. Dysautonomias are hard to diagnose, treat, live with, and understand.

There are several reasons for this. It's important to explain at the outset why the field of dysautonomias is so hard.

Dysautonomias are Multi-Disciplinary

The field of dysautonomias spans multiple disciplines of medicine. Specialists within these disciplines often cannot serve dysautonomia patients.

If your only tool is a hammer, the world looks like a nail. If a dysautonomia patient sees a cardiologist, the cardiologist looks for an abnormal heart rhythm or heart block, something a pacemaker or ablative therapy can treat. If the patient sees a neurologist, the neurologist looks for a seizure disorder, a problem with blood flow to the brain, a brain structural abnormality, or a neuropathy. If the patient sees an endocrinologist, the endocrinologist looks for diabetes or a thyroid, adrenal, or pituitary problem. If the patient sees an immunologist, the immunologist looks for autoimmunity or mast cell activation. If the patient sees a gastroenterologist, the gastroenterologist looks for gastro-esophageal reflux, decreased gut motility, or irritable bowel syndrome. If as often happens the patient finally sees a psychiatrist, the psychiatrist looks for depression, anxiety, a "conversion reaction," or panic disorder.

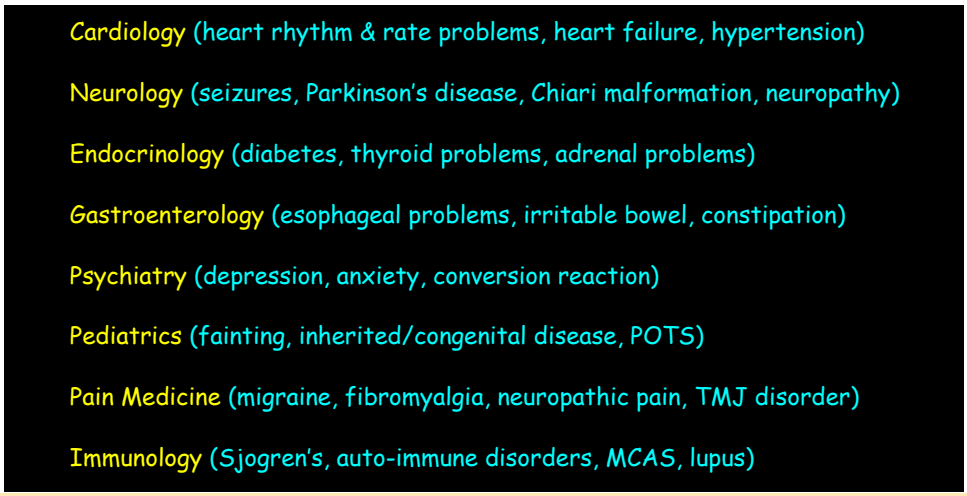


Fig. 4: Dysautonomias are multi-disciplinary. *Several medical disciplines involve dysautonomias. In none of these is autonomic medicine an integral part.*

The NIH is a major source of research funding in American biomedicine. Clinical disorders of the autonomic nervous system don't fit well under the umbrella of any NIH Institute. Dysautonomias seem foreign or of secondary importance. Considering the public health burden posed by dysautonomias, research grants to reduce that burden are remarkably scarce.

Dysautonomias are Complex

Many factors determine levels of pulse rate, blood pressure, body metabolism, pain, fatigue, and the sense of psychological well-being. These factors interact complexly with each other.

Further complicating the picture, patients with dysautonomias

often are treated with multiple drugs, which not only can interact with each other but also with the disorders. Scientific theories taking this complexity into account have lagged behind.

Diagrams depicting disorders of feedback regulated systems can appear dauntingly complex. At their core, though, they all involve abnormal functioning of negative feedback loops.

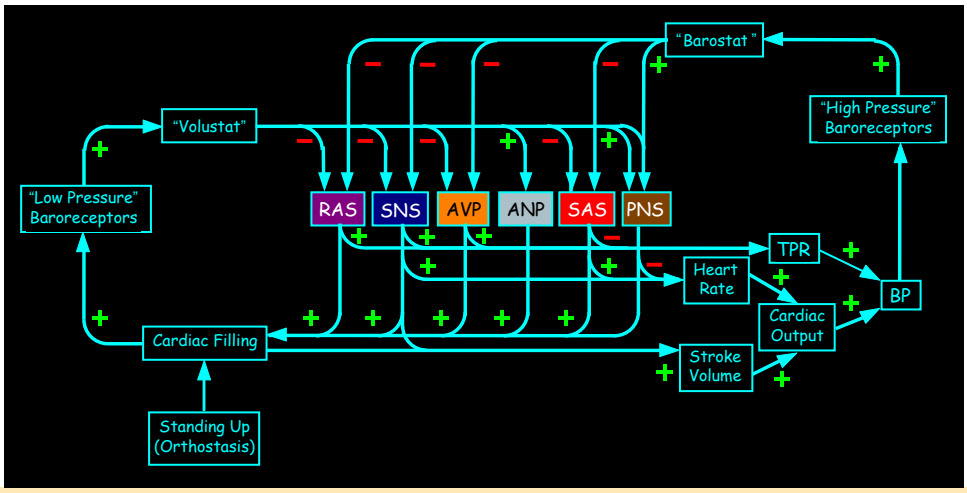


Fig. 5: Dysautonomias are complex. *Dysautonomias are integrative medical disorders and therefore involve many complex networks, effector systems, and feedback loops. This diagram shows some of the factors regulating blood pressure when a person stands up.*

This book teaches that dysautonomias are usually if not always disorders of integration, of regulation, of systems that change during life as a function of the balance of wear and tear vs. resilience.

Different centers have different emphases in the workup and management of dysautonomias. One center traditionally has

focused on familial dysautonomia, a rare pediatric disease. Another has emphasized dysautonomia associated with diabetes, another disorders of sweating, another chronic orthostatic intolerance and multiple system atrophy, and another autoimmune autonomic ganglionopathy.

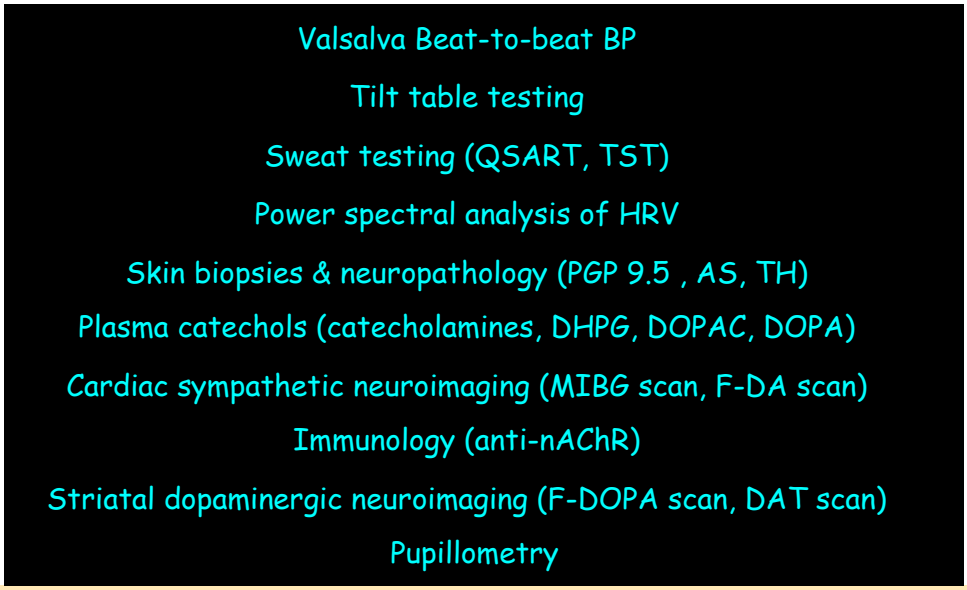


Fig. 6: There are numerous autonomic function tests. *Different centers offer different batteries of tests. No center offers them all.*

Different centers offer different tests, often depending on factors such as finances, insurance coverage, and regulatory constraints and delays. In my opinion these aspects have impeded the efficient adoption and application of valuable, powerful clinical laboratory technologies.

In particular, no center outside the NIH has an integrated program of autonomic neuroimaging and neurochemistry. Tests that are done at the NIH for research purposes are not approved by the FDA as diagnostic tests.

Difficult Pronunciations & Abbreviations

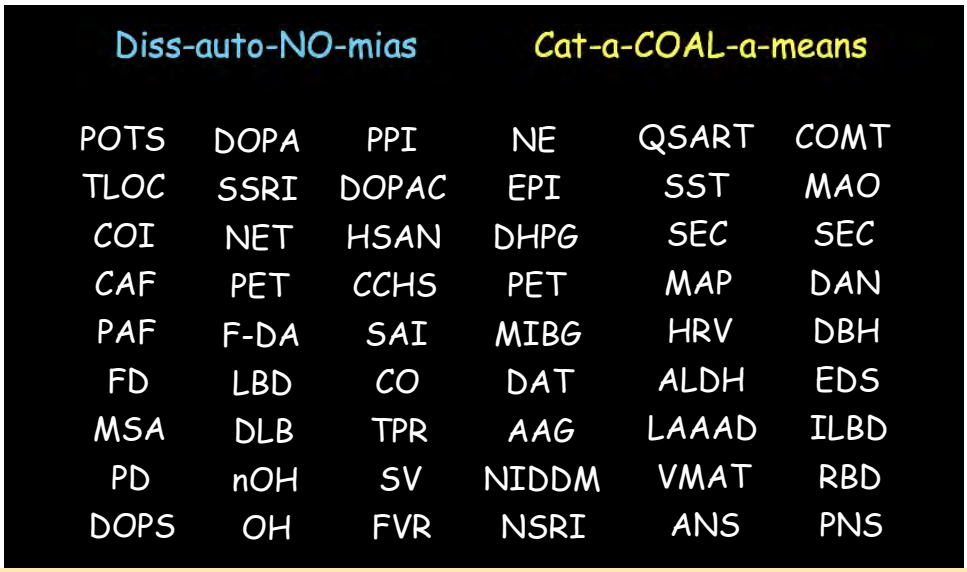


Fig. 7: Difficulties because of complex words and abbreviations. *The field of autonomic medicine involves numerous difficult to pronounce words and abbreviations.*

The word, “dysautonomia,” is difficult to pronounce. So are the words, “norepinephrine” and “acetylcholine,” which are the key chemical messengers of the autonomic nervous system. The field is rife with abbreviations that only an expert can comprehend.

Dysautonomias are Mind-Body Disorders

Dysautonomias are “mind-body” disorders. This view goes against a distinction between mental and physical body processes.

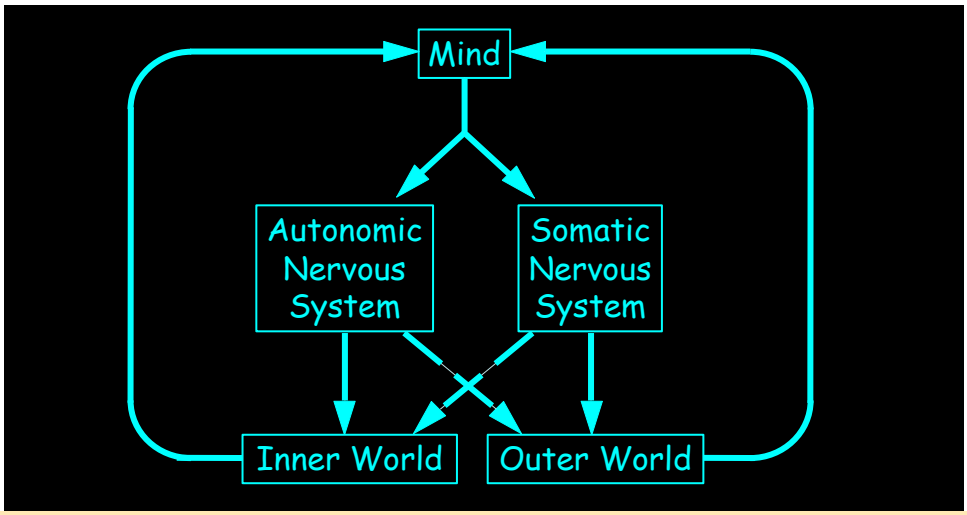


Fig. 8: Dysautonomias are mind-body disorders.

Are dysautonomias in the mind or body? The answer is: they are in both.

A major purpose of this book is to teach that the many symptoms of dysautonomias reflect real biological or chemical changes. If a clinician cannot identify the cause of a patient's symptoms, this ignorance should not lead to dismissing the patient as having a psychiatric rather than a "real" problem.

It is unhelpful to classify dysautonomias—or the patients suffering with them—as "psychiatric" or "medical."

For centuries, traditional medicine has separated mental from physical illness. In trying to understand dysautonomias, distinctions between the "body" and the "mind," between the physical and the mental, and between problems imposed on the

individual as opposed to those originating in the mind of the individual, are unhelpful. The autonomic nervous system operates exactly at the ineffable border of the mind and body. In this book you will learn a systems approach to the mind-body issue.

Different Centers Have Different Emphases

In almost every aspect of autonomic medical practice and research, doctors—even experts in the field—can disagree about answers to key questions.

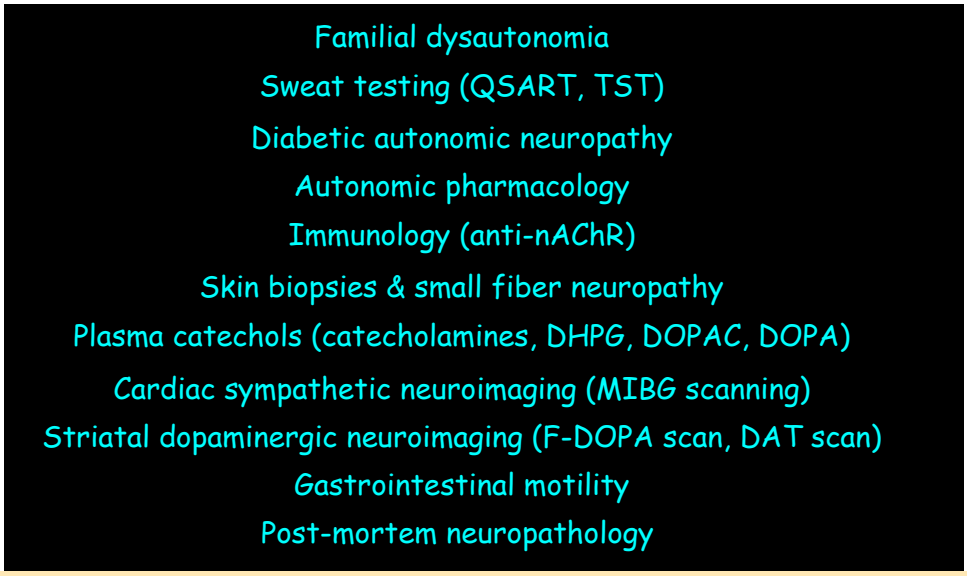


Fig. 9: Different centers have different emphases. *This includes different forms of dysautonomia and different topics of specialization.*

How should dysautonomias be classified? What are the types and subtypes? Of what do patients with particular

dysautonomias complain? Which tests are useful to diagnose particular dysautonomias or monitor responses to treatments? What are the disease mechanisms? Which treatments work for which forms of dysautonomia? What happens to patients with dysautonomias over time?

Dysautonomias are Not Taught Well

I don't think the field of clinical disorders of the autonomic nervous system is taught well at any educational level. Medical and graduate school curricula rarely contain coursework on dysautonomias. Compared to the large patient demand and public health burden, clinical and basic training and scientific knowledge about dysautonomias are disproportionately sparse.

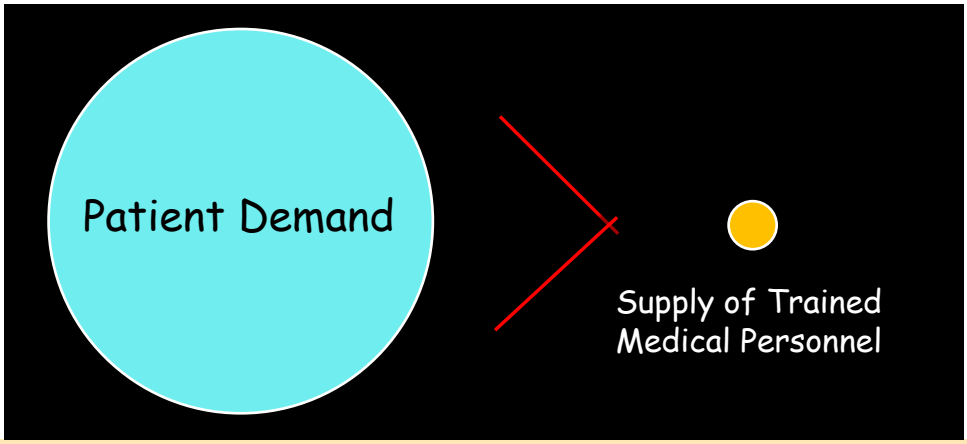


Fig. 10: Dysautonomias are not taught well. *Autonomic medicine is not part of the curriculum at most professional or graduate schools in the United States. The patient demand outstrips the supply of trained medical personnel.*

The accreditation program for fellowships in autonomic disorders by the United Council for Neurologic Subspecialties

(UCNS) is a step in the right direction. As of this writing, however, there are only a handful of institutions with accredited fellowships in autonomic medicine.

Whether you are a lay person, a patient, a caregiver, a student, a general physician, or even a specialist in neurology, cardiology, endocrinology, or psychiatry, my guess is that the field of dysautonomias is almost completely foreign to you.

I feel "cursed by knowledge," meaning I can't tell when there are gaps in the logical flow of ideas and facts in the text. I'm hoping for feedback from readers to improve future versions. I'd greatly appreciate your corrections, comments, and suggestions.

Please let me know if this book works for you, by sending me an email at goldsteind@ninds.nih.gov.

WHAT IS THE ANS?

We all have a nervous system. What makes up this system? What do the parts of the nervous system do? And what is the "autonomic" part of the nervous system?

The autonomic nervous system is the body's "automatic nervous system."

This section is about your nervous system and how it functions when there is nothing wrong with it. You will need to understand the basics before you can understand the problems that can develop.

To keep you alive and thrive, your body has to be able to coordinate many different activities. Some of these activities are voluntary and conscious, like moving your legs to walk across the room, while others are involuntary and unconscious, like breathing and digesting.

The autonomic nervous system is responsible for many of the automatic, usually unconscious processes that keep the body alive and stable, such as:

— controlling blood flows to the brain and other organs, both while you are at rest and while you are exercising

— keeping the right body temperature

— digesting food for energy production and fuel

delivery

— getting rid of waste products in the urine and feces

— generating warning signs such as sweating, turning pale, and trembling in dangerous situations.

THE CNS IS LIKE A TOOTSIE ROLL POP

Here is a classical diagram of the arrangement of the ANS in the body.

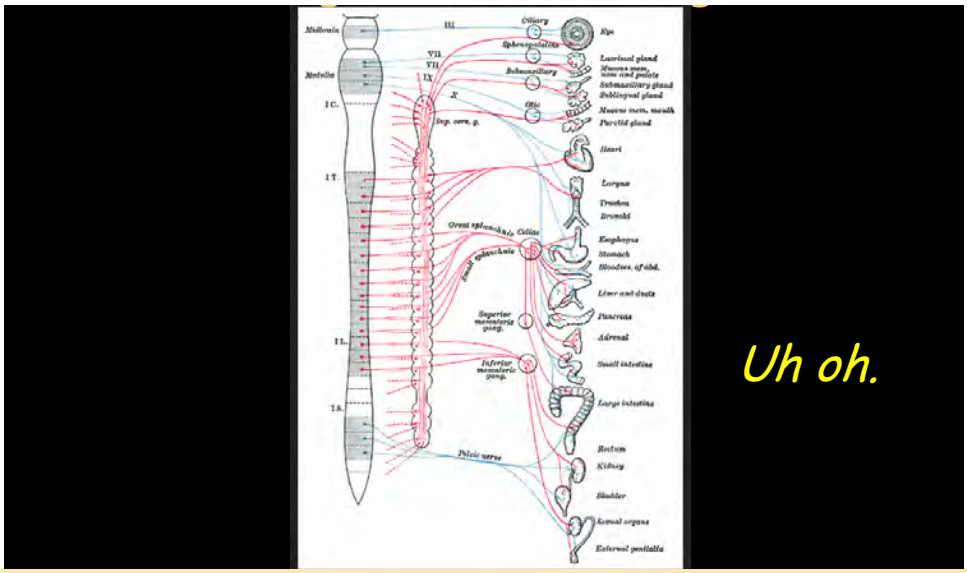


Fig. 11: Classical diagram of ANS organization. *This sort of depiction is very difficult to comprehend.*

I think you'll agree that the organization of the ANS seems impossibly complex. Let's start to build up from scratch.

The central nervous system is made up of the brain and the spinal cord. The brain is like a command and control center.

The spinal cord is a rope of nerves that runs from the base of your brain down through your back within your spinal column.

Fig. 12: The Tootsie Roll Pop Analogy. *The central nervous system is like a Tootsie Roll Pop.*

The central nervous system (CNS) is like a Tootsie Roll pop. The brain is the candy. The spinal cord is the stick. The chewy chocolate center is the brainstem.

The spinal cord is divided up into regions or levels. The cervical spinal cord is in the neck. Below this are the thoracic and lumbar spinal cord (the two parts together are the thoracolumbar spinal cord), and the lowest level is the sacral spinal cord.

Autonomic nerves are derived from the brainstem and the thoracolumbar and sacral spinal cord.

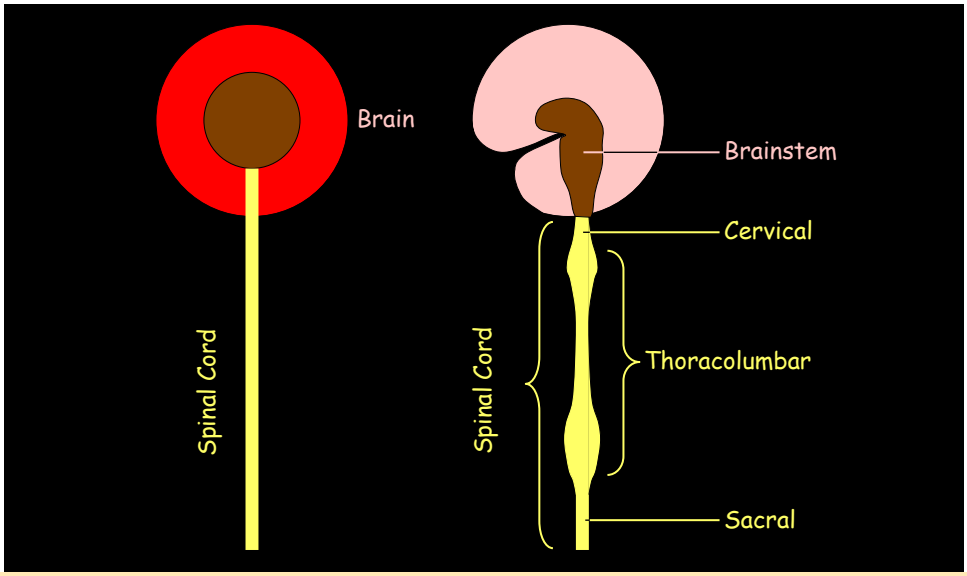


Fig. 13: The chewy chocolate center. *The brainstem is in the brain at the top of the spinal cord, like the chewy chocolate center of a Tootsie Roll pop.*

THE AUTONOMIC NERVOUS SYSTEM ISN'T AUTONOMIC

Control signals travel from your brain to your limbs and organs by way of the peripheral nervous system. The peripheral nerves are all the nerves that lie outside the brain and spinal cord.

Inside you is the “inner world” of your body, with its many internal “variables,” such as blood oxygen and glucose, blood pressure, and core temperature. Normally these variables actually don’t vary by much. They are kept in check. This is a key task in maintaining organismic integrity. The task is accomplished largely because of the component of the

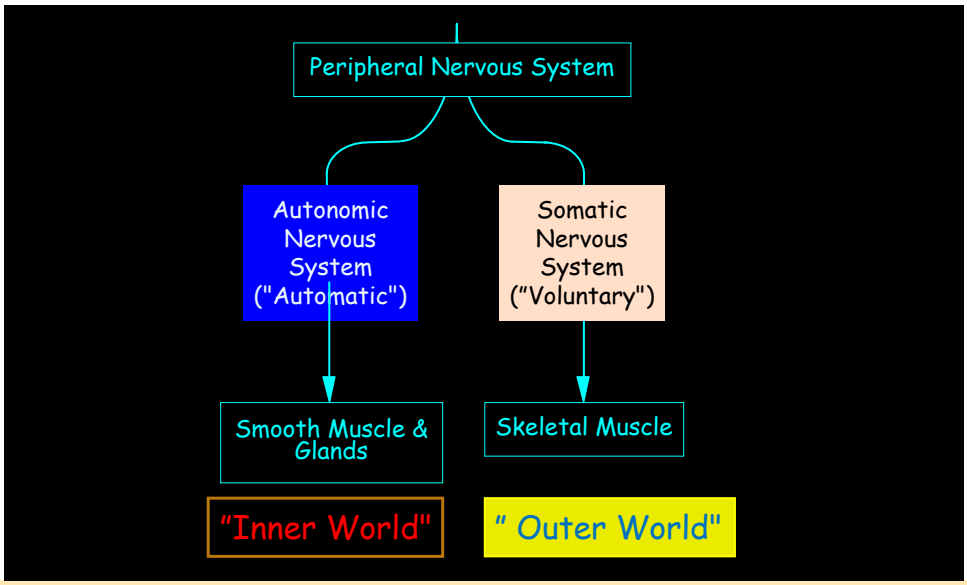


Fig. 14: The ANS & the Inner World. *The peripheral nervous system consists of the autonomic nervous system and the somatic nervous system.*

peripheral nervous system that helps regulate the body's inner world—the autonomic nervous system (ANS).

The peripheral nervous system has two main divisions—somatic and autonomic. The somatic nervous system deals with the "outside world" of everything around us. It uses sense organs to detect what is going on outside, and it uses skeletal muscles to move.

The autonomic nervous system is a key system by which the brain regulates the "inner world" inside the body.

In general, voluntary behaviors arising from the central nervous system are linked to changes in organ function mediated by the

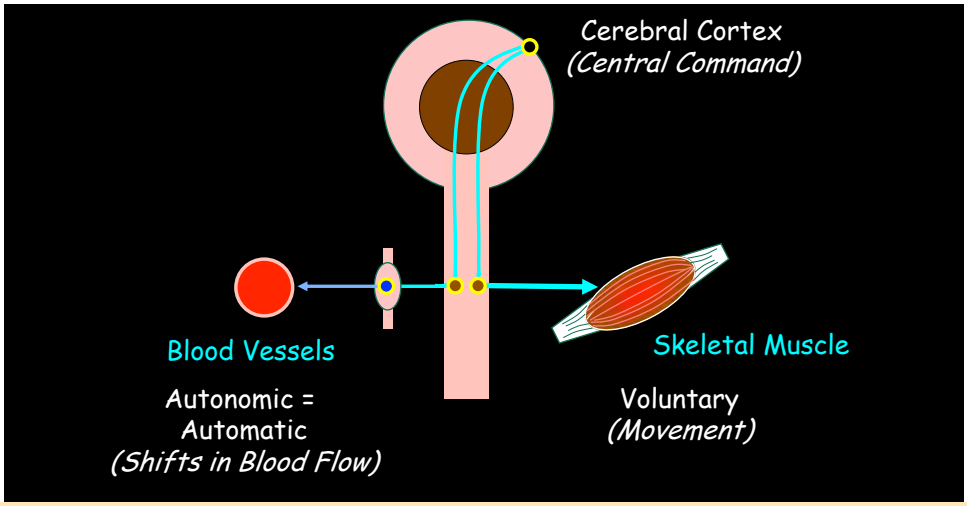


Fig. 15: The ANS isn't autonomous. *The ANS isn't autonomic in the sense of being autonomous of the brain. For instance, when you exercise, voluntary contraction of skeletal muscle is linked to automatic shifts in blood flow distribution. "Central command" results in appropriate delivery of fuel to and removal of products of metabolism from the exercising muscle.*

The autonomic nervous system really isn't "autonomic," but it is "automatic."

autonomic nervous system. When you clench your fists, after several seconds your blood pressure increases. When you get out of a hot shower and walk into a cool locker room, you develop goose bumps. When you stand up from lying down, your blood vessels tighten reflexively. When you walk out of a cool restaurant into the hot outdoors, you sweat.

Since changes in somatic and autonomic functions usually are closely tied, the autonomic nervous system doesn't really function autonomously of the central nervous system. It does function automatically, unconsciously, and involuntarily. I

prefer the phrase, automatic nervous system, but the phrase "autonomic nervous system" (ANS) is deeply engrained in the tradition of medical physiology.

THE UTILITY POLE OUTSIDE YOUR HOUSE

Nerves that travel to skeletal muscle and regulate movement come directly from the central nervous system. Nervous signals of the autonomic nervous system, however, travel indirectly to internal organs, via clumps of cells called "ganglia."

Nervous signals of the autonomic nervous system come indirectly from the central nervous system, by way of clumps of cells called ganglia.

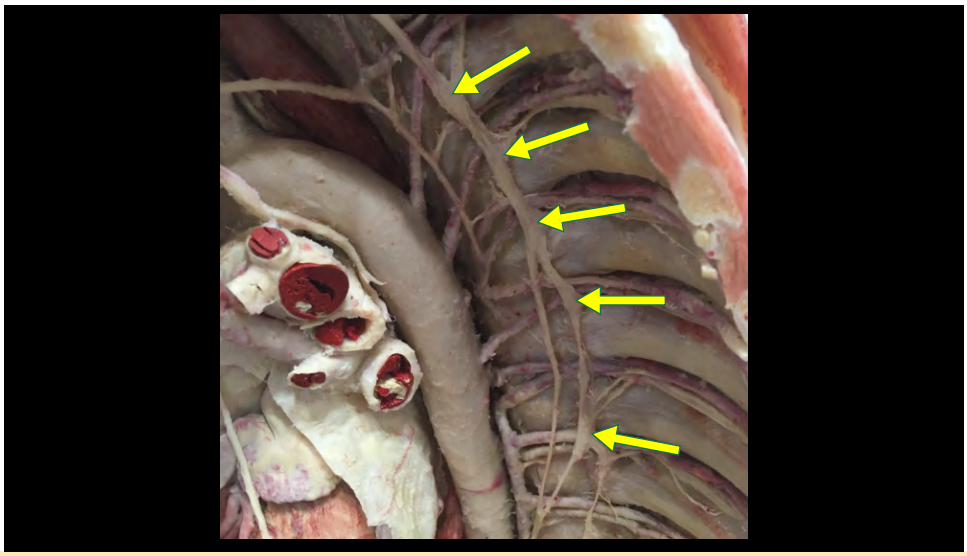


Fig. 16: Sympathetic chain in a plasticized human. *The sympathetic chain and ganglia (yellow arrows) are in the back of the chest, in gullies on each side of the spinal column.*

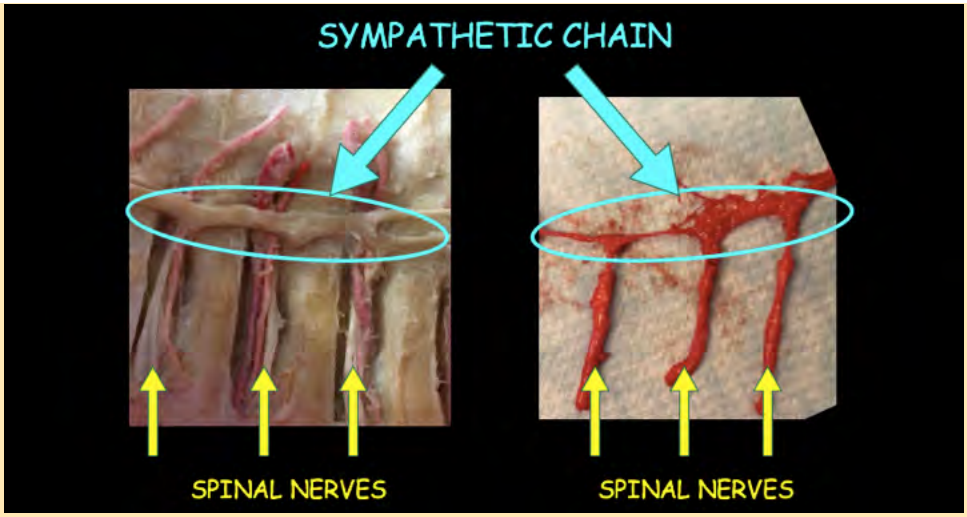


Fig. 17: Sympathetic chain and spinal nerves. *Plasticized and freshly harvested autopsy tissue showing the sympathetic chain at right angles to the spinal nerves.*

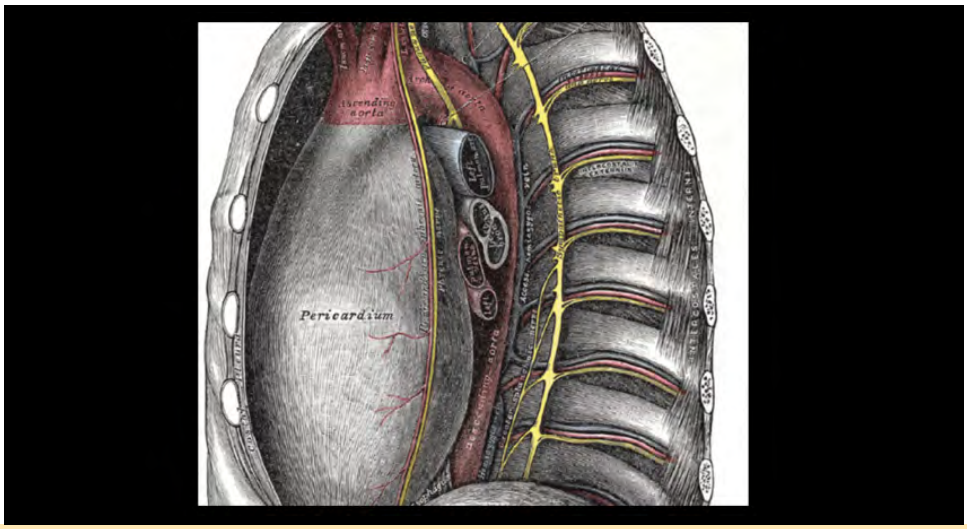


Fig. 18: Textbook diagram of the sympathetic chain. *This drawing from an anatomy textbook shows the position of the sympathetic chain just in front of the posterior ribs in the chest.*

Later we will cover the meaning of "sympathetic chain," but by way of introduction the ANS has component parts, and a major

part is the sympathetic nervous system. The sympathetic ganglia are arranged like pearls on a necklace on each side of the spinal column. The nerve cells, the neurons, of the sympathetic nervous system therefore are not in the brain or spinal cord.

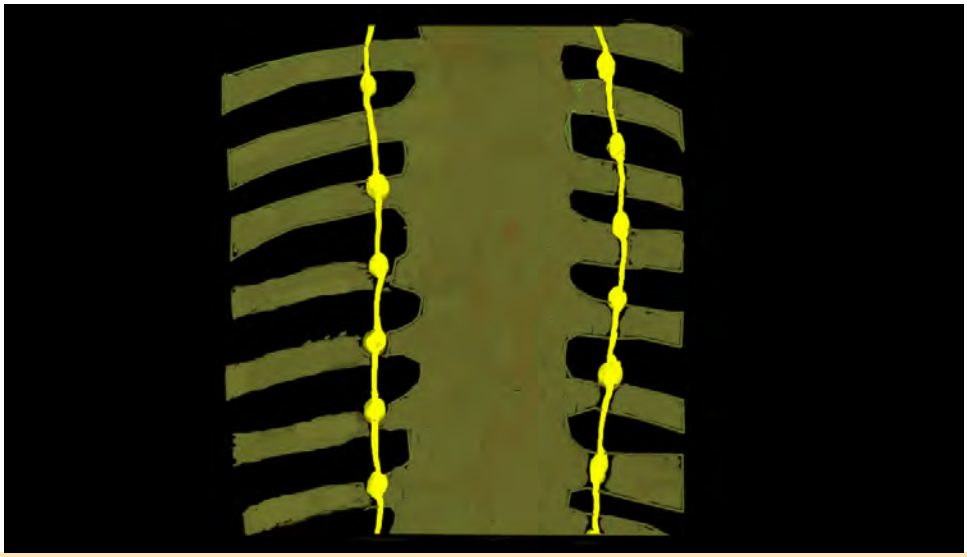


Fig. 19: The pearl necklace analogy. *Autonomic ganglia are arranged like strands of pearls on each side of the spinal column.*

To convey what the ganglia of the autonomic nervous system do, think of how electricity is delivered to your home. From the generator plant and distribution center come thick, high voltage lines that transmit electricity along large towers. Outside your house is a utility pole that contains a transformer. From the utility pole much thinner, low voltage wires connect to your house.

The ganglia act like transformer boxes. The nerves from the

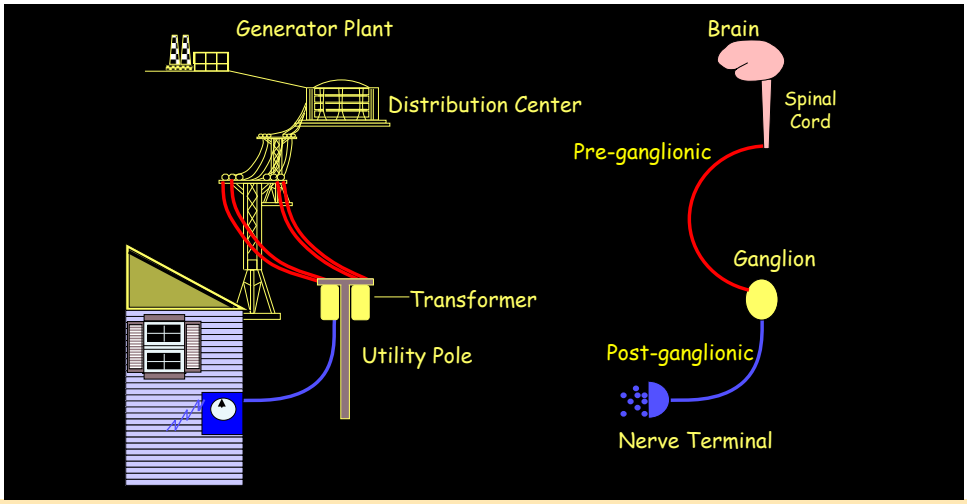


Fig. 20: The electrical transformer analogy. *Ganglia are like the electrical transformers on the utility pole outside your house.*

spinal cord are called “pre-ganglionic.” They are thick and conduct electricity quickly, because they have a myelin sheath. Myelin is a complex chemical consisting mainly of water, fat, and protein that appears white to the eye. The “white matter” of the brain is white because of myelin, and myelinated nerves look white. Electric signals are conducted more rapidly in myelinated than in non-myelinated nerves. The nerves from the ganglia to the target organs are “post-ganglionic.” They are thin, slow conducting, and non-myelinated. They look gray.

In keeping with the idea that adrenaline is an emergency hormone that should be released rapidly, the cells of the adrenal gland that release adrenaline into the bloodstream receive myelinated nerve fibers, as if there were a direct wiring connection from the electrical distribution center to the terminal box.

THE ANS HAS PARTS

HISTORY OF THE "AUTOMATIC" NERVOUS SYSTEM

Langley's "Autonomic Nervous System"

About the turn of the 20th century, the English physiologist, John Newport Langley, consolidated findings from his and others' research to propose the concept of the "autonomic nervous system" (ANS). Langley invented this phrase.

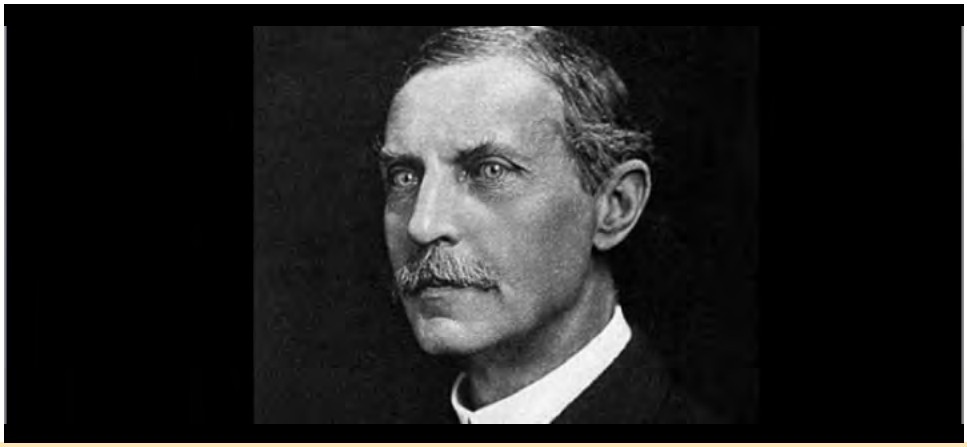


Fig. 21: John Newport Langley (1852-1925). *Langley coined the term, "autonomic nervous system."*

Langley was referring to networks of nerves outside the central nervous system that are derived from ganglia. He described three components of the autonomic nervous system—sympathetic, parasympathetic (a word he invented), and enteric. Sympathetic nerves are derived from the thoraco-lumbar spinal cord, and parasympathetic nerves are derived from the brainstem and sacral spinal cord, while enteric neurons are found within the walls of the gastrointestinal tract.

The concept of there being sacral parasympathetic innervation is actually a matter of current dispute. In this book we are accepting Langley's viewpoint.

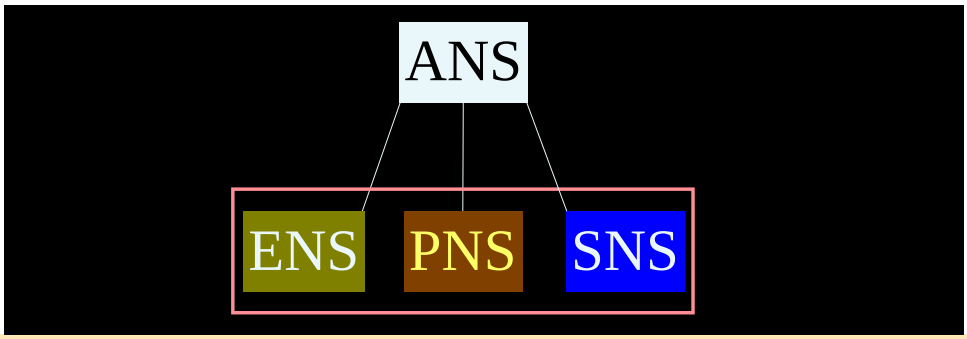


Fig. 22: **Langley's "autonomic nervous system"** ***(ANS).*** *The ANS consists of the enteric nervous system (ENS), parasympathetic nervous system (PNS), and sympathetic nervous system (SNS).*

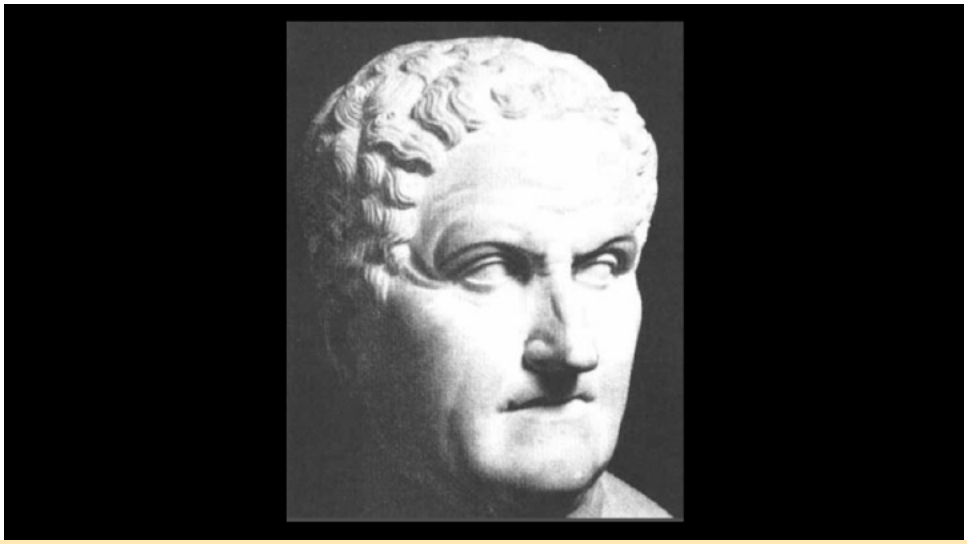


Fig. 23: Galen (ca. 129-216). *Galen was the father of the "sympathetic nervous system."*

The third part of Langley's autonomic nervous system is the sympathetic nervous system. This term he didn't invent.

Instead, the phrase, “sympathetic nervous system,” goes back to ancient times—to the 2d century Greek physician, Galen. Galen’s ideas and teachings dominated medical thought and practice for 14 centuries. He taught that the body has “spirits”—animal, vital, and natural—and he viewed the nerves as conduits for delivering the animal spirits to body organs. The organs would then function in harmony with each other, in concert with each other—in “sympathy” with each other. No one ever has come up with evidence for the existence of the spirits; however, the idea that the sympathetic nervous system coordinates functions of body organs is essentially, ironically correct.

On the Risk of Being a Physician's Son

In the early 1890s, Dr. George Oliver, an English physician and amateur inventor, tested one of his homemade devices on his son. The device was supposed to measure the caliber of arteries. Oliver applied the device to his son’s wrist at the radial artery, which carries blood to the hand. Oliver then administered an extract of adrenal gland to his son. The extract did appear to elicit constriction of the radial artery. Meanwhile, in London, Dr. E. A. Schäfer, a renowned Professor of Physiology at the University College, was carrying out experiments on laboratory animals involving measurement of blood pressure by the height of a column of mercury in a tube connected to an artery. Oliver visited Schäfer's laboratory and brought with him a vial of the adrenal extract. Schäfer allowed injection of the material into the vein of a dog. This set the stage for one of the great discoveries in medical history.

The injection produced an immediate, startling increase in the animal's blood pressure, an increase so large that the column of mercury actually overflowed the tube. In 1894 Oliver and Schäfer published the first report ever about the cardiovascular actions of an extract from a body organ.

According to Sir Henry Dale (to whom we will be returning later) the extract had been injected, but according to others, and based on the writings of both Oliver and Schäfer themselves, the extract had been given orally. At first glance this disagreement would seem trivial, but it isn't. An enzymatic "gut-blood barrier" prevents ingested catecholamines and related compounds from making their way into the bloodstream. Swallowed adrenaline is broken down efficiently by enzymes in the gut.

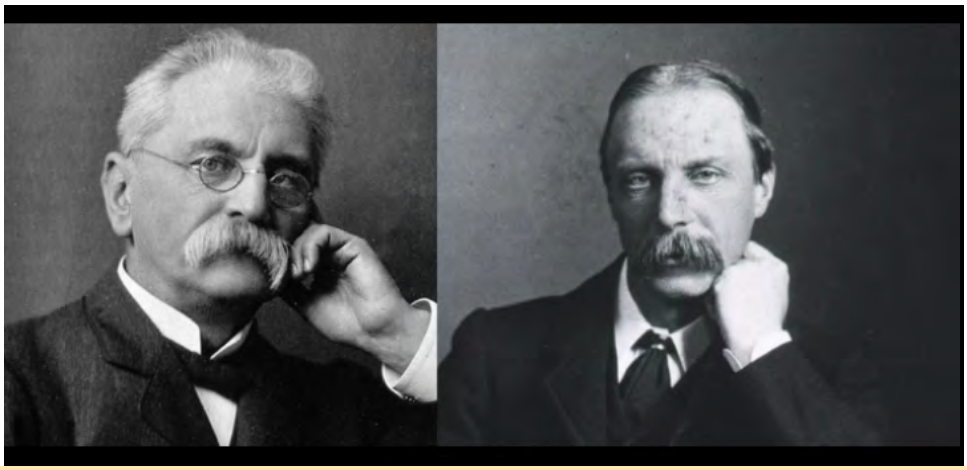


Fig. 24: Oliver & Schäfer. *George Oliver and E.A. Schäfer first reported the cardiovascular actions of adrenal extract in 1894.*

In fact, at least three enzymes carry out this crucial task. Moreover, most of the blood coming from the gut travels to the liver via the portal vein, and the liver also efficiently

metabolizes catecholamines. One reason you can buy adrenal concentrate as a dietary supplement in health food stores is that after swallowing adrenaline solution, levels of the catecholamine itself in the general circulation hardly increase at all.

If you lacked one or more of the gut enzymes that detoxify catecholamines, however, or were taking a medication that inhibited activities of the enzymes making up the “gut-blood barrier,” then ingesting adrenal concentrate could be disastrous.

If Oliver had administered the extract directly by injection, he could well have killed his son.

What's in a Name?

The most famous member of the catecholamine family has two names—adrenaline and epinephrine (EPI). Here is how this came about.

Beginning soon after Oliver and Schäfer reported the powerful effects of injected adrenal extract, researchers worldwide began a kind of race to identify the “active principle” of the adrenal gland. One of those in the race was John Jacob Abel, of Johns Hopkins. He devoted about a decade of his life to the project. Abel partially isolated a substance he called epinephrin, but this proved not to be epinephrine itself.

The first person to isolate the active principle of the adrenal gland was a chemist in the laboratory of the Japanese researcher and entrepreneur, Jokichi Takamine.

Takamine had set up a laboratory in New York City, under the patronage of Parke, Davis & Company.

Fig. 25: Abel & Takamine. *John Jacob Abel and Jokichi Takamine raced to identify the active principle of the adrenal gland around 1900. Takamine won.*

Keizo Uenaka, whom Takamine had hired as a chemist, successfully crystallized—and therefore isolated in pure form—what Takamine called adrenaline. Thomas Aldrich, a colleague of Takamine at Parke-Davis (and, possibly not coincidentally a former assistant of Abel at Johns Hopkins) correctly deduced its chemical structure. Abel never published the correct structure, and so medical historians give Takamine and Aldrich the credit for two of the most important medical scientific feats ever—the first isolation in pure form and the first identification of the structure of a hormone.

Indeed, this happened a few years before the word, “hormone,” was first used, by Ernest Starling in 1905. Starling described secretin in 1902. One can make a case that adrenaline was the first known hormone.

Adrenaline (trademarked as Adrenalin™) was also the first natural substance to be patented (whether a natural substance is

Fig. 26: Cherry trees at the Tidal Basin. *J. Takamine, who discovered adrenaline, funded the Japanese cherry trees at the Tidal Basin in Washington, DC.*

patentable continues to be an issue). This made Takamine rich. He founded three companies, one of which, Sankyo Pharmaceutical Company, continues to this day as Daiichi/Sankyo, a large drug company in Japan. Takamine also funded the gift of cherry trees that have graced the Tidal Basin in Washington, DC. Parke-Davis retained the trademark for Adrenalin.

Abel continued to pursue his career goal of identifying, isolating, and purifying hormones. He helped found the American Society for Pharmacology and Experimental Therapeutics and served as editor of the society's official journal, the Journal of Pharmacology and Experimental Therapeutics (JPET). He also founded the Journal of Biological Chemistry (JBC). JPET and JBC are still prestigious journals in pharmacology and biochemistry. Scientific reports in American journals, such as JPET, use the word that Abel introduced, “epinephrine,” whereas European journals commonly use

Takamine's “adrenaline.” In this book I use epinephrine (EPI) and adrenaline interchangeably.

The Fat above the Kidneys

Within several years after Langley formulated his idea of the autonomic nervous system, the American physiologist, Walter B. Cannon, added what can be considered to be a fourth component of the ANS. I call it the sympathetic adrenergic system (SAS). This is the part of the autonomic nervous system where adrenaline is released from the inner part (medulla, from the Latin word for “marrow”) of the adrenal gland. The SAS is a form of what is now called a neuroendocrine system.

Fig. 27: Walter B. Cannon (1871-1945). *Among many accomplishments, Cannon discovered that during distress a substance is released from the adrenal glands into the bloodstream—adrenaline.*

The outer part of the adrenal gland, the cortex (from the Latin word for “bark,” as in the bark of a tree) is the source of a

variety of steroid hormones that are also very important in the body economy.

No one knew of the existence of the adrenal glands until Bartholomeo Eustachius (for whom the eustachian tube is named) described their anatomy in 1563, but there may have been a hint from a much older source.

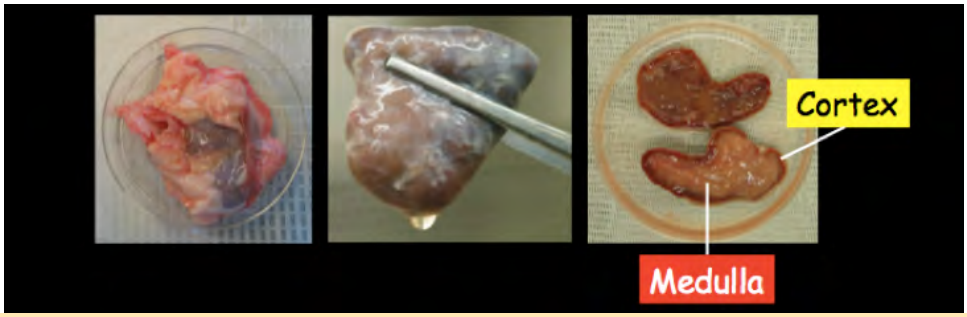


Fig. 28: The fat above the kidneys. *The adrenal glands are in the fat above the kidneys. The medulla contains adrenaline. The cortex contains steroids.*

The Hebrew Bible, in Exodus and Leviticus, describes in detail the rituals of animal sacrifice. Some tissues were specified for ritual burning; eating them was strictly forbidden. One of these tissues was the "fat above the kidneys." The text stipulates—not once but thirteen times— that the fat above the kidneys was to be burned and not to be eaten by anyone. Why was eating the fat above the kidneys proscribed? Here is a possible answer. The fat above the kidneys is unique for its contents, because buried within it are the adrenal glands, which store the powerful adrenocortical hormones, cortisol, aldosterone, and adrenal androgens, and the even more powerful adrenomedullary hormone, adrenaline. Depending on the efficiency of metabolic breakdown of these chemicals in the gut, eating adrenal gland

tissue could result in entry of one or more of these physiologically active compounds into the bloodstream. Ingestion of adrenal gland tissue repeatedly by the priests over a long period could have made them ill or killed them.

BIBLICAL LIE DETECTION

The Bible contains a unique and remarkable instance of trial by ordeal and "lie detection"—actually distress detection.

Adrenaline produces marked effects on many body functions. These effects have been recognized throughout human history.

This was in the case of a woman accused by her husband of adultery. She would be brought to the priest, who would conduct the trial according to a specific ritual.

The key sign of guilt was when the accused woman was forced to drink "waters of bitterness," consisting of water and dust from the floor of the tabernacle. The priest would incant, "If thou has gone aside, being under thy husband, and if thou be defiled . . . this water that causeth the curse shall go into thy bowels, and make thy belly to swell, and thy thigh to fall away" (Numbers 5:19-21). The accused woman would reply, "Amen, Amen" (the first use of the term in the Bible). The woman would then drink the test potion. If she had been unfaithful, her belly would swell.

Why would abdominal distention be a sign of distress and

therefore, in biblical lie detection, of guilt? Adrenaline potently relaxes smooth muscle of the gastrointestinal tract. Indeed, this relaxation provided the basis for the first successful method, introduced by Walter B. Cannon, for detecting adrenaline release during emotional distress.

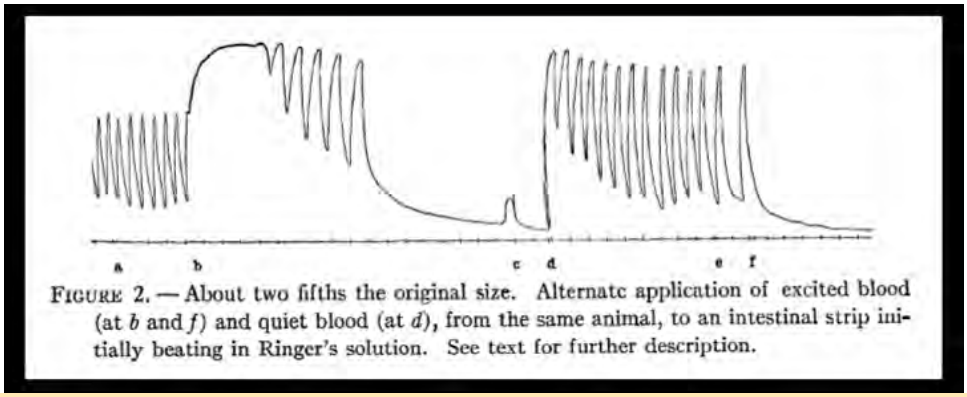


FIGURE 2. — About two fifths the original size. Alternate application of excited blood (at *b* and *f*) and quiet blood (at *d*), from the same animal, to an intestinal strip initially beating in Ringer's solution. See text for further description.

Fig. 29: Distress relaxes the gut. *Cannon's 1911 demonstration of relaxation of an intestinal strip upon application of blood from a cat exposed to a barking dog was the first published evidence for adrenaline release during distress.*

Cannon drew blood from a cat exposed to a barking dog. This evoked release into the cat's blood of a substance that relaxed a strip of gut tissue. Exposure of the strip to blood from the adrenal veins produced the same relaxing effect, and tying off the adrenal veins eliminated the effect, indicating that distress released a substance from the adrenal glands into the bloodstream.

The woman would have a form of functional ileus (decreased propulsion of gut contents). In this setting, a non-palatable liquid would not pass through the gut, and the belly would swell.

It is not widely appreciated that high circulating levels of catecholamines can produce ileus. The distended loops of

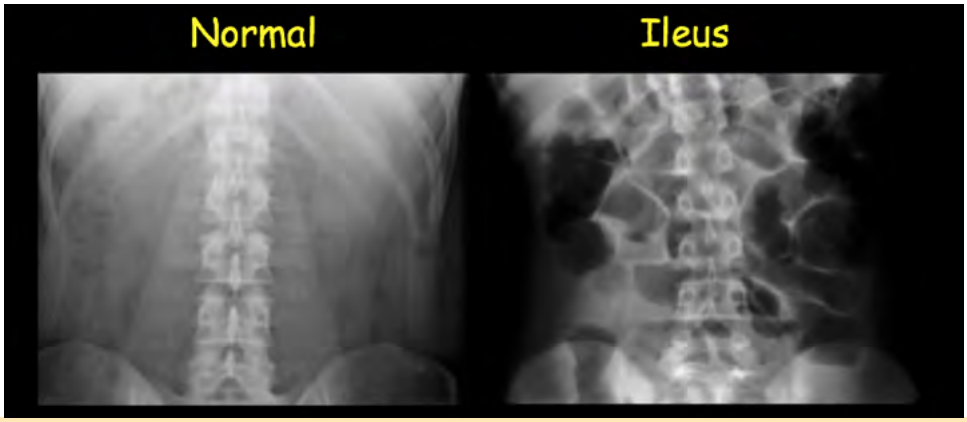


Fig. 30: Ileus. *In ileus there is abdominal distention from dilation of loops of bowel by air. Something like ileus could explain the belly swelling in the biblical trial by ordeal. Emotional distress, via adrenaline, would relax the gut.*

bowel result in abdominal swelling. Ileus can even be an initial manifestation of pheochromocytoma, a tumor that secretes catecholamines into the bloodstream.

What would be the meaning of the guilty woman's thigh "falling away"? If the accused woman were innocent, she would be able to "retain seed." This might mean she would be able to conceive. It is well known that in distressing circumstances women can have anovulatory periods or stop menstruating. Both of the key signs of guilt in the biblical trial by ordeal therefore can be understood in terms of bodily effects of distress.

Cannon's Sympathoadrenal System

Cannon taught that the sympathetic nervous system and adrenal gland act as a functional unit in emergencies. This functional unit has been called the "sympathico-adrenal," "sympathoadrenomedullary," or "sympathoadrenal system."

According to Cannon, this system mediates bodily changes in "fight-or-flight" situations. ("Fight-or-flight" is a term he introduced.) He viewed the sympathoadrenal system as the key effector for maintaining "homeostasis" (a word he invented).

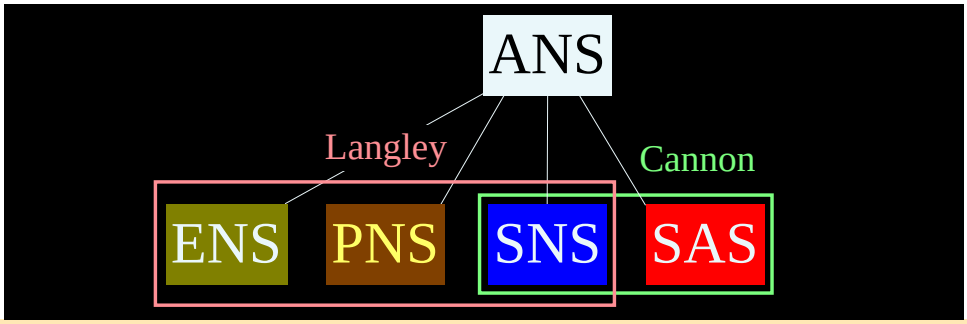


Fig. 31: Cannon's sympathoadrenal system. *This diagram illustrates the relationship between Langley's autonomic nervous system and Cannon's sympathico-adrenal, sympathoadrenomedullary, or sympathoadrenal system.*

Dale's Sympathetic Cholinergic System

In the 1930s Sir Henry Dale (Nobel Prize, 1936) added what may be considered a fifth component of the autonomic nervous system, the sympathetic cholinergic system, or SCS.

The sympathetic cholinergic system is the main ANS

component involved with sweating when you are exposed to environmental heat (thermoregulatory sweating).

Fig. 32: Sir Henry Dale (1875-1968). *Dale shared a Nobel Prize in 1936 for his discoveries related to chemical neurotransmission (discussed later).*

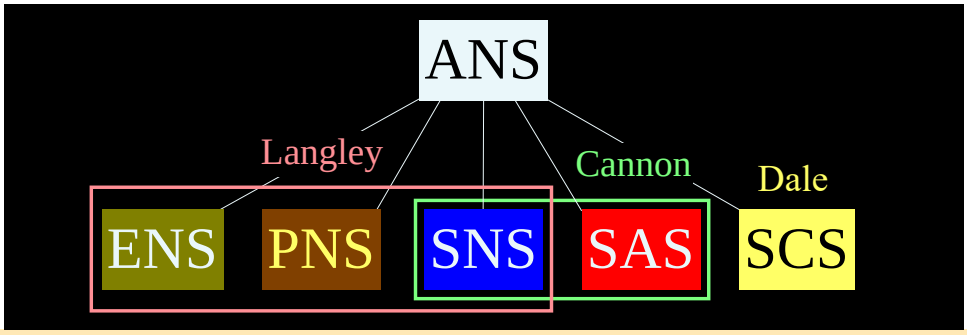


Fig. 33: Dale's sympathetic cholinergic system. *The sympathetic cholinergic system (SCS) can be considered to be a fifth component of the autonomic nervous system.*

ORGANIZATION OF THE ANS

The autonomic nervous system is not one thing. It has parts.

Distribution of the ANS in the Body

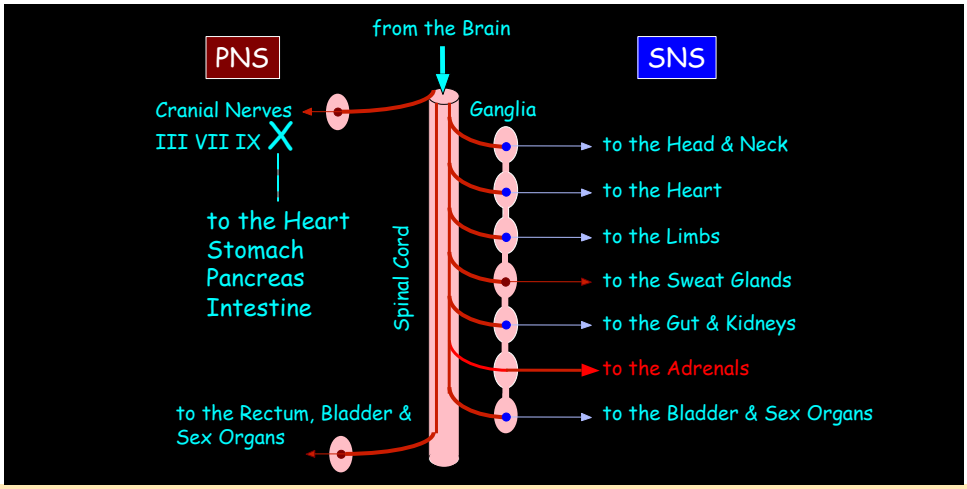


Fig. 34: PNS, SNS, SAS, & ganglia. *This diagram provides an overview of the organization of the autonomic nervous system (ANS) in the body. There are some organizational differences in the distributions of the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS).*

You've learned that Langley's autonomic nervous system consists of the enteric nervous system (ENS), the parasympathetic nervous system (PNS), and the sympathetic nervous system. Cannon added a component, the sympathetic adrenergic system (SAS), and Dale added a component, the sympathetic cholinergic system (SCS). You've also learned that autonomic nerves pass through ganglia, so that there are pre-

ganglionic and post-ganglionic autonomic nerves. This section is about how components of the autonomic nervous system are distributed in the body.

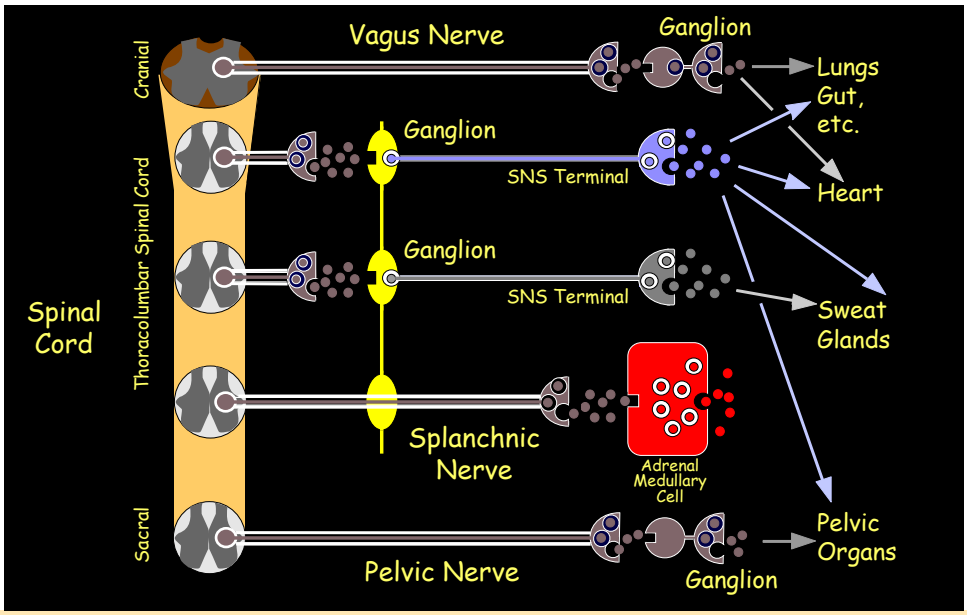


Fig. 35: ANS organization overview. *The enteric nervous system isn't shown. The cranial portion of the parasympathetic nervous system is represented by the vagus nerve.*

You may feel intimidated because of the complexity. This section breaks it down. It will help to keep in mind that the ANS has parts, that the ganglia are arranged like pearls on a necklace on each side of the spinal column, and that there are pre- and post-ganglionic autonomic nerves, along the lines of the electrical transmission analogy. (Transmission of autonomic signals in ganglia actually is electrochemical and not purely electrical. We'll come back to this later.)

The autonomic nerves come from the brainstem as cranial nerves and from the thoracolumbar and sacral spinal cord. The

autonomic nerves coming from the thoracolumbar spinal cord are sympathetic nerves. The autonomic nerves coming from the brainstem and traveling with the cranial nerves are parasympathetic nerves.

Autonomic nerves derived from the sacral spinal cord have been thought to be parasympathetic, although this concept has been questioned recently.

THE PARASYMPATHETIC NERVOUS SYSTEM (PNS)

You can think of the parasympathetic nervous system as regulating "vegetative" body functions—things you do privately or at night.

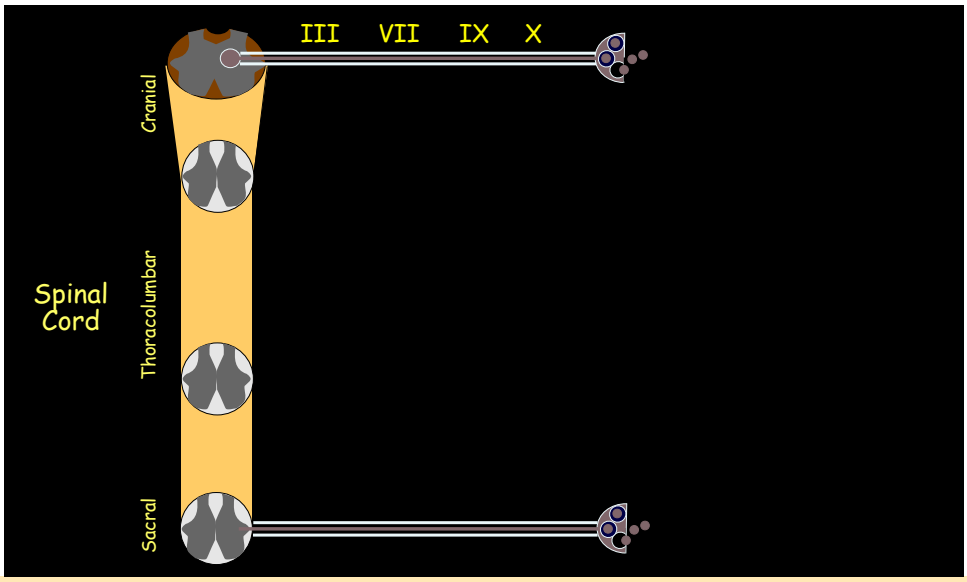


Fig. 36: PNS organization overview. *Nerves of the parasympathetic nervous system (PNS) come from the brainstem and from the bottom of the spinal cord.*

The parasympathetic nervous system (abbreviated as PNS) in some ways acts like the opposite of an emergency system. Increased activity of this system is associated with "vegetative" behaviors, activities that increase rather than use up energy. Examples are sleeping, eating, salivating, and digesting.

The upper part of the parasympathetic nervous system consists of nerves that come from the brainstem. These nerves travel to many parts of your body, including the eyes, face, tongue, heart, and most of the gastrointestinal tract.

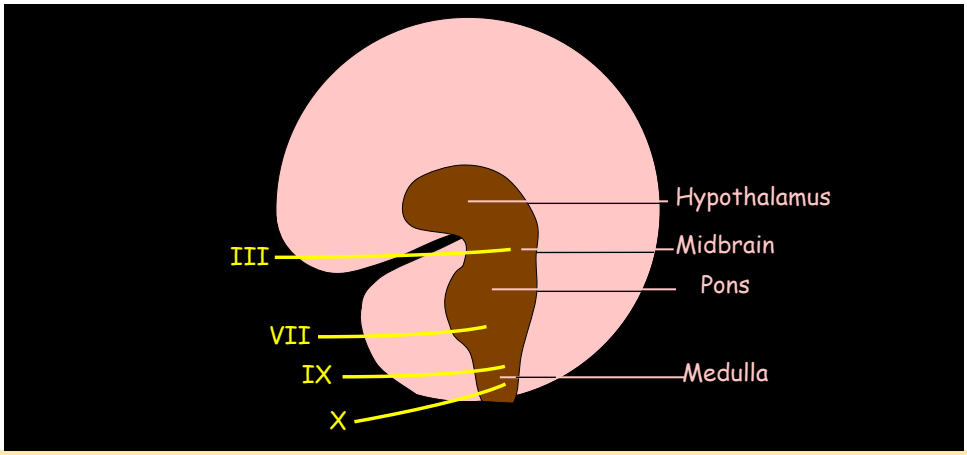


Fig. 37: Cranial parasympathetic nerves. *Parasympathetic nerves to structures in the head travel in the third, seventh, and ninth cranial nerves. Parasympathetic nerves to the visceral organs such as the heart, lungs, and most of the gastrointestinal tract travel in the vagus nerve, which is the tenth cranial nerve.*

Stimulation of the parasympathetic fibers in the head causes the pupils to constrict, the lacrimal glands to secrete tears, and the salivary glands to secrete watery saliva.

The parasympathetic fibers to the head are considered (somewhat irrationally, I would say) to be part of the peripheral

nervous system, even though they travel in cranial nerves. This is because the parasympathetic nerves to the target structures are post-ganglionic. For instance, parasympathetic nerves supplying the sphincter muscle of the iris come from the ciliary ganglion, those supplying the lacrimal glands come from the sphenopalatine ganglion, and those supplying the salivary glands come from the submaxillary or otic ganglion. As for other ganglia that contain parasympathetic nerves, these ganglia are located near or in the innervated structures.

The vagus nerve, which is the tenth cranial nerve (cranial nerve X), comes from the lower brainstem. The vagus contains most of the parasympathetic nerves in the body.

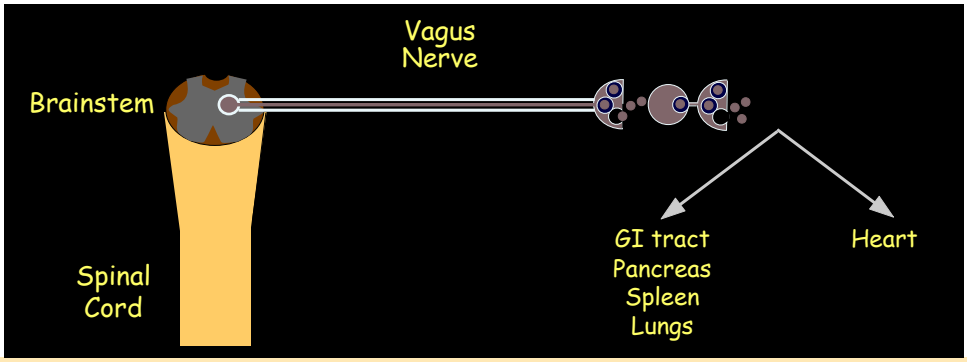


Fig. 38: Vagus nerve overview. *The vagus nerve travels from the brainstem to ganglia near or inside the target organs in the lungs, splanchnic organs, most of the gastrointestinal tract, and the heart. The vagus nerve therefore is pre-ganglionic and myelinated.*

"Vagus" comes from the Latin word for wandering. As the name suggests, the vagus goes to several places inside the chest, abdomen, and pelvis, and it supplies the heart, lungs, and most of the gastrointestinal tract.

Stimulation of the vagus nerve decreases the heart rate, increases smooth muscle tone and mucus secretion in the airways, and increases secretion of stomach acid and digestive hormones such as insulin. Vagal stimulation also decreases the force of cardiac contraction (in contrast with an older teaching that there is no effect).

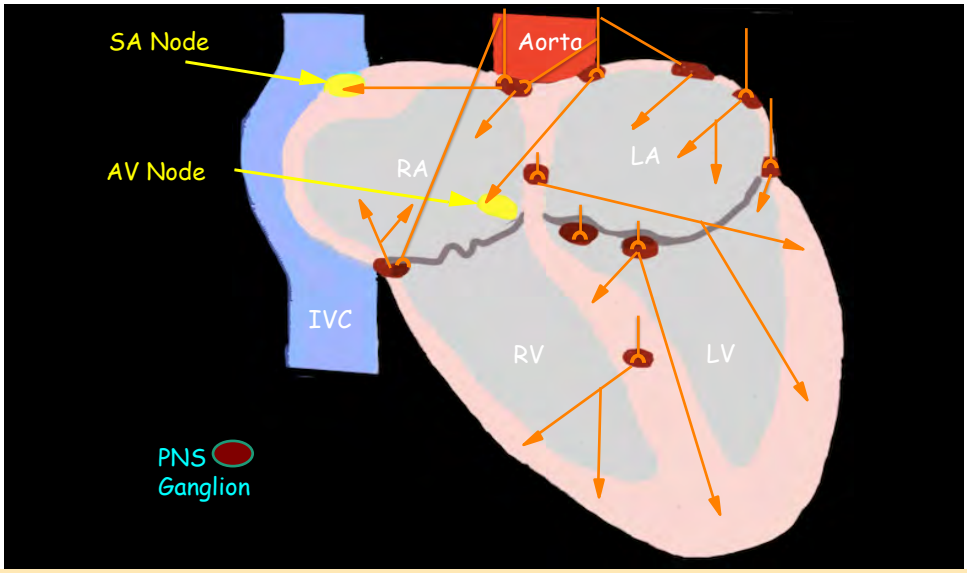


Fig. 39: Parasympathetic ganglia in the heart. *Parasympathetic ganglia are embedded within the myocardium. There are also intrinsic ganglia.*

There are ganglia within the heart muscle (intrinsic ganglia), just as there are intrinsic ganglia in the wall of the gastrointestinal tract. It is possible that intrinsic ganglia are phylogenetically ancient and were superseded during the course of evolution by hormones and autonomic nerve networks.

Most of the nerve fibers in the vagus actually are afferents, meaning that carry signals to the brain, rather than carrying signals from the brain. As you will learn later, a scientifically

and clinically important source of afferent signals to the brain is distortion receptors (baroreceptors) in the walls of the heart, large arteries, and pulmonary veins.

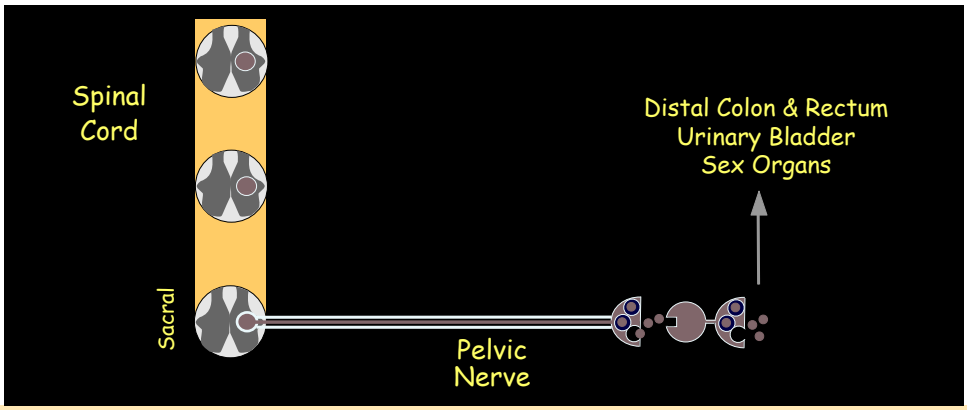


Fig. 40: Sacral parasympathetic nerves. *Parasympathetic nerves coming from the sacral spinal cord travel in pelvic nerves to innervate the distal colon and rectum, urinary bladder, and sex organs.*

The lower part of the parasympathetic nervous system consists of nerves from the bottom level of the spinal cord, the sacral spinal cord. These nerves travel to the lower gastrointestinal tract, urinary bladder, and genital organs.

Sacral parasympathetic stimulation increases peristalsis in the colon and contraction of the rectum while relaxing the anal sphincter, so that defecation occurs. Such stimulation also increases peristalsis in the ureters and activates the detrusor muscle of the urinary bladder while relaxing the urethral sphincter, so that urination occurs. Parasympathetic stimulation augments filling of the corpora cavernosum and corpus spongiosum of the penis with blood and thereby promotes penile erection.

Interference with sacral parasympathetic outflows manifests with constipation, urinary retention, and erectile dysfunction in men.

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

THE SYMPATHETIC NORADRENERGIC SYSTEM (SNS)

You can think of the sympathetic noradrenergic system (SNS) as the part of the autonomic nervous system that is involved with processes that happen during the day or out in the open.

The nerves of the sympathetic nervous system come from the spinal cord at the levels of the chest and upper abdomen (thoracolumbar spinal cord). The sympathetic nerves to most organs are post-ganglionic, coming from cell bodies in the ganglia, the clusters of nerve cells like a transformer on the utility pole that supplies the electricity to your house.

Probably the most prominent effect of stimulation of the sympathetic noradrenergic system (SNS) is constriction of blood vessels—especially of arterioles, the tiny arteries that are the main determinant of total peripheral resistance to blood

flow in the body. Decreased blood flow to the skin causes pallor. Blood flow is also decreased to the gut, skeletal muscles, and kidneys, and so the blood pressure increases. Blood flow to vital organs—the heart, lungs, and brain—is generally preserved during SNS stimulation.

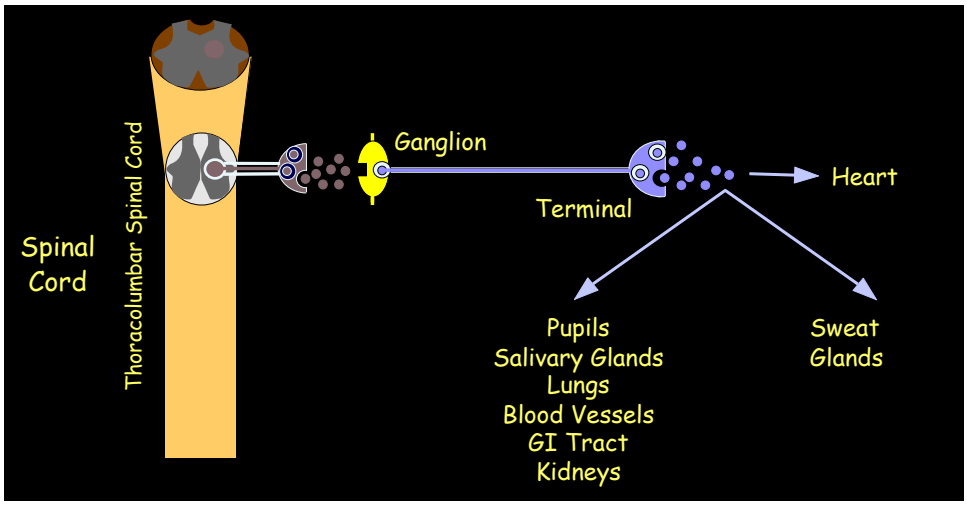


Fig. 41: Sympathetic noradrenergic system (SNS) overview. *Sympathetic noradrenergic nerves are long, post-ganglionic, and non-myelinated. Sweat glands receive mainly sympathetic cholinergic but also sympathetic noradrenergic nerves.*

THE SYMPATHETIC ADRENERGIC SYSTEM (SAS)

The sympathetic adrenergic system (abbreviated as SAS), or adrenomedullary hormonal system, is the part of the autonomic nervous system for which adrenaline is the main chemical messenger.

The location of the adrenal glands explains the origins of the word, adrenaline, from the Latin words for “near the kidney,”

and of the word, epinephrine, from the Greek words for "on the kidney."

The sympathetic adrenergic system regulates "emergency" processes such as in distress. Any threat to survival increases adrenaline levels.

The sympathetic adrenergic system plays a major role in responses to perceived or anticipated threats to overall homeostasis, such as lack of essential fuels (glucose and oxygen), inadequate blood flow to vital organs, and hostile encounters.

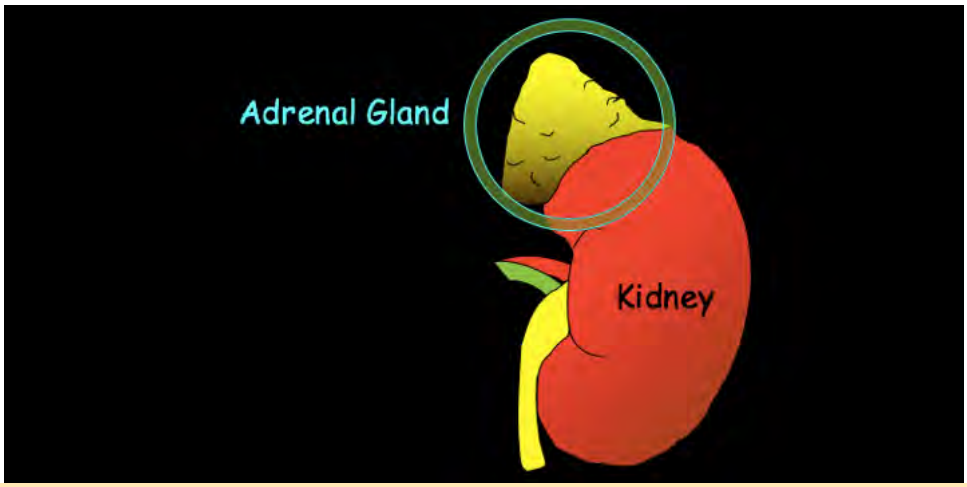


Fig. 42: Adrenal gland location. *The adrenal glands are located in the fat above the kidneys. (The actual size of an adrenal gland is much smaller than drawn here.)*

Adrenaline (epinephrine) is released from the adrenal glands, which sit near the tops of the kidneys.

In the sympathetic adrenergic system, the connection from the spinal cord to the adrenal medullary cells is direct, and so the adrenal medulla receives rapidly conducting, myelinated fibers. This fits with the teleologic notion of adrenaline being released with the goal to maintain homeostasis in sudden emergencies. We will return later to the concepts of teleology and homeostasis.

Adrenaline is secreted into the bloodstream and distributed widely in the body, so it is a hormone. A major determinant of adrenaline release is myelinated nerve fibers passing through the splanchnic ganglia. This means that the SAS is also a neuro-hormonal, or neuroendocrine, system.

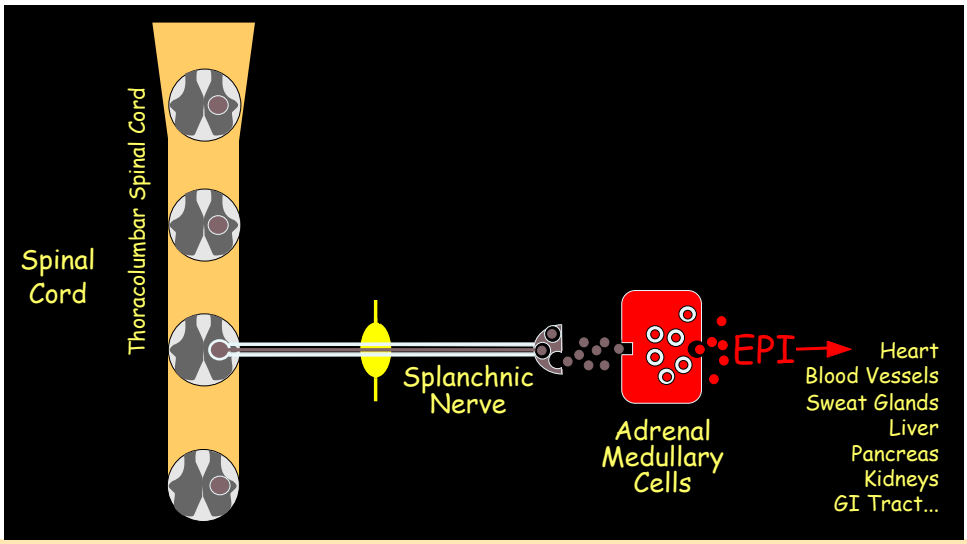


Fig. 43: The sympathetic adrenergic system (SAS). *In the sympathetic adrenergic system (SAS), the adrenaline-secreting cells of the adrenal medulla receive direct innervation. Adrenaline (epinephrine, EPI), is released into the bloodstream, and so it is a hormone.*

SAS activation potently increases blood flow to skeletal

muscle. Probably the systemic cardiovascular effect of adrenaline that occurs at the lowest concentration is a fall in skeletal muscle vascular resistance. At higher concentrations, adrenaline produces well known stimulation of the heart, increasing both the rate and force of contraction, and constricts blood vessels by stimulating alpha-adrenoceptors. Adrenaline also causes pallor, relaxes the gut, increases sweating, increases blood glucose levels, decrease serum potassium levels, and increases the core temperature.

THE SYMPATHETIC CHOLINERGIC SYSTEM (SCS)

The sympathetic cholinergic system (abbreviated as SCS) mediates sweating—especially thermoregulatory sweating, when you perspire upon exposure to heat. The SCS also participates in gustatory sweating when you sweat on your forehead after you eat spicy foods, and in emotional sweating when your palms and armpits sweat during distress.

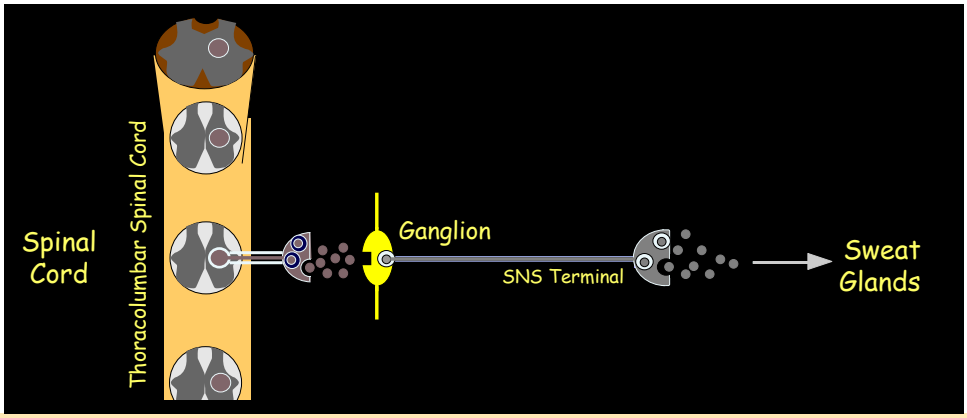


Fig. 44: The sympathetic cholinergic system (SCS). *The sympathetic cholinergic system consists mainly of non-myelinated post-ganglionic nerves that supply sweat glands.*

Eccrine sweat glands (from the Greek word for "secrete"), which are the major sweat glands in the human body, occur at highest density in the palms, soles, and head. They secrete watery, salty, odorless sweat and are the main mediators of thermoregulatory sweating. Eccrine sweat glands receive prominent sympathetic cholinergic fibers, which are long, post-ganglionic, and non-myelinated.

Apocrine sweat glands (from the Greek words for "separate" and "away"), release sweat near hair follicles and occur at high density in the armpits, groin, and peri-anal area, as well as in the nostrils, ear canals, and areolae of the nipples. Apocrine sweat glands secrete oily, opaque sweat; its characteristic odor results from metabolic breakdown by local bacteria. This is the type of sweating associated with severe exercise and strong emotions.

THE ENTERIC NERVOUS SYSTEM (ENS)

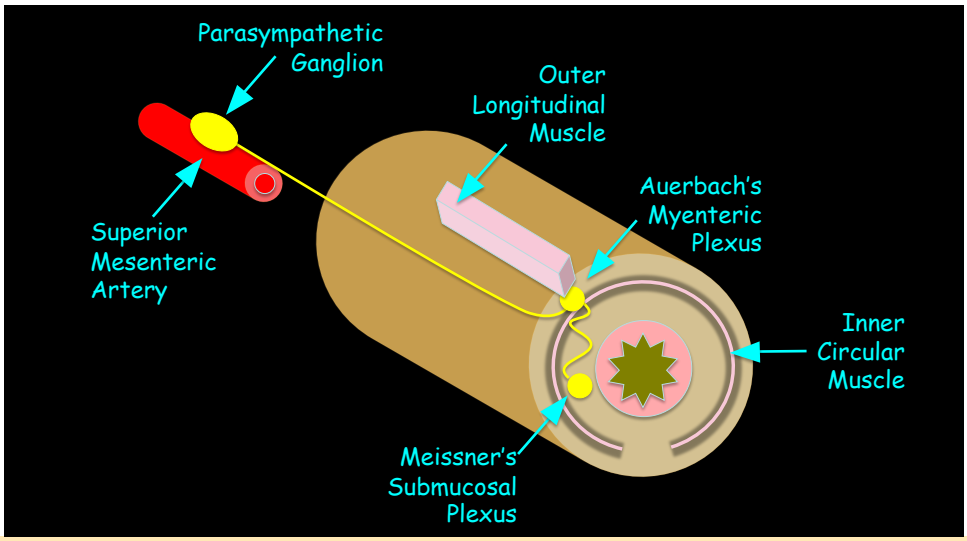


Fig. 45: Overview of the enteric nervous system (ENS).

The intrinsic neurons of the ENS (ganglion cells) migrate from the neural crest during fetal development. The ganglion cells are required for movement of intestinal contents. As you will learn in more detail later, in Hirschsprung's disease this migration is incomplete, and the affected segment of the colon that lacks the ganglion cells cannot relax and move stool through the colon. Hirschsprung's disease therefore manifests clinically with failure of the newborn to pass meconium or stool.

Interactions among ANS Components

Activation of a particular component of the autonomic nervous system can lead to effects on other components. This is an important principle of autonomic medicine.

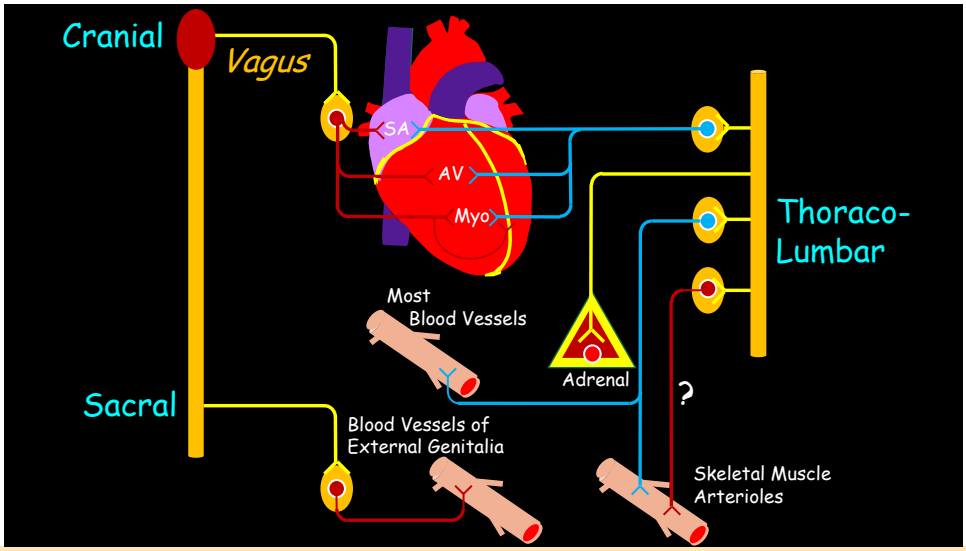


Fig. 46: Cardiovascular-autonomic interactions. *The parasympathetic cholinergic, sympathetic noradrenergic, and sympathetic adrenergic systems interact in regulating cardiovascular functions.*

Components of the autonomic nervous system interact with each other.

For instance, the sympathetic noradrenergic system and the parasympathetic nervous system usually seem to antagonize each other. When sympathetic nerves in the heart are stimulated, the heart rate speeds up, and the heart beats more forcefully, whereas when parasympathetic nerves in the heart are stimulated, the heart rate slows down, and the heart beats less forcefully.

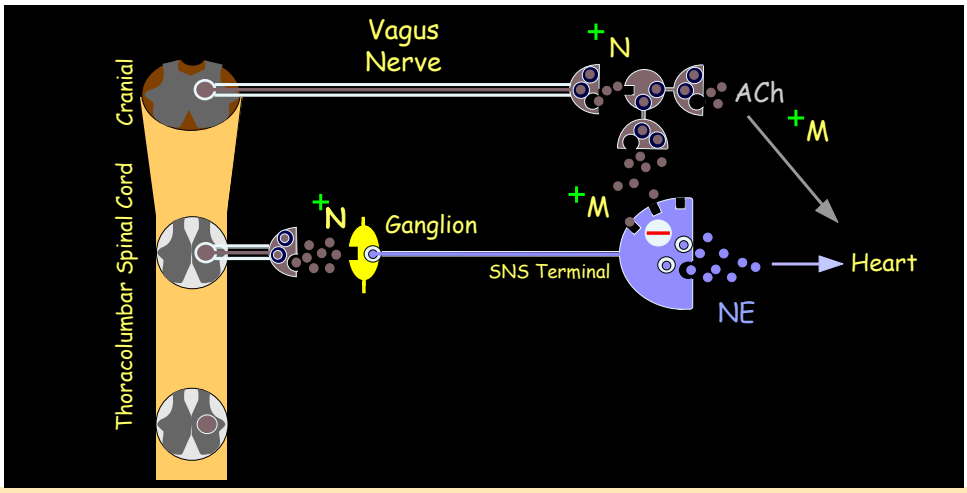


Fig. 47: Cardiovagal-sympathetic interactions. *An example of interactions between the parasympathetic and sympathetic nervous systems is that stimulation of vagal muscarinic receptors on sympathetic nerves in the heart inhibits release of the sympathetic neurotransmitter norepinephrine (NE).*

After eating a meal, stimulation of the parasympathetic nervous system aids digestion, by increasing gut motions and augmenting secretion of hormones such as insulin. Meanwhile, stimulation of a part of the sympathetic nervous system tightens blood vessels in particular body regions, shunting blood toward

the gut.

Parasympathetic cardiovagal stimulation decreases the rate and force of cardiac contraction directly as well as indirectly, by inhibiting release of the chemical messenger norepinephrine (NE) from sympathetic post-ganglionic nerves.

The sympathetic nervous system and the parasympathetic nervous system usually antagonize each other…but not always. In other situations, increases in activities of these systems go together.

After a meal, possibly because of increased levels of glucose in the bloodstream, activity of the sympathetic adrenergic system tends to decrease.

Fainting typically involves a particular pattern of changes in activities of components of the autonomic nervous system. When people faint, the parasympathetic nervous system is activated, producing changes such as nausea and retching. Activity of the sympathetic noradrenergic system often is decreased, resulting in a fall in blood pressure. The sympathetic adrenergic system is stimulated markedly, and this shunts blood toward the skeletal muscle. High adrenaline levels are probably responsible for constriction of blood vessels in the skin, resulting in pallor and dilation of the pupils. Finally, when people faint they typically have increased sweating, reflecting increased activity of the sympathetic cholinergic system or effects of high circulating adrenaline levels.

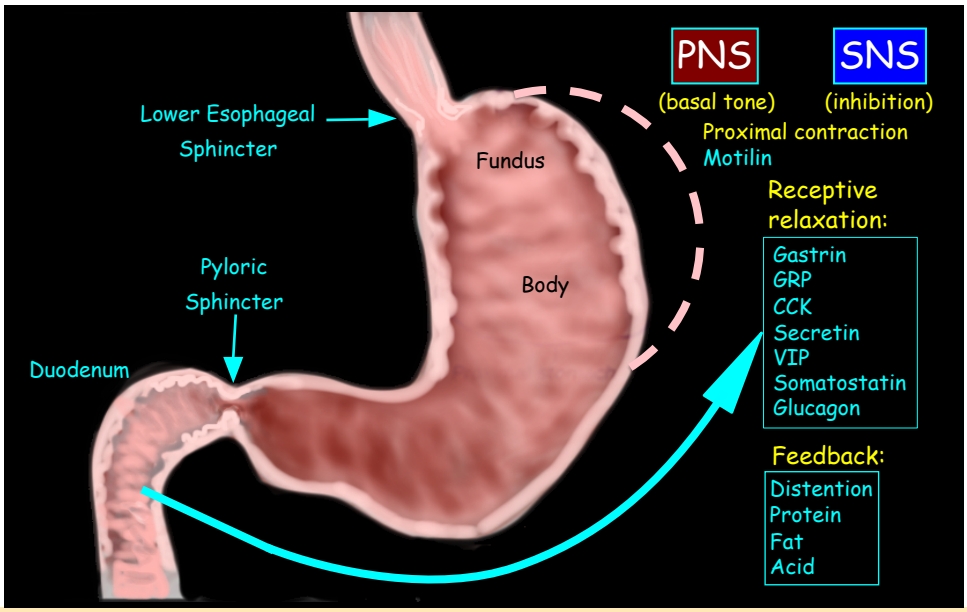


Fig. 48: Upper GI autonomic interactions. *Autonomic regulation of the stomach and duodenum involves a complex combination of factors.*

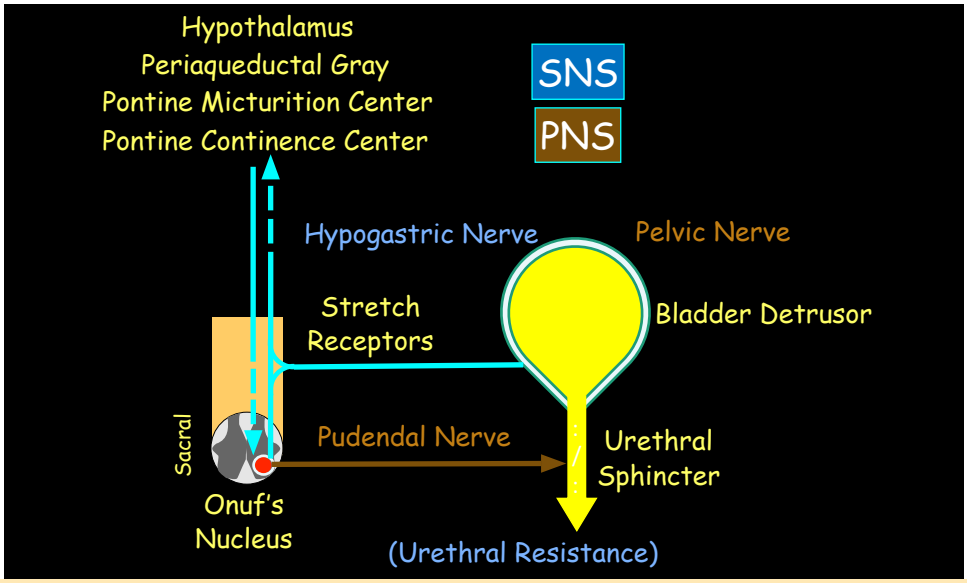


Fig. 49: ANS interactions and urination. *The sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) are coordinated complexly and dynamically.*

Summary of the Organization of the ANS

Let's review the information so far about the ANS. It can be a bit confusing, because of the different "nervous systems" involved.

You have a central nervous system (your brain and spinal cord) and a peripheral nervous system (the rest of your nerves). Your peripheral nervous system has two divisions, the somatic nervous system and the autonomic nervous system. The somatic nervous system is concerned with the "outer world," and the nerves in this system travel to skeletal muscle. Your autonomic nervous system is concerned with the "inner world" within the body, and it usually works automatically, so that you can think of the autonomic nervous system as the "automatic nervous system."

The control signals of the autonomic nervous system travel indirectly from your central nervous system through ganglia (clusters of nerve cells) to smooth muscle, found in areas like your blood vessels, heart, and glands throughout the body. Nerves coming to the ganglia from the spinal cord are pre-ganglionic, and nerves coming from the ganglia are post-ganglionic. Some nerves, such as those to the adrenal glands, pass through the ganglia without relaying within the ganglia, so that there is a direct connection from the central nervous system to the target organs.

You have also learned that there are several components of the autonomic nervous system. Two of the main components are the sympathetic nervous system and the parasympathetic

nervous system.

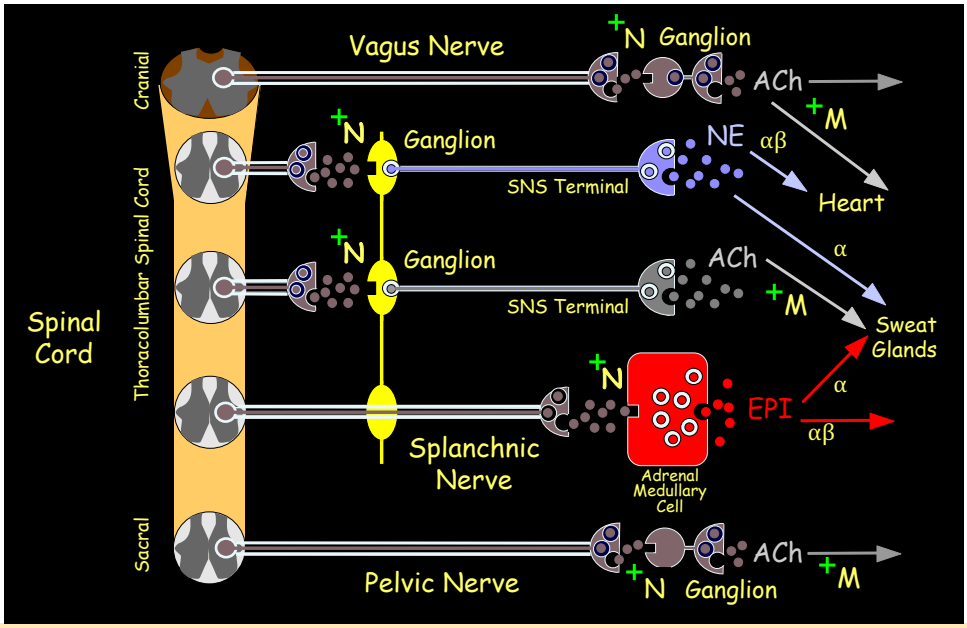


Fig. 50: Overview of the distribution of autonomic nerves. *There are several abbreviations and symbols that haven't been covered yet. These relate to how the ANS works—the topic of the next section.*

The adrenal glands, located near the tops of the kidneys, are the source of the hormone adrenaline. The combination of the adrenal medulla with the sympathetic nervous system has been called the "sympathoadrenal system," which has been thought to function as a unit in emergencies such as "fight-or-flight" situations. Sometimes components of the autonomic nervous system work together, sometimes they antagonize each other, and sometimes changes activities of the different components occur in characteristic patterns.

Finally, you have learned about the distribution of autonomic nerves in the body. Parasympathetic nerves come from the

brainstem and sacral spinal cord, and sympathetic nerves (noradrenergic, adrenergic, and cholinergic) come from the thoracolumbar spinal cord. Parasympathetic nerves have long, myelinated pre-ganglionic and short, non-myelinated post-ganglionic fibers. Sympathetic nerves have short, myelinated pre-ganglionic fibers and long, non-myelinated post-ganglionic fibers. Sympathetic adrenergic nerves going to the adrenal medulla are myelinated fibers, but instead of post-ganglionic nerves the adrenal medullary cells secrete adrenaline into the bloodstream.

Now that you've learned about the components of the autonomic nervous system and its anatomic organization in the body, it is time to cover how the ANS works. This is crucial for understanding what goes wrong in dysautonomias, how to diagnose them, and how to treat them.

HOW DOES THE ANS WORK?

INTRODUCTION TO CHEMICAL MESSENGERS OF THE ANS

The autonomic nervous system works by releasing chemicals inside the body.

In a single phrase, the autonomic nervous system works via chemical messengers. Some understanding of clinical neurochemistry is required to grasp concepts about mechanisms, testing, and treatment of dysautonomias.

The components of the autonomic nervous system use particular chemical messengers.

Major chemical messengers of the autonomic nervous system are norepinephrine (pronounced nor-epi-NEPH-rin), acetylcholine (pronounced a-see-til-CO-lean), and adrenaline.

Norepinephrine (NE) and adrenaline (epinephrine, EPI) are in a small chemical family that has a chemical structure called catecholamine. Acetylcholine (ACh) has a chemical structure that includes a quaternary ammonium cation.

This section goes into some detail about catecholamines and acetylcholine (ACh)—how they are produced, stored, released, recycled, and metabolized and how they exert their effects on

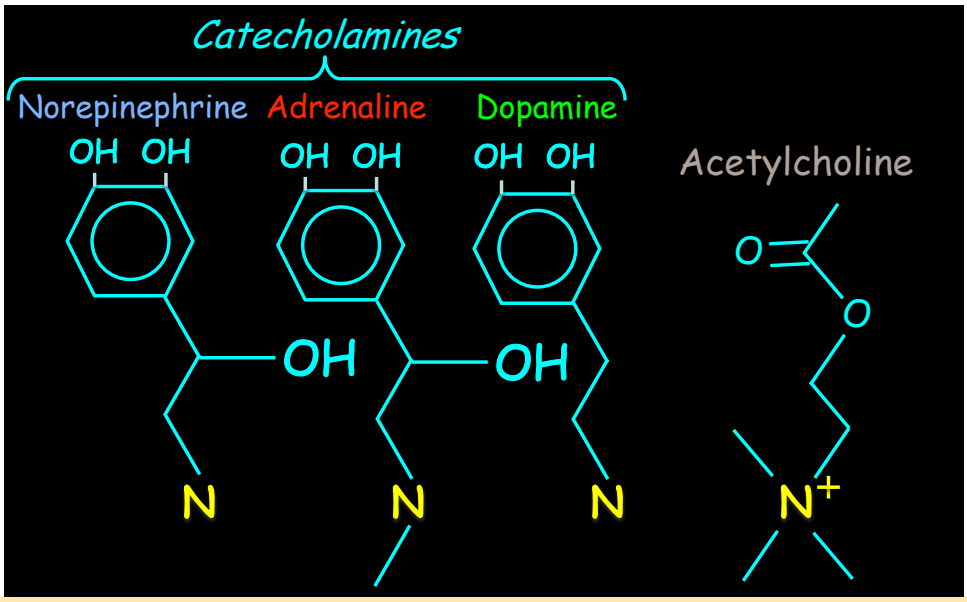


Fig. 51: Catecholamines and acetylcholine. *Chemical messengers of the autonomic nervous system include the catecholamines norepinephrine, adrenaline (epinephrine), and dopamine and the quaternary ammonium compound acetylcholine.*

target cells.

We will also be describing another important catecholamine in the body, dopamine (DA). Dopamine is a major chemical messenger in the brain and has other less well understood functions outside the brain.

The chemical messengers of the autonomic nervous system are small molecules. They all contain a prominent, single nitrogen (N) atom—an amine group in norepinephrine, adrenaline, and dopamine and a quaternary ammonium ion in acetylcholine. At a neutral pH, all four compounds are positively charged. This is important, because all four compounds are actively taken up

into and stored in vesicles, and the insides of the vesicles are acidic, which tends to keep the positively charged chemical messengers within the vesicles. As a quaternary ammonium compound, acetylcholine is always positively charged, regardless of the acidity of the medium.

Neurotransmitters are chemical messengers that are released from nerves and produce effects at target cells within the organ.

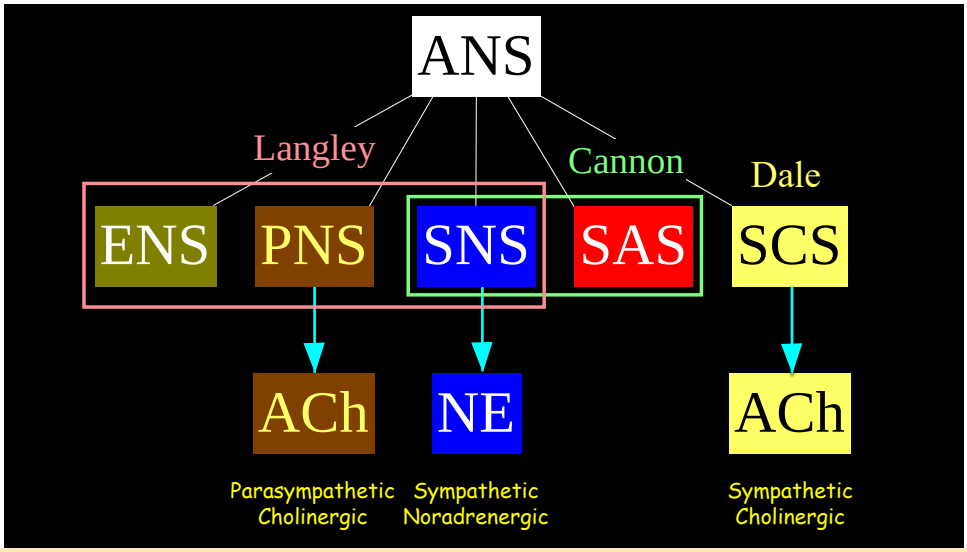


Fig. 52: Neurotransmitters of the ANS. *Norepinephrine (NE) and acetylcholine (ACh) are two major neurotransmitters of the autonomic nervous system (ANS).*

Neurotransmitters released from nerves act locally and are inactivated locally. Only a small fraction of released neurotransmitter makes its way to the bloodstream unchanged. This makes it complex or impossible to monitor release of neurotransmitters by measuring levels in the plasma.

In particular, acetylcholine released from nerves of the parasympathetic nervous system and from nerves of the sympathetic cholinergic system is broken down (metabolized) so rapidly and efficiently that acetylcholine is not normally detectable in the plasma. Therefore, tests of the parasympathetic and of the sympathetic cholinergic system rely on other types of measurements.

Thomas Renton Elliott was a student of Langley—the same Langley who coined the phrase, "autonomic nervous system." A statement by Elliott in 1904 is thought to be the earliest proposal of the existence of a neurotransmitter.

Elliott's idea arose from the observation that stimulation of sympathetic nerves and injection of adrenal gland extract

Fig. 53: T. R. Elliott. *Elliott, a student of Langley, was the first to propose the existence of a neurotransmitter.*

produce similar effects in the body. In a stroke of genius, he hypothesized that the similarity resulted from a chemical like adrenaline actually being released from the nerves and acting

on nearby cells.

His brief note published in the Journal of Physiology proposed "a mechanism developed out of the muscle cell, in response to its union with the synapsing sympathetic fibre, the function of which is to receive and transform the nervous impulse. Adrenalin(e) might then be a chemical stimulant liberated on each occasion when the impulse arrives at the periphery."

The first conceptualized neurotransmitter therefore was adrenaline. As will be seen, two giants in the history of autonomic medicine, Otto Loewi and Walter B. Cannon, took up the same theme.

The Heart of a Frog

One of the most famous experiments in medical history—an experiment that led to a Nobel Prize for the investigator, Otto Loewi—was based on the heart of a frog.

The experimental setup consisted of the exposed beating hearts of two frogs, a "donor" frog and a "recipient" frog. Loewi perfused the heart of the donor frog with a fluid that was led to the beating heart of the recipient frog.

When he electrically stimulated the vagus nerve to the heart of the donor frog, the heart rate decreased. The stimulation also decreased the heart rate of the recipient frog, implying that the stimulation released something into the perfusion fluid delivered from the donor heart to the recipient heart.

Fig. 54: Otto Loewi (Nobel Prize, 1936). *Loewi was the first to demonstrate chemical neurotransmission.*

Loewi inferred that the nerve stimulation released a chemical substance that caused the recipient frog's heart to slow down too. He called the substance "*Vagusstoff*" or "substance of the vagus."

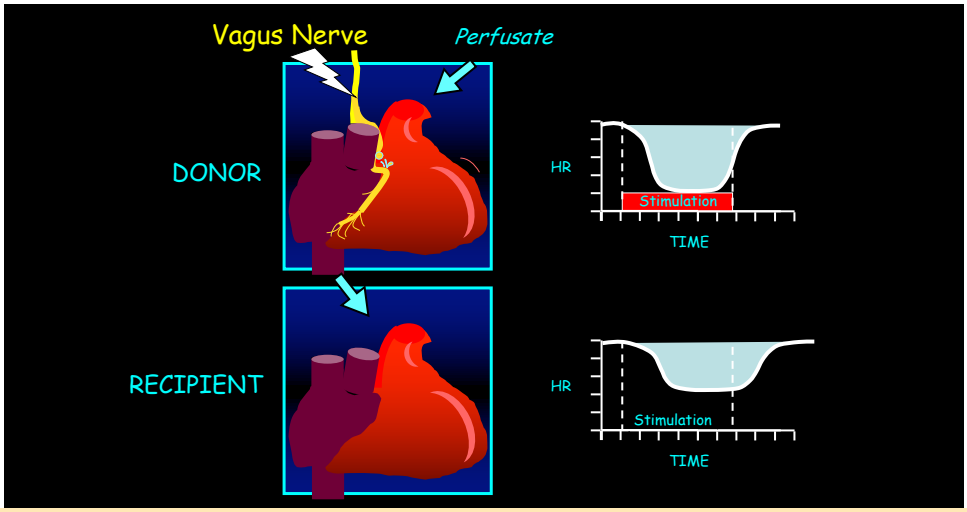


Fig. 55: Loewi's frog heart experiment. *The experiment demonstrated that stimulation of the vagus nerve releases a chemical messenger.*

He then showed that the *Vagusstoff* produced a variety of responses in other tissues that were identical to those produced by the chemical, acetylcholine. In 1926 Loewi and a coworker identified the *Vagusstoff* as acetylcholine.

Otto Loewi was the first person to demonstrate the existence of a chemical messenger coming from nerves—a neurotransmitter. He identified the neurotransmitter as acetylcholine. For this he received a Nobel Prize.

In his Nobel Lecture in 1936, Loewi claimed he had also proven that adrenaline is the neurotransmitter of the sympathetic nerves. Others had found that in the presence of oxygen and alkali adrenaline produces fluoresces with a green color. Loewi reported that in his preparation the heart perfusate coming from the stimulated heart showed this reaction. He considered this to be proof that adrenaline is the chemical messenger of the sympathetic nerves.

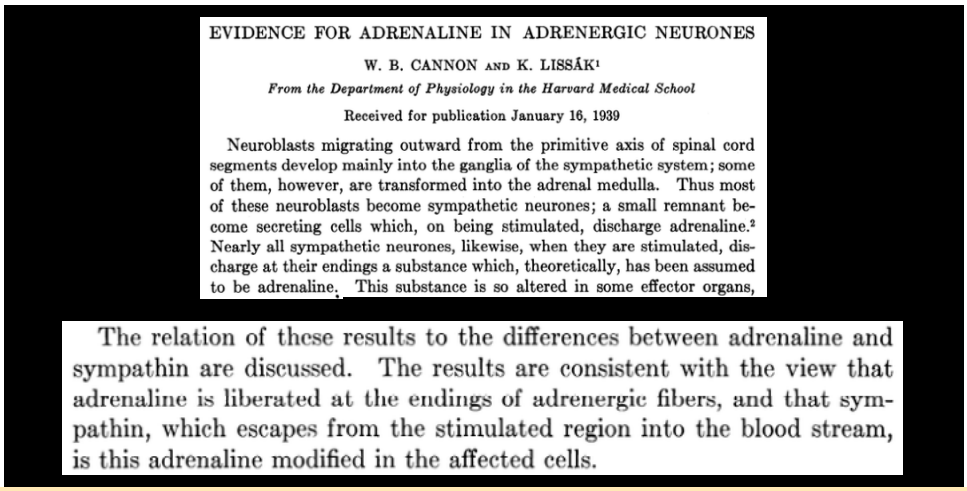
He was wrong. At the time it was not appreciated that other catecholamines (in particular, norepinephrine) give off the same green fluorescence. Walter B. Cannon made a similar mistake.

Why Cannon Never Won a Nobel Prize

In 1930, the Mexican physician and physiologist Arturo Rosenblueth joined Walter B. Cannon's lab at Harvard. Their efforts to explain the dual actions of adrenaline as excitatory at some sites and inhibitory at others led to their proposal that

adrenaline is released from sympathetic nerves but is modified in the affected target cells.

The chemical messenger would react with a hypothetical substance, H, to form "sympathin." Cannon and Rosenblueth proposed that there were two types of H—HE and HI—which would result in the formation of an excitatory substance, sympathin E, or an inhibitory substance, sympathin I.



EVIDENCE FOR ADRENALINE IN ADRENERGIC NEURONES

W. B. CANNON AND K. LISSÁK[1]

From the Department of Physiology in the Harvard Medical School

Received for publication January 16, 1939

Neuroblasts migrating outward from the primitive axis of spinal cord segments develop mainly into the ganglia of the sympathetic system; some of them, however, are transformed into the adrenal medulla. Thus most of these neuroblasts become sympathetic neurones; a small remnant become secreting cells which, on being stimulated, discharge adrenaline.[2] Nearly all sympathetic neurones, likewise, when they are stimulated, discharge at their endings a substance which, theoretically, has been assumed to be adrenaline. This substance is so altered in some effector organs,

The relation of these results to the differences between adrenaline and sympathin are discussed. The results are consistent with the view that adrenaline is liberated at the endings of adrenergic fibers, and that sympathin, which escapes from the stimulated region into the blood stream, is this adrenaline modified in the affected cells.

Fig. 56: Why Cannon never won a Nobel Prize. *In 1939 Cannon proposed that adrenaline was the sympathetic neurotransmitter. Although the experimental data were correct, the interpretation was not—a common theme in the history of autonomic medicine.*

They were wrong, and this mistake could have cost Cannon a Nobel Prize. The reason I think this is that in the mid-1940s the Swedish physiologist Ulf Svante von Euler correctly identified the neurotransmitter of the sympathetic nerves in mammals as not adrenaline but norepinephrine (synonymous with noradrenaline).

For this discovery von Euler received a Nobel Prize in 1970.

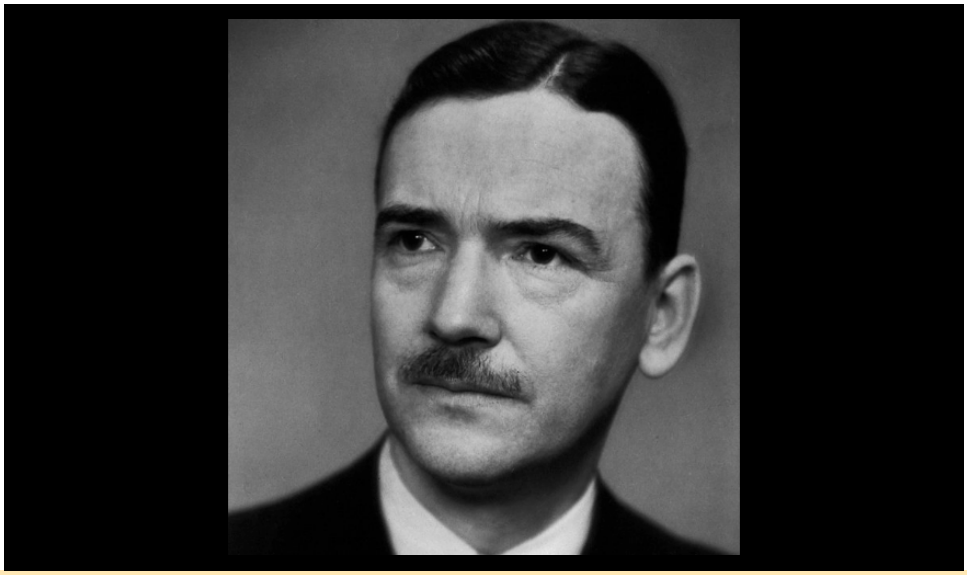


Fig. 57: U.S. von Euler (Nobel Prize, 1970). *von Euler identified norepinephrine as the neurotransmitter of the sympathetic nervous system.*

The identification by von Euler of norepinephrine as the sympathetic neurotransmitter in 1946, for which he would later receive a Nobel Prize in 1970, refuted the view that adrenaline is the sympathetic neurotransmitter; however, Cannon's incorrect concept about sympathins did not disappear from the literature until the 1950s.

Because of widespread acceptance of the notion of sympathins, when Raymond Ahlquist, based on his findings of two different orders of potency of seven sympathomimetic drugs in different tissues, postulated that there were two different receptors, alpha and beta, his paper, which challenged the validity of the concept of two kinds of sympathin, was initially rejected as speculative.

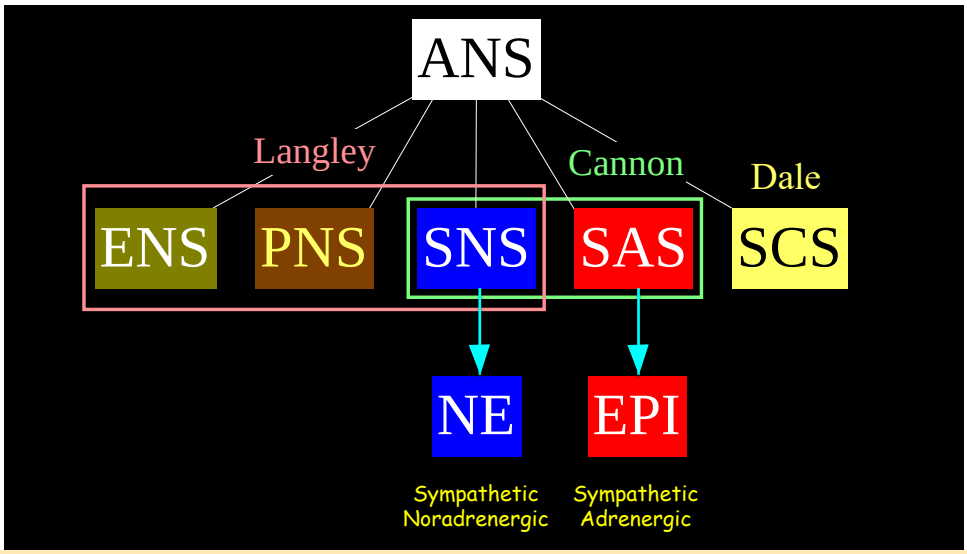


Fig. 58: The SNS & SAS. *Norepinephrine (NE) is a major neurotransmitter of the sympathetic nervous system, whereas adrenaline (epinephrine, EPI), is the hormone of the sympathetic adrenergic system (SAS).*

From here on in this book, the abbreviation SNS refers to the sympathetic noradrenergic system. This is the part of the autonomic nervous system where norepinephrine (NE) is the neurotransmitter.

Three Routes to Sympathy

Acetylcholine is the neurotransmitter of the parasympathetic nervous system (PNS) and the sympathetic cholinergic system (SCS). One can therefore conceptualize three chemical messengers of the sympathetic nervous system—norepinephrine (NE), adrenaline (epinephrine, EPI), and acetylcholine (ACh). ACh is the neurotransmitter of the PNS and SCS, and NE is the neurotransmitter of the SNS. In the

sympathetic adrenergic system (SAS), EPI is a neuroendocrine substance, because sympathetic nerve stimulation releases EPI as a hormone into the circulation.

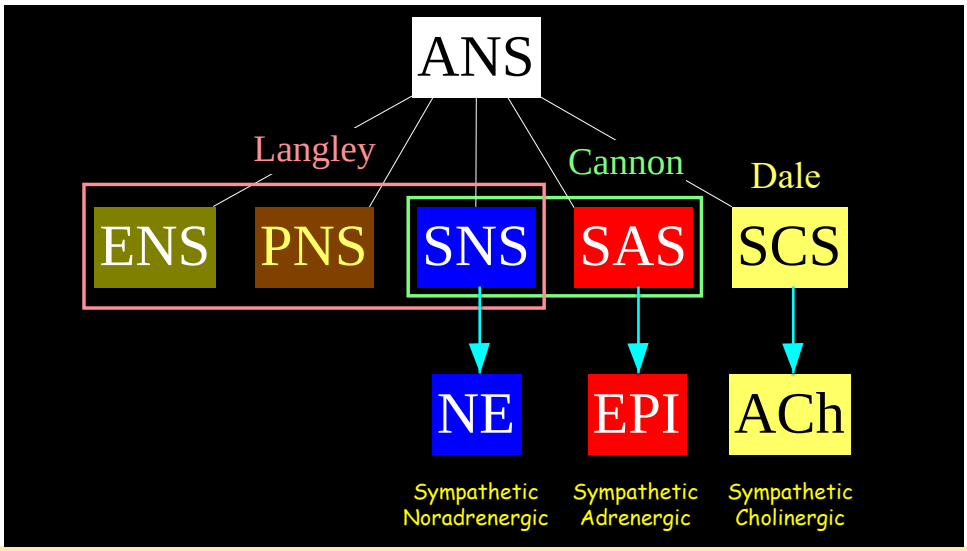


Fig. 59: Three sympathetic chemical messengers. *Three sympathetic sub-systems are the SNS, SAS, and SCS.*

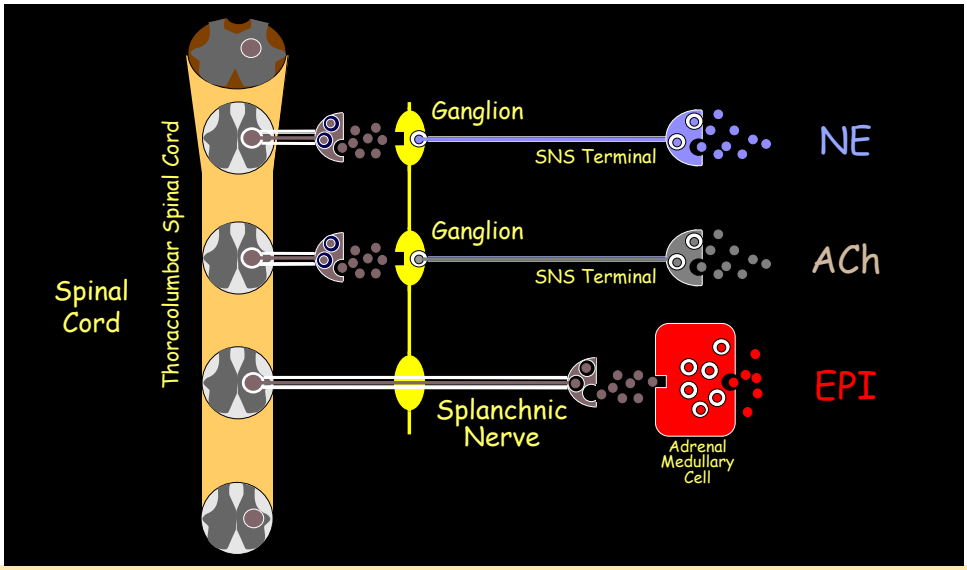


Fig. 60: Three sympathetic sub-systems. *Each sub-system has an associated chemical messenger.*

There is no single neurotransmitter of the enteric nervous system (ENS). There are many, and they interact in a highly complex manner. I think of the ENS as a conglomerate of intrinsic neurons, neurotransmitter systems, hormones, and autocrine-paracrine systems.

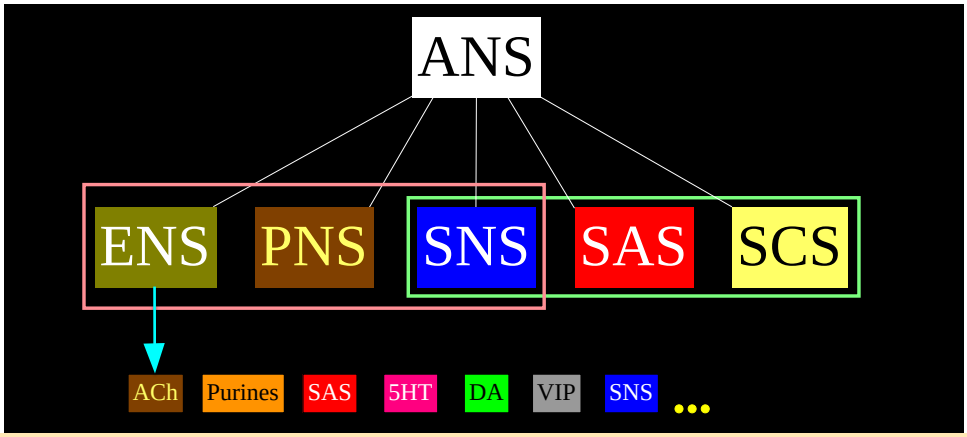


Fig. 61: Chemical messengers of the ENS. *Many chemical messenger systems interact in the gut in the enteric nervous system (ENS).*

It is of interest that most of three major neurotransmitters in the brain—serotonin, dopamine, and norepinephrine—are made in the gut.

Hormones

Hormones are a second general type of chemical messenger. One of the most famous hormones—and the first to be identified—is adrenaline, which is released into the bloodstream by the adrenal gland.

Essentially all body organs take up circulating adrenaline; however, an exception is the brain, where an efficient blood-

brain barrier normally prevents entry of catecholamines into most brain regions.

Hormones are released directly into the bloodstream and are delivered to all body organs.

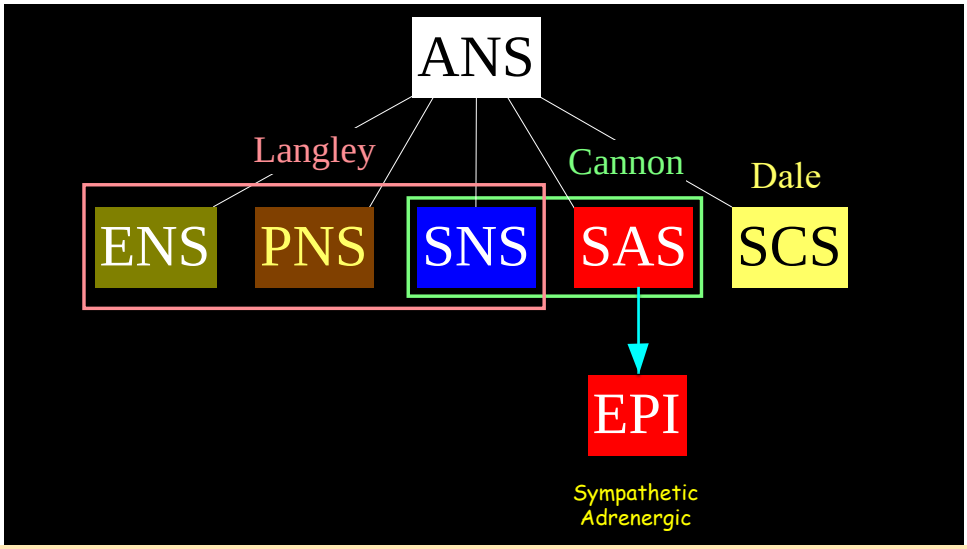


Fig. 62: The sympathetic adrenergic system (SAS). *Adrenaline, or epinephrine (EPI), is the chemical messenger of the sympathetic adrenergic system (SAS). EPI is a hormone.*

The SAS can be viewed as a neuroendocrine system, because nervous stimulation leads to release of the hormone. Other neuroendocrine hormones of the body include insulin and gastrin, which are released by vagal stimulation.

It may be reasonable to conceptualize that neuroendocrine systems expand the meaning of the term, autonomic. At a minimum, neuroendocrine systems and components of the autonomic nervous system interact. For example, the sympathetic noradrenergic system and hypothalamic-thyroid

axis interact in regulation of overall metabolism; thus, thyroidectomy increases SNS outflow. Similarly, hypopituitarism and adrenocortical failure increase SNS activity. Meanwhile, release of corticotropin-releasing hormone in the brain increases SNS and SAS activities.

Another extension of the concept of autonomic relates to the immune system. A large family of proteins called cytokines are released from cells of the immune system. Cytokines play key roles in immunity and bodily responses to infection, inflammation, trauma, sepsis, and cancer. Neuroimmunology is a rapidly evolving field that focuses on interactions between the nervous system (including the autonomic nervous system) and immune functions. We will be returning to interactions among autonomic, neuroendocrine, and neuroinflammatory systems in the section on homeostasis.

An example of neuroimmune-autonomic interactions is co-regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, which plays a role in coordinated functions of the adrenal cortex (the main source of anti-inflammatory steroids in the body) and the adrenal medulla (the main source of adrenaline in the body). Another example is regulation of cytokines by the vagus nerve.

Autocrine-paracrine substances

Besides neurotransmitters and hormones, there is a third type of chemical messenger—probably the oldest in evolutionary terms. This class of chemicals are autocrine/paracrine substances. These chemicals are made in, released from, and act

on the same or nearby target cells.

Autocrine/paracrine substances are made in, released by, and act on the same or nearby cells in an organ.

Unlike hormones and neurotransmitters, which are stored at particular sites within cells and are released from the storage sites in response to nerve traffic, autocrine/paracrine substances are released as soon as they are made within the cells.

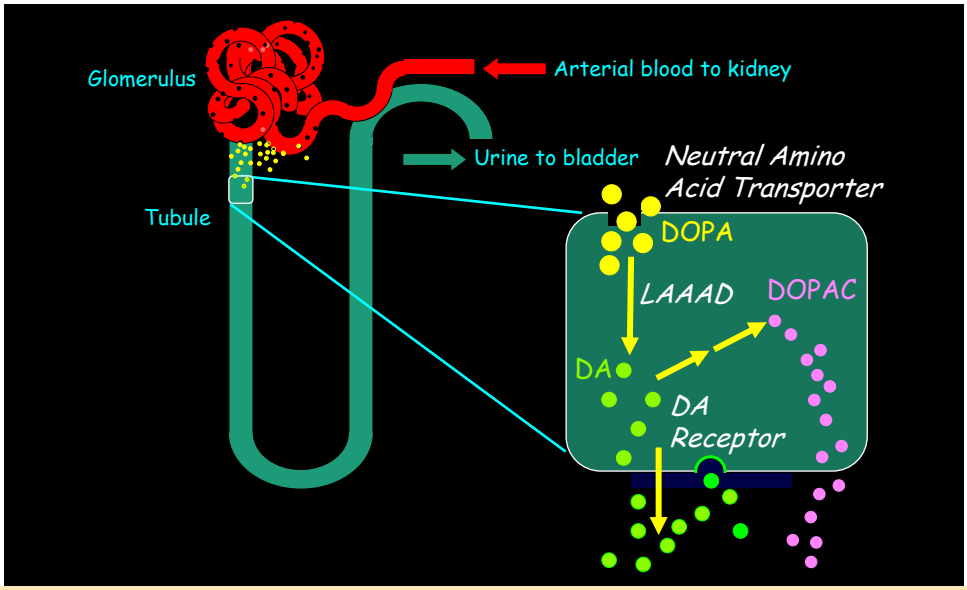


Fig. 63: The renal DOPA-dopamine system. *In this autocrine/paracrine system, the catecholamine dopamine (DA) is made from DOPA that is taken up from the circulation. The DA is not stored but instead exits the cell as it is made and acts locally on the same or nearby cells.*

Of several autocrine/paracrine substances in the body, one involves the catecholamine, dopamine. In proximal tubular cells of the kidneys, DOPA is converted to dopamine by the enzyme

L-aromatic-amino-acid decarboxylase (LAAAD). Dopamine released from the cells acts on receptors on the same or nearby cells, and this increases excretion of sodium and water.

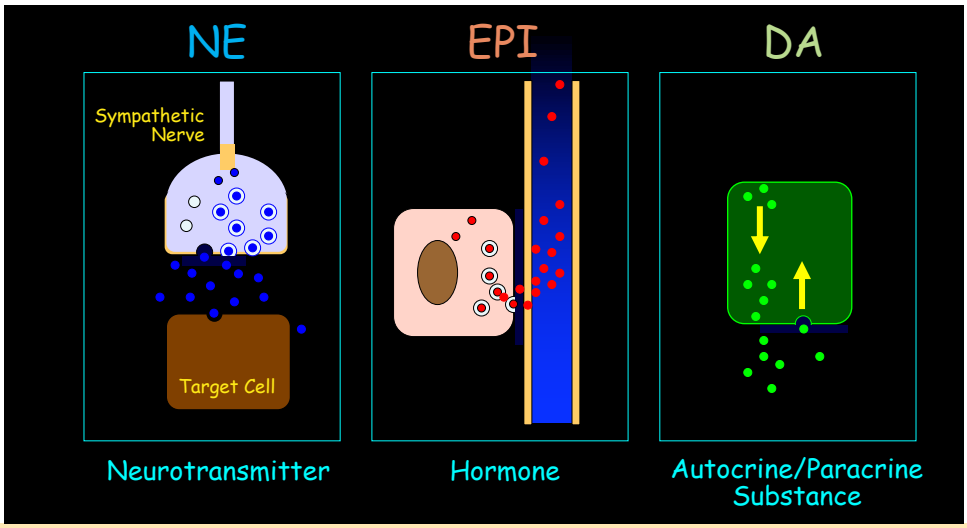


Fig. 64: Catecholamine messaging systems. *Norepinephrine (NE) is the neurotransmitter of the sympathetic noradrenergic system (SNS), adrenaline (epinephrine, EPI) is the hormone of the sympathetic adrenergic system (SAS), and dopamine (DA) is the autocrine-paracrine substance of the renal DOPA-dopamine system.*

This means that the three catecholamines of the body, norepinephrine, adrenaline, and dopamine, exemplify three types of chemical messenger systems. NE is the neurotransmitter of the SNS, EPI is the hormone of the SAS, and DA is the autocrine-paracrine substance of the renal DOPA-dopamine system.

Here is a summary diagram showing the components of the autonomic nervous system and the chemical messengers associated with them.

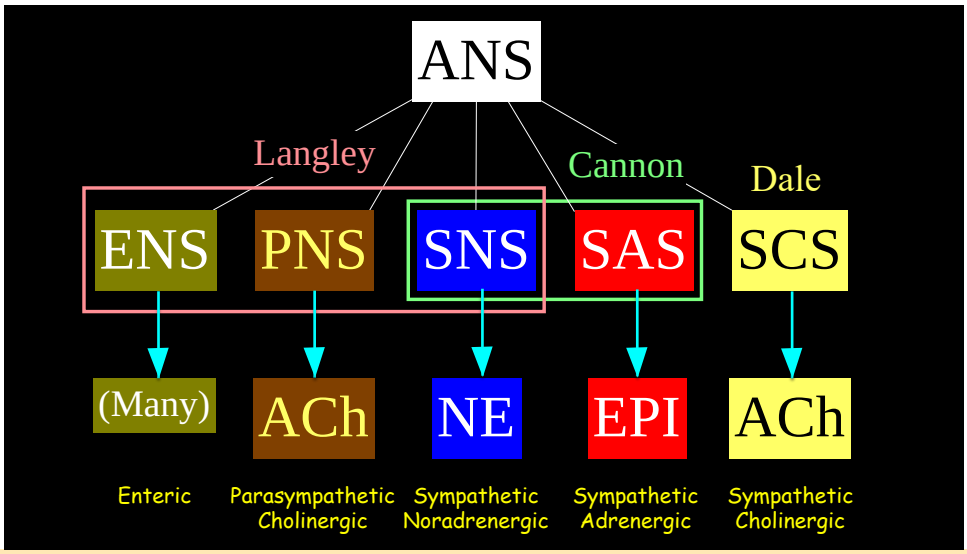


Fig. 65: ANS components & messengers.

COMMON THEMES IN CHEMICAL MESSAGING

Chemical messaging in the autonomic nervous system involves some common themes.

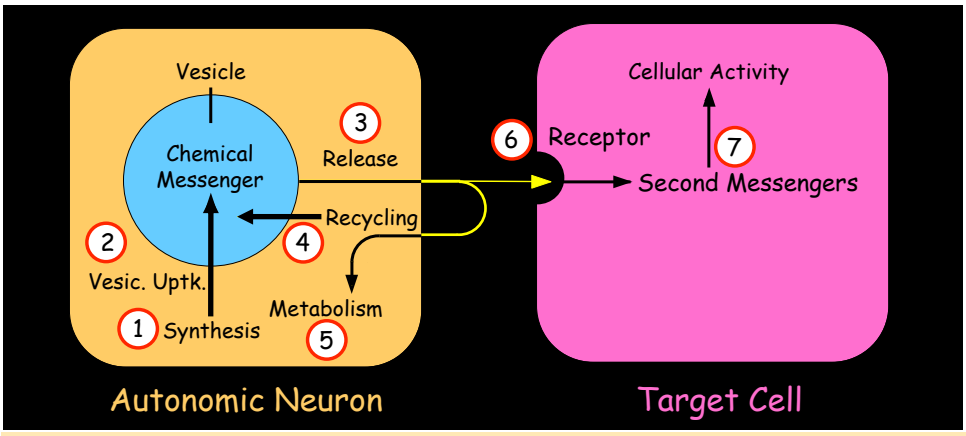


Fig. 66: Chemical messaging overview. *The autonomic nervous system works by variations on the same chemical messaging theme.*

The details for each theme depend on the particular chemical messenger.

Key steps in the functioning of the components of the autonomic nervous system are:

(1) production **(synthesis)** of the chemical messengers;

(2) storage of the messengers in bubble-like vesicles by **vesicular uptake**;

(3) release of the chemical messengers by fusion of the vesicles with the membrane surface, followed by formation of holes at the vesicle-membrane junction (poration) and release of the contents of the vesicles into the interstitial fluid **(exocytosis)**;

(4) vesicular recycling by the vesicles coming off the membrane surface and going back to the cytoplasm **(endocytosis)**. In the case of catecholamines, another form of recycling is via neuronal reuptake of released catecholamines.

(5) **metabolism** of the chemical messengers.

(6) binding of the chemical messengers to **receptors** on the target cells;

(7) **second messengers** that relate receptor occupation to cellular activation or inhibition;

In order for the ANS to do its jobs, production, storage and release of chemical messengers, delivery of the messengers to receptors, and recycling and metabolic breakdown of the messengers are tightly coordinated.

This section is divided up in terms of these steps, first for the catecholamines and then for acetylcholine (ACh).

CATECHOLAMINE SYNTHESIS

Catechols Look Like Cats

The catecholamines of the body— norepinephrine, adrenaline, and dopamine—are catechols.

The chemical, catechol, has a particular structure, consisting of a hexagon of carbon atoms with hydroxyl (OH) groups attached to adjacent points of the hexagon. The hexagonal ring is the face. The two hydroxyl groups are the pointy ears.

A catechol looks like the head of a cat.

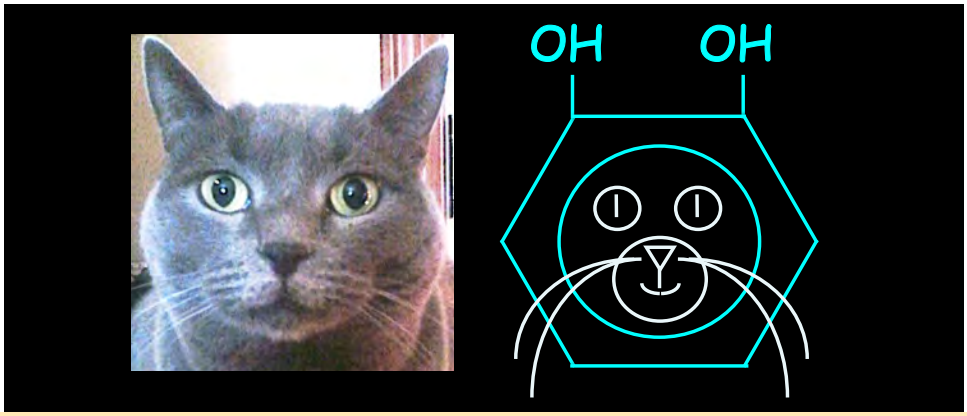


Fig. 67: Catechols look like cats. *The chemical structure called catechol looks like a cat's head.*

Catechol itself does not exist in the human body, but chemicals that contain catechol as part of their molecular structure are called catechols.

Catecholamines look like the entire cat, including its tail.

The tail of the cat is a short hydrocarbon strand consisting of carbon and hydrogen atoms. At the end of the tail is an amine (ammonia) group. Think of the cat in its litter box, with the ammonia coming off the tail end producing a smell like urine.

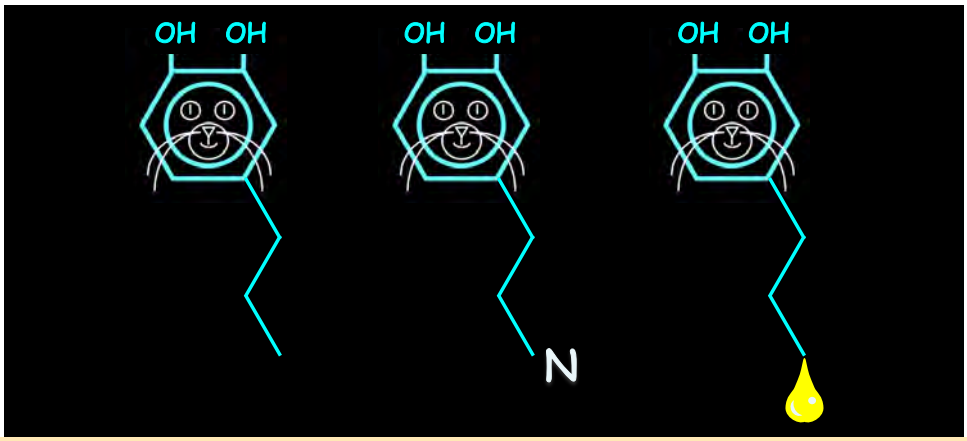


Fig. 68: Catecholamines: The cat head to tail. *Catecholamines look like the entire cat, from head to tail—in its litter box. The catecholamine shown in the middle is dopamine.*

The Catecholamine Assembly Line

This section describes the stations on the catecholamine assembly line—the steps in catecholamine biosynthesis.

The body's catecholamines come from DOPA.

If you are a healthy adult human, then you are making your own levodopa (DOPA, technically called 3,4-

dihydroxyphenylalanine) all the time. The levels attained in the bloodstream, however, are about one-thousandth those required to treat Parkinson's disease.

Amino acids are the building blocks of proteins. All three of the body's catecholamines come from DOPA, which is an amino acid, and DOPA comes from tyrosine, which is also an amino acid. Tyrosine is an amino acid that is not a catechol; DOPA is a catechol.

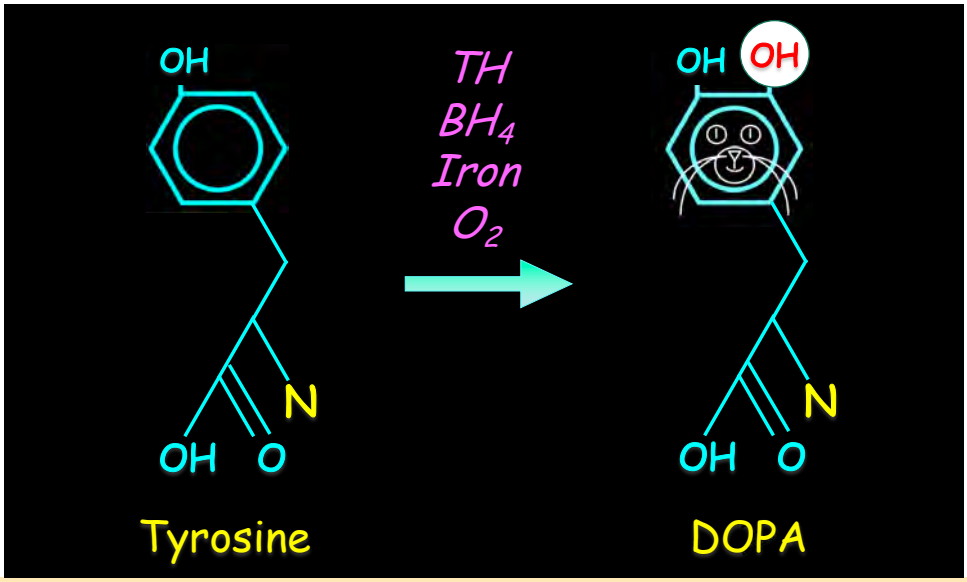


Fig. 69: TH & DOPA synthesis. *The first step in catecholamine synthesis is conversion of the non-catechol amino acid tyrosine to the catechol amino acid, DOPA.*

Tyrosine is converted to DOPA by the actions of an enzyme (a protein that speeds up a particular chemical process). The enzyme that speeds up the conversion of tyrosine to DOPA is tyrosine hydroxylase (TH). For tyrosine hydroxylase to work requires oxygen, iron, and tetrahydrobiopterin, abbreviated BH_4. BH_4 is a very important co-factor.

Deficiency of enzymes required to produce BH_4 can produce a pediatric neurodegenerative disease or else a particular movement disorder (called DOPA-responsive dystonia).

To people with Parkinson's disease, DOPA (also called L-DOPA and levodopa) is a miracle drug. Levodopa is like "vitamin L." Within minutes levodopa can convert a shuffling, tremulous, slow-moving person with stooped posture to a vigorous, normally moving person with head held erect.

I will never forget the first time I witnessed this phenomenon, while I was a medical student. Onstage at the beginning of the lecture, the professor introduced a patient with Parkinson's disease who had not yet taken his levodopa that day. Slowly, unsteadily, and with assistance the patient then made his way up the steps of the amphitheater and exited the doors at the top. Outside the lecture hall he took a dose of levodopa.

At the end of the lecture, the professor reintroduced the patient and asked him to walk down to the stage. The patient literally bounded down the steps of the amphitheater. When he was on the stage he turned around swiftly to face the assembled students, like a pirouetting ballet dancer, with a broad grin on his face. The audience erupted in applause.

NEURONAL SODA POP

The next station on the catecholamine assembly line is the conversion of DOPA (which is a catechol but not a catecholamine), to dopamine, the grandfather in the

catecholamine family. This step takes place in many types of cells and not just in cells that possess the rest of the machinery to store and recycle catecholamines.

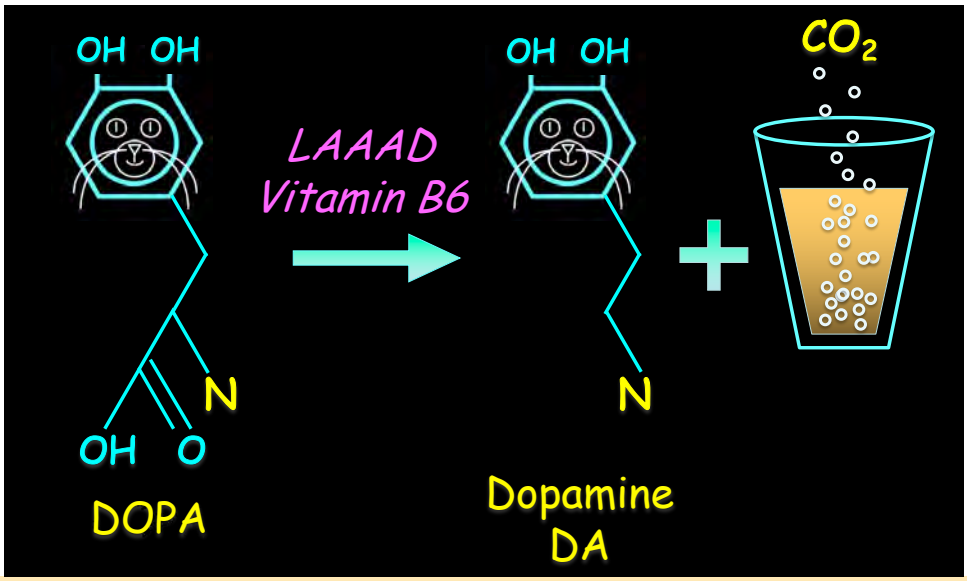


Fig. 70: LAAAD and dopamine synthesis. *Conversion of DOPA to dopamine (DA) generates carbon dioxide, the same gas that is in the bubbles of soda pop.*

To make dopamine from DOPA requires the enzyme, L-aromatic amino-acid decarboxylase (LAAAD, sometimes called DOPA decarboxylase, or DDC), and the co-factor pyridoxal phosphate, which is vitamin B6. (Incidentally, the word "vitamin" comes from "vital amine," even though some vitamins, such as vitamin B6, are not amines at all.)

DOPA is a neutral amino acid, and it is taken up by all types of cells in the body, because all cells express a neutral amino acid transporter. Many cell types, such as kidney and liver cells, contain abundant LAAAD, and in several organs dopamine is made from the DOPA after uptake of the DOPA from the

bloodstream.

The conversion of DOPA to dopamine involves cleaving off carbon dioxide from the molecule of DOPA. If this chemical reaction were carried out in a glass of water, the generated carbon dioxide gas would bubble up to the surface, like the effervescence in seltzer.

Maybe this will help you remember that by this reaction DOPA turns into a cat-a-COLA-mean. (Actually, because of the rapid oxidation of dopamine in solution to form a tan breakdown product, it would be more accurate to think about the reaction generating ginger ale—but then there wouldn't be any pun with cola soda.)

WITHOUT VOMITING

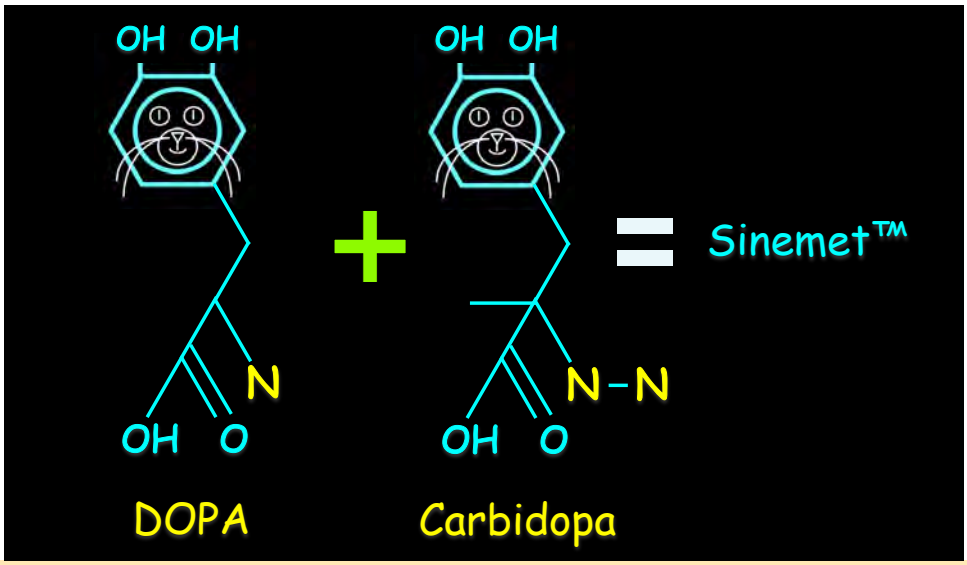


Fig. 71: DOPA and carbidopa are catechols. *DOPA combined with carbidopa is Sinemet™, from the words for "without vomiting."*

A drug called carbidopa blocks LAAAD. Carbidopa is also a catechol. Carbidopa does not cross the blood-brain barrier. This means that if a patient were to take DOPA with carbidopa, the DOPA would not be converted efficiently to dopamine by LAAAD outside the brain, whereas DOPA entering the brain can be turned into dopamine by LAAAD in brain cells.

The combination of DOPA with carbidopa improves the efficiency of levodopa treatment for Parkinson's disease, while decreasing the toxic effects from too much dopamine being made outside the brain.

The main toxic effect of DOPA given as a drug is vomiting, due to effects of dopamine in the brain's vomiting center, which is at the back of the brainstem in a region that lacks an efficient blood-brain barrier. Giving carbidopa with DOPA decreases the amount of dopamine production from DOPA outside the brain and therefore helps prevent DOPA-induced vomiting. This explains one clever brand name for the levodopa-carbidopa combination to treat Parkinson's disease, Sinemet™. Sinemet is a combination of the Latin words for "without vomiting."

Theoretically, carbidopa could prevent the production of all the catecholamines; however, at the doses used clinically it inhibits but does not block catecholamine production. In fact, because of the tremendously high plasma DOPA levels attained by oral levodopa, in patients taking Sinemet™ plasma levels of dopamine and its metabolites are actually substantially increased, not decreased. Since the plasma dopamine levels in patients on levodopa-carbidopa are not high enough to produce pharmacological effects, I'd guess that the lack of vomiting with Sinemet treatment is from carbidopa inhibiting conversion

of DOPA to dopamine within the vomiting center.

The body's three catecholamines, dopamine, norepinephrine, and adrenaline, are like the grandfather, father, and son in a small chemical family. Dopamine is turned into norepinephrine, and norepinephrine is turned into adrenaline.

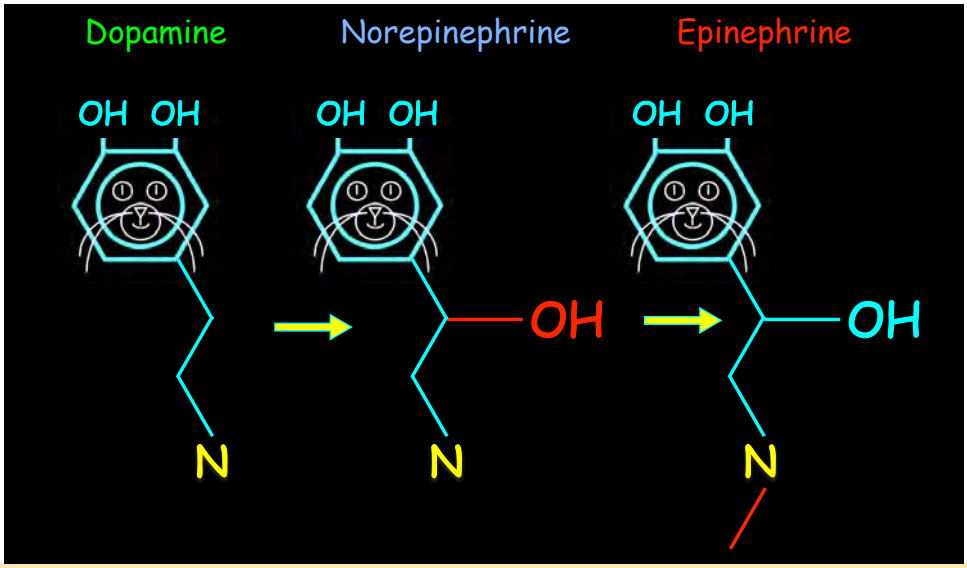


Fig. 72: Catecholamine synthesis sequence. *Dopamine is converted to norepinephrine, and norepinephrine is converted to epinephrine (adrenaline). All three compounds are catechols and catecholamines.*

VESICULAR UPTAKE AND STORAGE

Dopamine is made from DOPA in the cytoplasm ("cell juice") of neurons and cells that make catecholamines. For dopamine to be converted to norepinephrine (NE), however, dopamine must be taken up into tiny bubble-like structures called vesicles within the neurons or cells.

Chemical messengers of the autonomic nervous system are packaged in tiny bubble-like structures called vesicles.

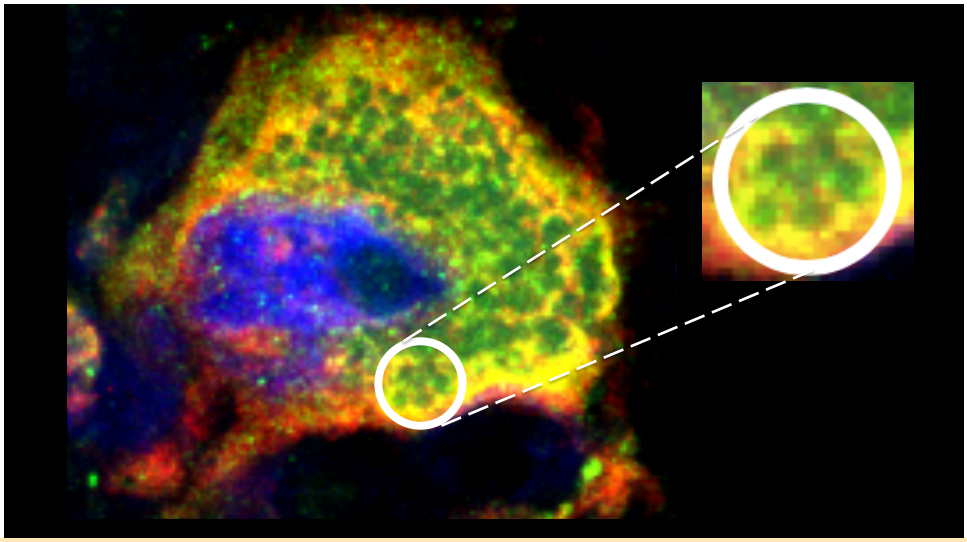


Fig. 73: DBH-related particles in a sympathetic neuron. *Green corresponds to dopamine-beta-hydroxylase (DBH), which is localized to vesicles. This magnificent image was provided by Dr. Risa Isonaka.*

All the chemical messengers of the autonomic nervous system, including norepinephrine, adrenaline, dopamine, and acetylcholine, are stored in vesicles. The vesicles seem to be arranged in clusters (the DBH-containing particles in Fig. 73 are too large to be vesicles themselves).

Vesicular uptake not only is a mechanism for packaging chemical messengers but also for detoxifying potentially toxic compounds that are in the cytoplasm. We will return to vesicular sequestration as a detoxification mechanism later when we discuss the catecholamine autotoxicity theory.

The Weakest Link

There are several requirements for converting DA to NE, and a problem with any of them could result in decreased NE synthesis. Because of this I think of this step as the "weakest link" in norepinephrine biosynthesis.

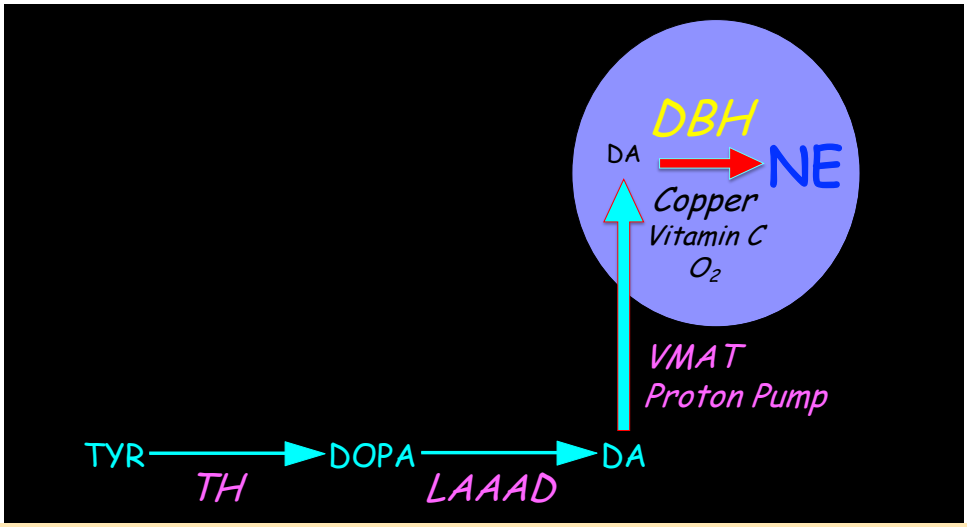


Fig. 74: NE synthesis in vesicles. *NE synthesis takes place in vesicles that contain the enzyme dopamine-beta-hydroxylase (DBH).*

Unlike dopamine and acetylcholine, which are produced in the cytoplasm and then actively pumped into the vesicles, norepinephrine is produced within the vesicles. This is because dopamine-beta-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine, is localized to the vesicles in noradrenergic neurons and in cells of the adrenal medulla. In order to synthesize norepinephrine, dopamine, which is made from DOPA in the cytoplasm, must be taken up into the vesicles.

In sympathetic noradrenergic nerves, adrenomedullary cells, and noradrenergic neurons in the brain, a transporter called the type 2 vesicular monoamine transporter (VMAT2) mediates the uptake of dopamine into the vesicles. Predictably, mice with very low VMAT2 activity have norepinephrine deficiency in the brain and heart.

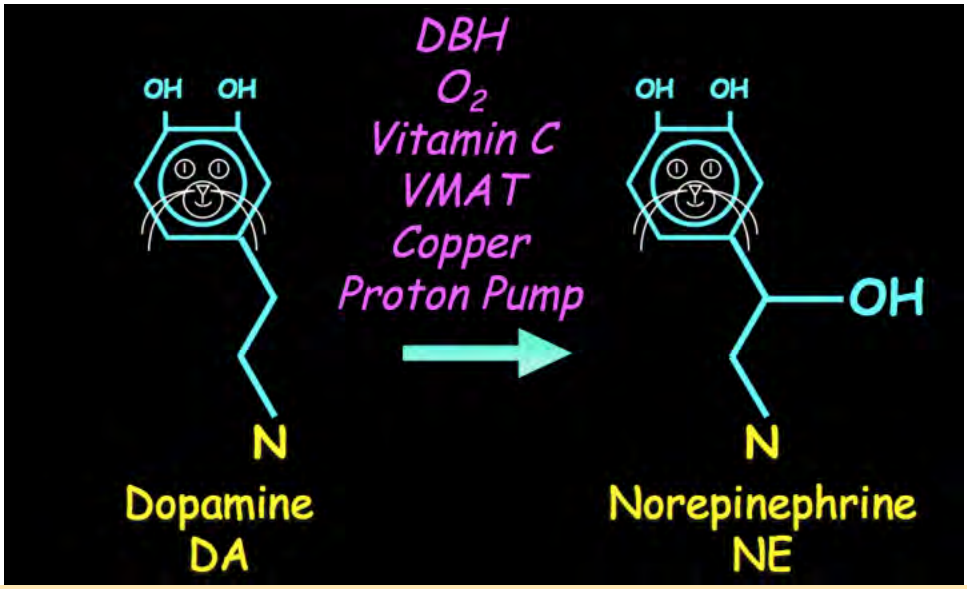


Fig. 75: Requirements for NE synthesis. *Several factors and processes are necessary in order to make norepinephrine from dopamine in the body.*

DBH deficiency constitutes a rare cause of SNS failure due to the inability to synthesize norepinephrine. Because of isolated noradrenergic deficiency, sympathetic cholinergic function is intact, and DBH-deficient patients therefore sweat normally when exposed to heat, even though they have severe orthostatic hypotension due to SNS failure. (Actually, SNS nerve traffic is unimpaired in DBH deficiency, but instead of NE being released it is dopamine that is released from the nerve terminals.)

Vitamin C (ascorbic acid) is required for the transfer of electrons when DBH acts on vesicular dopamine. A recently described rare form of autonomic failure results from cytochrome CYB561 deficiency. The CYB561 protein defect leads to a shortage of ascorbic acid in the vesicles, resulting in a form of functional DBH deficiency, without an abnormality of DBH itself.

DBH is a copper enzyme. DBH contains—and its activity absolutely depends on—copper. In order to convert dopamine to norepinephrine, copper must be incorporated in the DBH molecule. In a pediatric disease called Menkes disease there is a mutation of the gene encoding a form of copper ATPase. This interferes with incorporation of copper in DBH. Patients with Menkes disease therefore do not synthesize norepinephrine normally.

Vesicular uptake is an energy requiring process that uses adenosine triphosphate (ATP) for pumping protons into the vesicles by a proton pump. This makes the inside of the vesicles acidic. As the protons leak passively out of the vesicle, dopamine enters the vesicle via the VMAT.

A variety of proton pump inhibitors (PPIs) are available by prescription or over the counter. Theoretically they could interfere with vesicular uptake and thereby with norepinephrine synthesis. I once had a patient who had physiological, neurochemical, and neuroimaging abnormalities consistent with decreased vesicular uptake and decreased norepinephrine synthesis, and I diagnosed him with probable pure autonomic failure. He was on a prescription PPI for severe gastroesophageal reflux. A couple of years later I saw him in

follow-up. Remarkably, all the autonomic abnormalities were gone. In the interim he had undergone surgery for the gastroesophageal reflux and was no longer taking a PPI.

Since then I've wondered about whether the prescription PPI could have the vesicular proton pump sufficiently to produce symptoms and signs of sympathetic noradrenergic failure. After reviewing records about medications from many other patients, I'm not convinced that over-the-counter PPIs produce this problem.

Ascorbic acid (vitamin C) is a co-factor for DBH, and so it is theoretically possible that patients with scurvy have decreased norepinephrine synthesis. In normal volunteers deprived of vitamin C, however, there is no evidence of a problem with norepinephrine production.

Mitochondria in cells are the main source of ATP. Because vesicular uptake is an energy-requiring process, almost any problem that impedes mitochondrial functions can lead to decreased vesicular uptake of cytoplasmic catecholamines. Vesicular contents leak passively continuously into the cytoplasm. Therefore, any cellular "energy crisis" in sympathetic noradrenergic neurons will lead to depletion of the neurotransmitter.

Stress Vitamins

Production of adrenaline and other catecholamines in the body requires at least two vitamins. The conversion of DOPA to dopamine, and therefore the synthesis of all the catecholamines,

depends on the availability of pyridoxal phosphate, which is vitamin B6. As noted above, the conversion of dopamine to norepinephrine in the body requires ascorbic acid, which is vitamin C.

Fig. 76: Stress vitamins. *"Stress" formulas contain vitamin B6 and vitamin C. Both are required for norepinephrine synthesis.*

In my office I have a large "stress collection" consisting of items sold to alleviate stress. (A section later deals with the meaning of stress as a scientific idea.) As near as I can tell, all stress formulas contain vitamins B6 and C.

The Case of the Depressed Dog

Many years ago I was exploring whether an analog of dopamine tagged with radioactivity (^{18}F-dopamine, about which you'll learn much more later) could successfully visualize sympathetic nerves by a type of nuclear medicine scanning called PET scanning. To test this idea I carried out

^{18}F-dopamine PET scanning in a dog that had been treated with the drug reserpine. Reserpine exerts a highly specific effect in the body. It blocks uptake of catecholamines from the cytoplasm into storage vesicles. If my hypothesis were correct, then treatment with reserpine would prevent uptake of the ^{18}F-dopamine into the vesicles and prevent visualization of the sympathetic nerves by PET scanning.

In conducting this experiment I didn't appreciate adequately that reserpine rapidly gets into and exerts major effects in the brain. Soon after the testing was over and the dog had been returned to its kennel, I received a phone call from the veterinarian, who was very concerned. She reported that the dog was lying listless in a corner. Its tail was tucked underneath it, and it wouldn't wag its tail when a caretaker approached. It was poorly responsive, it wouldn't eat, and its core temperature and blood pressure were low. The veterinarian thought the dog was seriously ill.

Instead it was suffering from effects of reserpine. Because of VMAT blockade and ongoing passive leakage of neurotransmitters from the vesicles into the cytoplasm, reserpine rapidly decreases brain stores of the monoamines norepinephrine, dopamine, and serotonin. Depletion of dopamine causes decreased spontaneous movement, decreased oral intake, and a tendency to depression. Depletion of norepinephrine decreases vigilance behavior and also can cause a tendency to depression. Depletion of serotonin probably also depresses mood. Reserpine-induced deficiency of all three chemicals in the brain probably produced the dog's depressed affect.

Reserpine-induced loss of norepinephrine in the sympathetic noradrenergic system probably also resulted in the dog's low blood pressure. Indeed, the leaf of the plant from which reserpine was isolated, ***Rauwolfia serpentina***, was one of the first successful medicinal treatments for clinical hypertension. Low core temperature could also have been a sign of catecholamine deficiency in the poor dog.

Tetrabenazine (Xenazine™), an FDA approved drug for Huntington's disease-related chorea that has been used for other hyperkinetic movement disorders, inhibits the type 2 VMAT, (VMAT2). Theoretically, tetrabenazine should decrease norepinephrine synthesis, but whether at clinically used doses tetrabenazine affects plasma or cerebrospinal fluid levels of norepinephrine or its metabolites does not appear to have been studied.

The Adrenal Bon-Bon

The synthesis of adrenaline (epinephrine, EPI) by cells of the adrenal medulla seems to be a special case involving orchestration of processes in two different cell types.

Do you remember that a catecholamine is like a cat in its litterbox? EPI basically is norepinephrine with a methyl group added to the amine group at the end of the hydrocarbon tail in the norepinephrine molecule. S-adenosyl methionine (SAMe) is the source of the methyl group. The enzyme phenylethanolamine-N-methyltransferase (PNMT) catalyzes the transfer of the methyl group from SAMe to the amine group in norepinephrine.

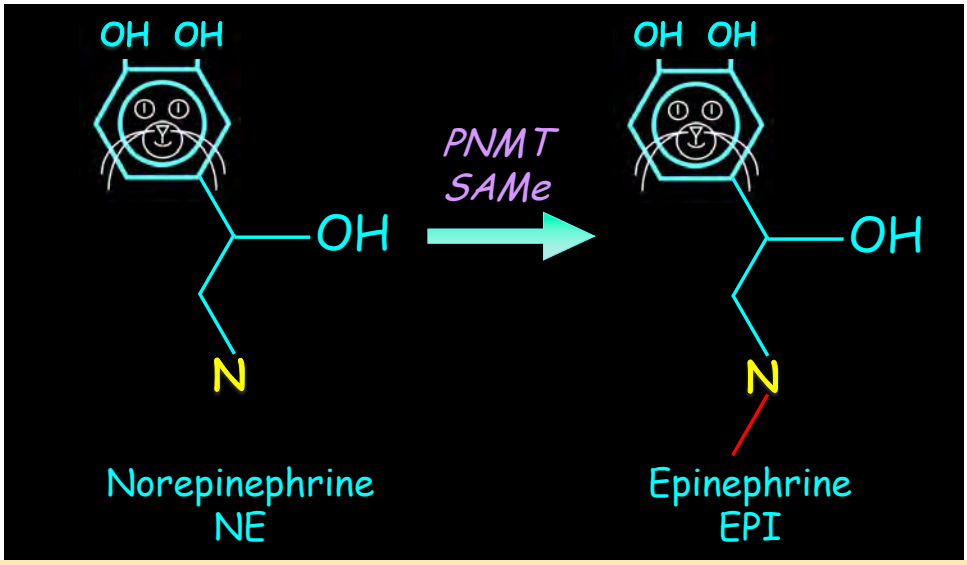


Fig. 77: Conversion of NE to EPI via PNMT. *The enzyme phenylethanolamine-N-methyltransferase (PNMT) catalyzes the conversion of norepinephrine (NE) to adrenaline (epinephrine, EPI) by transferring a methyl group to the terminal amine on the NE molecule. S-Adenosylmethionine (SAMe) is the methyl group donor.*

Where does the NE come from that is the substrate for PNMT? There may be two sources. One is NE that leaks from vesicles after intra-vesicular conversion of DA to NE via DBH.

A second is NE coming from uptake of NE after release of the NE from NE-producing cells. EPI-producing cells express PNMT and the cell membrane norepinephrine transporter (NET); the NE-producing cells do not. This raises the possibility that EPI can be made in the cytoplasm by PNMT acting on NE taken up into the cells via the NET.

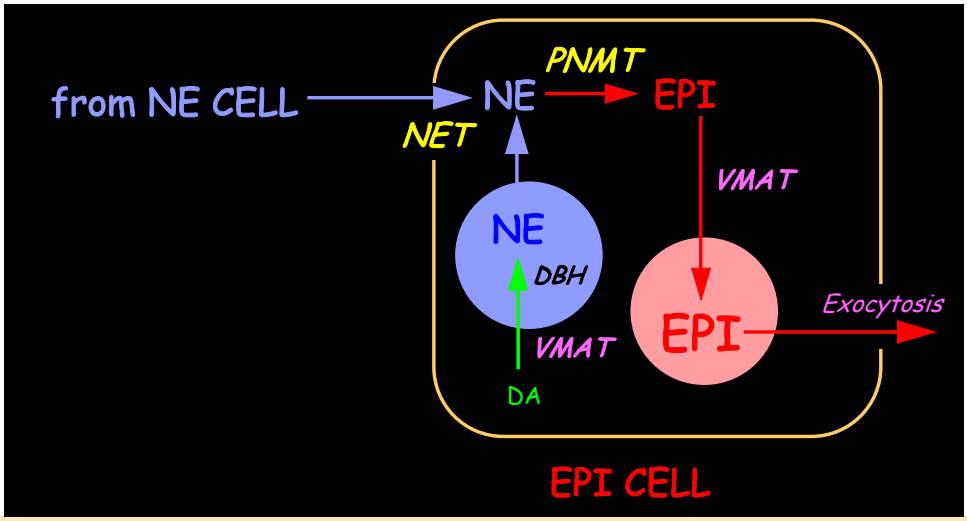


Fig. 78: Concept about adrenaline synthesis. *The concept is based on there being two types of cells in the adrenal medulla—noradrenergic and adrenergic.*

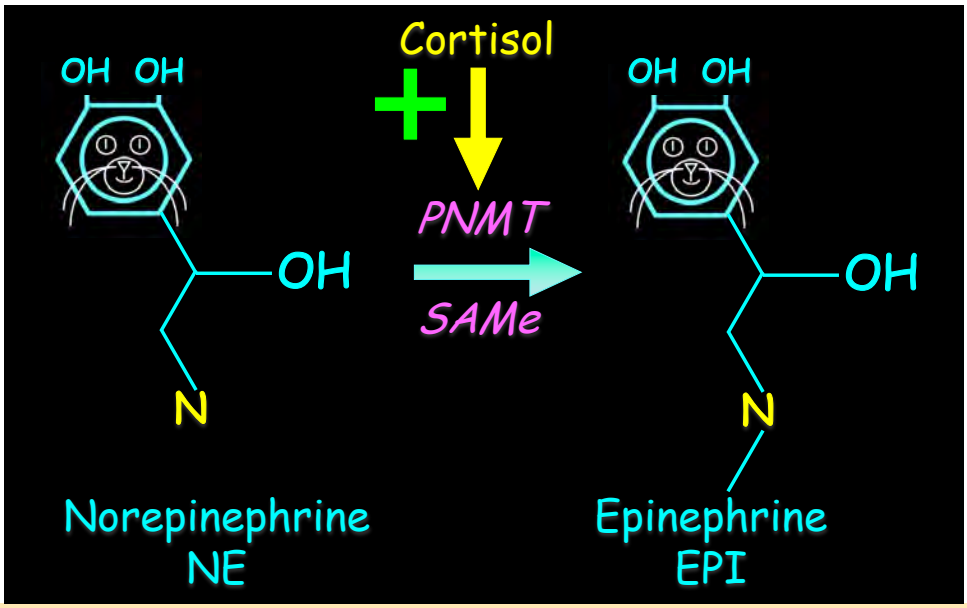


Fig. 79: Cortisol & EPI synthesis. *Cortisol coming from the adrenal cortex promotes the synthesis of adrenaline (epinephrine, EPI) in the adrenal medulla.*

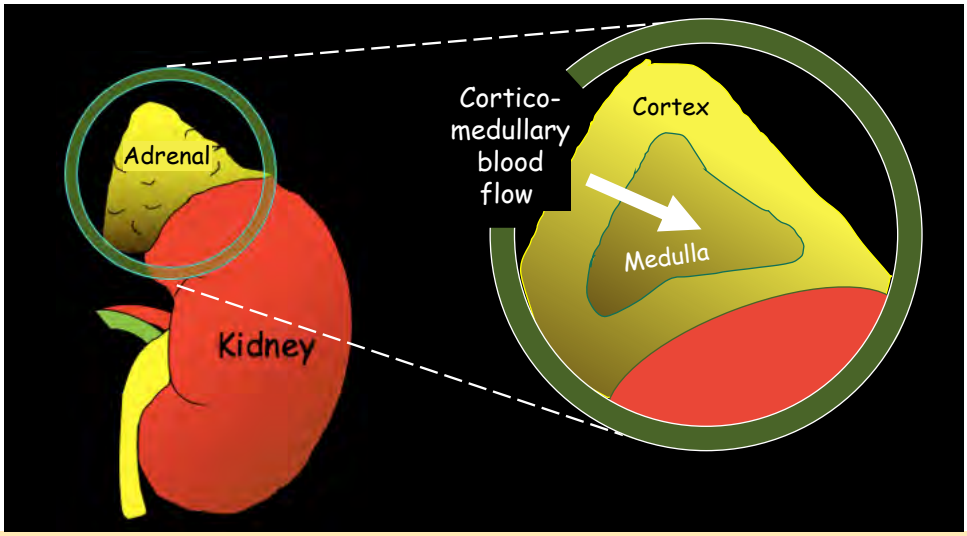


Fig. 80: The adrenal "bon-bon." *Blood flow in the adrenal gland goes from the outer cortical layer through the inner medullary layer. This means that the adrenal medullary cells are bathed continuously with blood that contains high concentrations of adrenocortical steroids such as cortisol.*

The direction of blood flow in the adrenal gland is from the outer shell, the cortex, through the inner portion, the medulla. As a result, adrenomedullary cells normally are bathed in very high concentrations of adrenocortical steroids. Cortisol, the main glucocorticoid in the human adrenal cortex, is trophic for PNMT. This trophism is one piece of evidence for functional links between the cortical and medullary layers of the adrenal "bon-bon."

The sympathetic adrenergic system (SAS) seems to be more susceptible than the sympathetic noradrenergic system (SNS) to hormonal influences. In addition to the local effects of the hormone cortisol due to the adrenal "bon-bon" arrangement, the adrenal medulla contains abundant receptors for angiotensin II (AII). AII, one of the key component biochemicals of the renin-

angiotensin-aldosterone system (RAS), evokes secretion of catecholamines from adrenomedullary cells.

CATECHOLAMINE RELEASE

The Search for the Omega Sign

A key chemical messaging step in the autonomic nervous system is release of the neurotransmitters that are stored in the

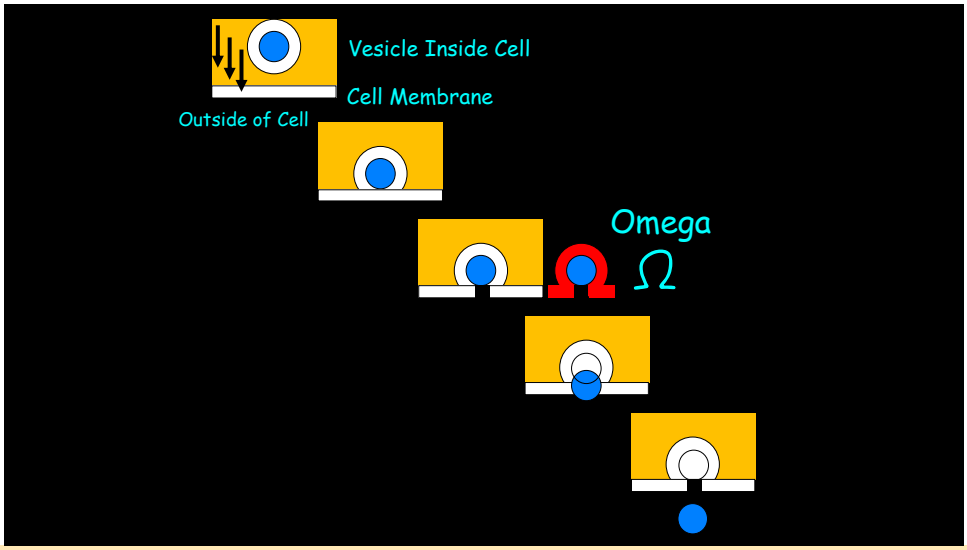


Fig. 81: Exocytosis and the omega sign. *Exocytosis is the process of neurotransmitter release.*

vesicles. The release occurs by a process called exocytosis.

According to the exocytosis theory, chemical neurotransmission results from physical movement of the bubble-like vesicles containing the neurotransmitter toward the cell membrane, fusion of the vesicle membrane with the cell membrane, pore

formation at the site of fusion of the two membranes, and entry of the contents of the vesicles into the fluid outside the cell. Among those contents is the neurotransmitter, which diffuses a short way to reach receptors on the membrane of the target cells.

One way to test the theory of exocytosis would be by direct microscopic visualization. If the vesicle membrane actually fused with the cell membrane and a hole formed at the junction, then if one looked under an electron microscope at the nerve terminal one would see tiny "omega signs." Recent highly

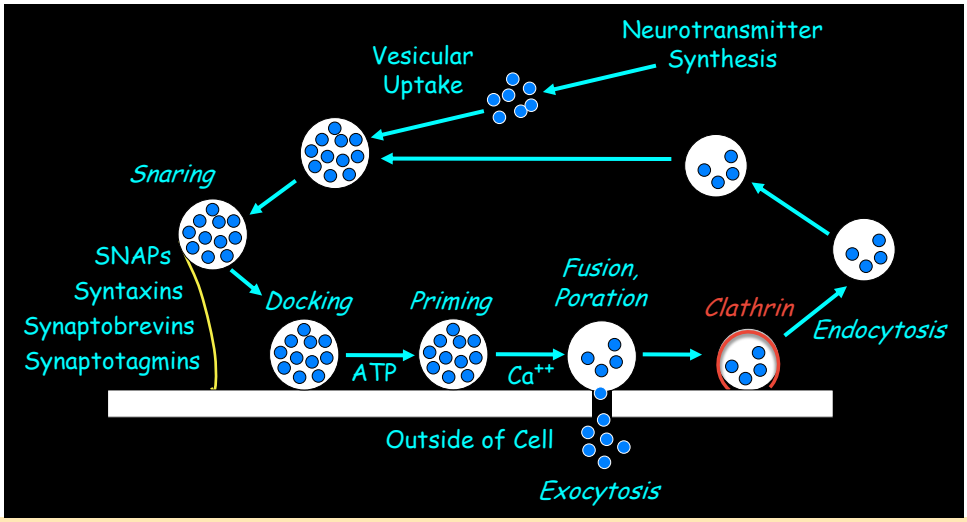


Fig. 82: The exocytosis-endocytosis cycle. *After discharging their contents by exocytosis, vesicles are recycled.*

sophisticated techniques have enabled such direct visualization; however, only a very tiny percentage of vesicles are actually found fused with the membrane surface.

The processes of vesicle movement toward the cell membrane, fusion, poration, and removal from the cell membrane (endocytosis) involve a bewildering array of proteins. A group

of proteins involved with the fusion process are called SNARE proteins (as if the vesicles were being snared and dragged to the membrane).

SNARE is short for SNAP REceptor, SNAP is short for soluble NSF attachment protein, and NSF is short for N-ethylmaleimide-sensitive factor. There are at least 35 proteins making up SNARE complexes in mammalian cells, including synaptotagmins, synaptobrevins, syntaxins, and SNAPs. The bacterial neurotoxins responsible for botulism and tetanus are thought to target SNARE proteins by preventing their assembly. The endocytotic process involves a large protein called clathrin, which coats the vesicles in a lattice-like mesh (clathrin comes from the Latin *clathratus*, meaning latticed), marking them for internalization.

Co-Transmission

Autonomic neurons and cells can store and release more than one chemical messenger. This means they can have more than one neurochemical "signature," or phenotype, suggesting the notion of biochemical "coding" in the autonomic nervous system.

It was not until the 1970s that the concept of co-transmission was proposed formally and became generally accepted. (One of the last skeptics was Sir John Eccles, who had received a Nobel Prize in 1963 for his research on mechanisms of intercellular transmission of nervous impulses). Adenosine triphosphate (ATP) has been reported to be co-released with acetylcholine, the catecholamines, and non-adrenergic, non-cholinergic

neurons of the enteric nervous system.

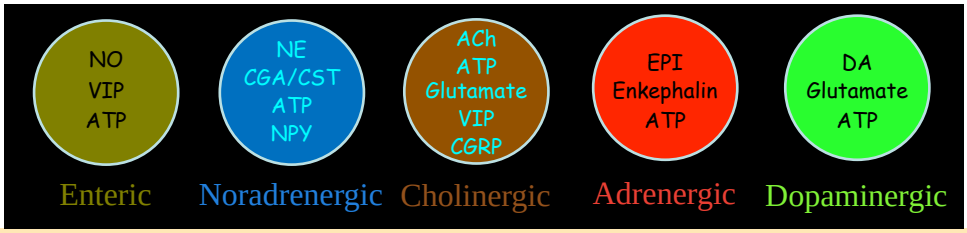


Fig. 83: Co-transmission. *More than one chemical messenger can be stored in vesicles and released by exocytosis.*

CATECHOLAMINE REUPTAKE

After release of catecholamines from nerves, the neurotransmitters undergo inactivation mainly by a conservative recycling process, in which the nerves take back up the released catecholamine. This process has been called Uptake-1.

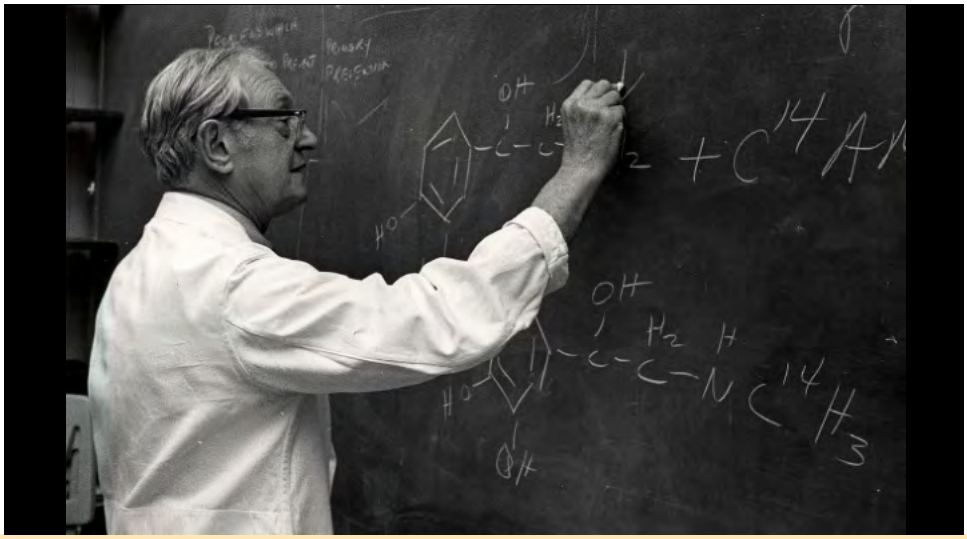


Fig. 84: Julius Axelrod (Nobel Prize, 1970). *For extra credit, what is the chemical labeled with C^{14} beneath his right elbow?*

Julius Axelrod introduced the idea that termination of the

Fig. 85: Julie Axelrod when he won a Nobel Prize. *Among the celebrants, the grinning man in the horn-rimmed glasses was Irwin J. ("Irv") Kopin. For many years Irv was my boss and mentor.*

actions of a neurotransmitter can occur by neuronal reuptake, as opposed to enzymatic degradation of the NE transmitter in the extracellular fluid (which is the fate of released acetylcholine). For this discovery Axelrod shared (with U.S. von Euler) the Nobel Prize for Physiology or Medicine in 1970. His lab at the NIH was in the same venerable Building 10 where I sit.

The neuronal reuptake process is relatively specific for the particular neurotransmitter. One might even define the type of nerve cell by the neurotransmitter it takes up. Uptake-1 involves at least two different transporters, which physically transport the neurotransmitter molecules into the cells. The transporter for norepinephrine is the cell membrane norepinephrine transporter, or NET. The transporter for

dopamine is called the dopamine transporter, or DAT.

One of the peculiarities of the functioning of these transporters is that dopamine is more avidly taken up via the NET than norepinephrine is. We exploited this neurochemical quirk in developing a form of dopamine tagged with radioactivity, to visualize sympathetic nerves in people by PET scanning, as you will read about later. The sympathetic nerves take up the radioactive dopamine via the NET.

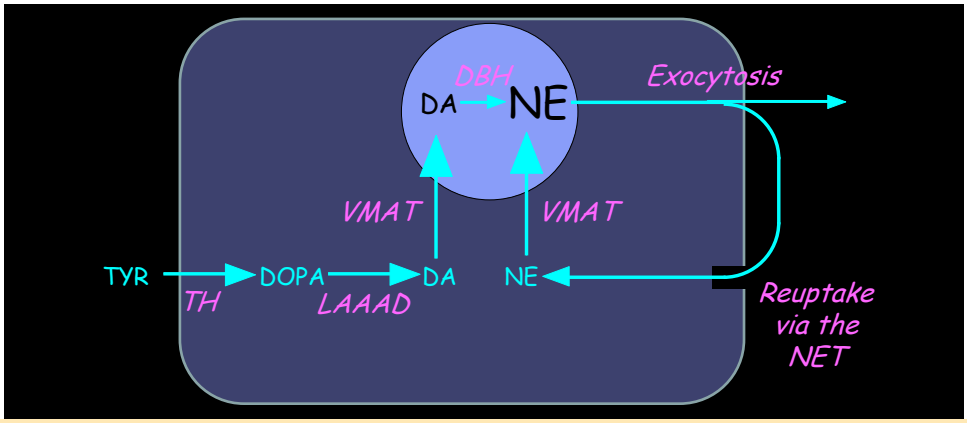


Fig. 86: Norepinephrine reuptake. *Most of released norepinephrine (NE) is taken back up into the neuronal cytoplasm by the Uptake-1 process mediated by the cell membrane norepinephrine transporter (NET). Some types of drugs interfere with norepinephrine reuptake. The most famous is cocaine.*

Cocaine administration can evoke severe heart problems, such as heart failure and sudden cardiac death, even in otherwise healthy people. A highly publicized example was that of Len Bias. Bias was a basketball star at the University of Maryland. He was drafted by the Boston Celtics, but before he ever played in the NBA he died of the cardiac toxic effects of cocaine.

Fig. 87: Len Bias. *Len Bias, a star basketball player at the University of Maryland, died of acute cocaine cardiotoxicity.*

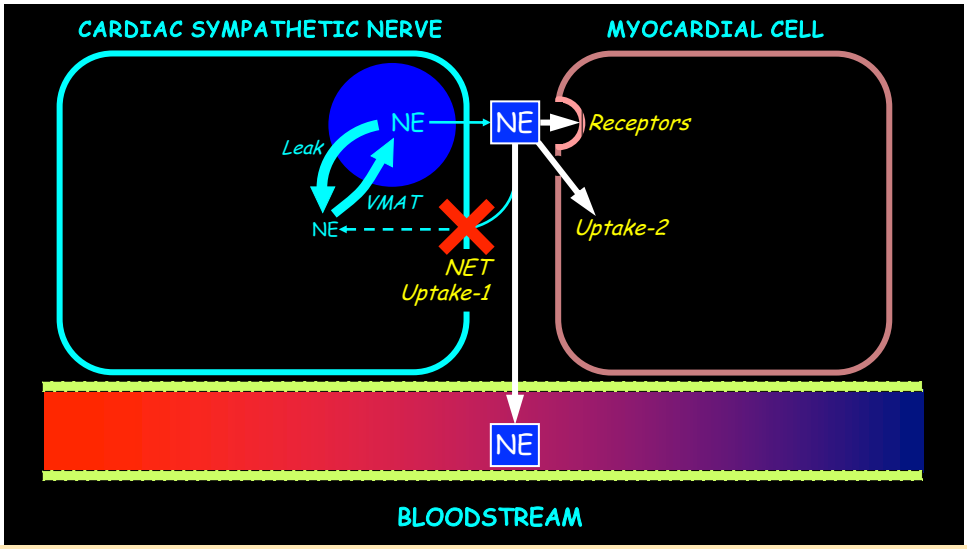


Fig. 88: Cocaine cardiotoxicity. *Cocaine blocks norepinephrine (NE) reuptake via the Uptake-1 process that is mediated by the cell membrane norepinephrine transporter (NET). This augments delivery of NE to non-neuronal cells. Because Uptake-1 is important for inactivating released NE in the heart, cocaine overdose causes death by cardiotoxicity.*

Possible mechanisms of cocaine cardiotoxicity are drastically augmented delivery of norepinephrine (NE) to receptors on myocardial cells and toxic direct effects of NE after non-neuronal uptake into the cells (Uptake-2).

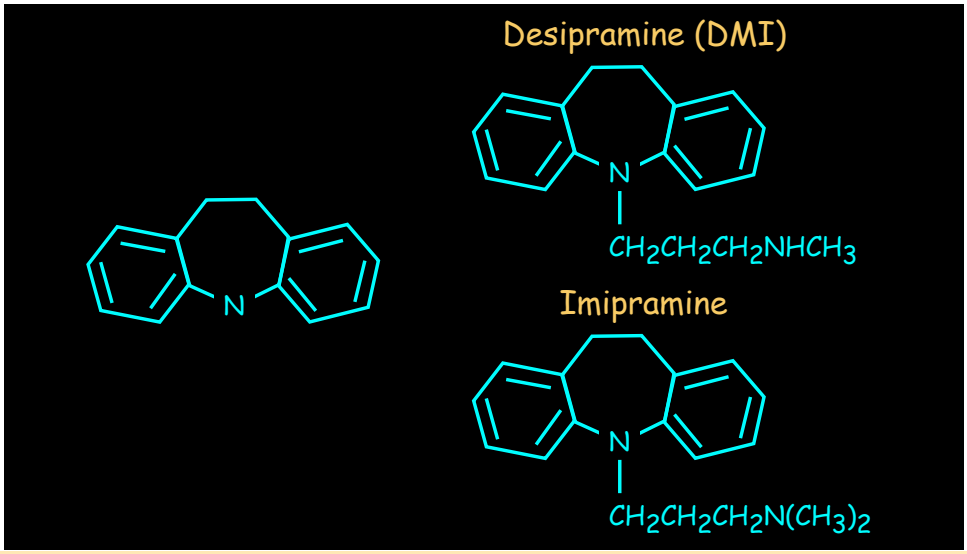


Fig. 89: Tricyclic antidepressants. *Tricyclic antidepressants (TCAs) readily enter the brain, where they inhibit neuronal reuptake of norepinephrine. They also inhibit reuptake of norepinephrine in the sympathetic noradrenergic system.*

A class of drugs called tricyclics are used clinically for depression. Some tricyclics are desipramine, imipramine, nortriptyline, and amitriptyline (brand names Norpramin, Tofranil, Pamelor, and Mylan).

Although tricyclic antidepressants inhibit Uptake-1, they also decrease sympathetic noradrenergic system outflows from the brain. As a result, they do not produce nearly as great an increase in the delivery of norepinephrine to its receptors in the heart as cocaine does.

Hypofunctional genetic mutation of the NET can occur, but this is very rare. Because of decreased ability to recycle norepinephrine, people with this type of mutation have excessive delivery of norepinephrine to its receptors in the heart in situations that activate SNS outflows. One of these situations is simply standing up. NET deficiency constitutes a rare cause of postural tachycardia syndrome (POTS), in which an inability to tolerate prolonged standing (orthostatic intolerance) is coupled with an excessive heart rate response to standing (postural tachycardia). POTS from NET deficiency is also associated with a tendency to panic.

Small amounts of norepinephrine are detectable in the plasma, and measurement of plasma norepinephrine is a common test in the evaluation of dysautonomias that are thought to involve the sympathetic noradrenergic system. Because of extensive neuronal reuptake of released norepinephrine, only a small proportion of released norepinephrine makes its way to the bloodstream unchanged. Blockade of the NET increases the plasma norepinephrine level for a given amount of release.

The norepinephrine recycling process is completed by translocation of the norepinephrine from the cytoplasm into storage vesicles by the VMAT. Because of the NET, the concentration of norepinephrine in the cytoplasm normally exceeds by many-fold that in the extracellular fluid outside sympathetic neurons; and because of the VMAT, the concentration of norepinephrine in the vesicles normally exceeds by many-fold that in the cytoplasm. Since the NET and VMAT act in series, the concentration of norepinephrine in the storage vesicles normally is several thousand times the

concentration in the extracellular fluid. Now that's recycling!

CATECHOLAMINE METABOLISM

Although catecholamines are recycled quite efficiently in sympathetic nerves, a small percent of the catecholamine in the cytoplasm undergoes metabolic breakdown via a process that is accelerated (catalyzed) by the enzyme monoamine oxidase (MAO). MAO plays a key role—as shown in the diagram a central role—in the metabolism of the catecholamines dopamine and norepinephrine.

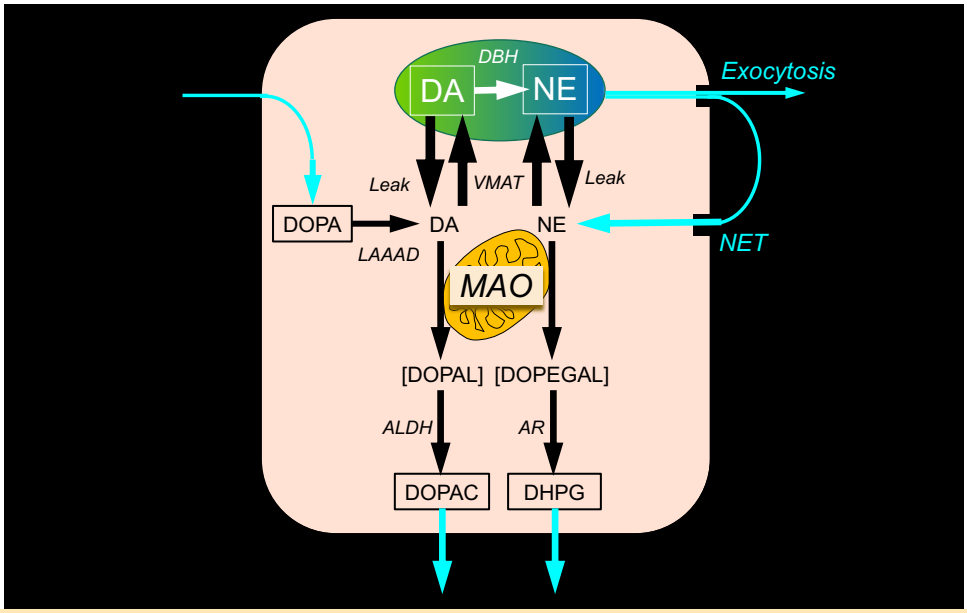


Fig. 90: MAO & the intra-neuronal metabolism of catecholamines. *Monoamine oxidase (MAO) plays a central role in the metabolism of dopamine and norepinephrine.*

MAO is found in the outer membrane of the mitochondria, the cell's energy plants.

In the brain MAO plays a key role in mood, and drugs that inhibit MAO are effective anti-depressants.

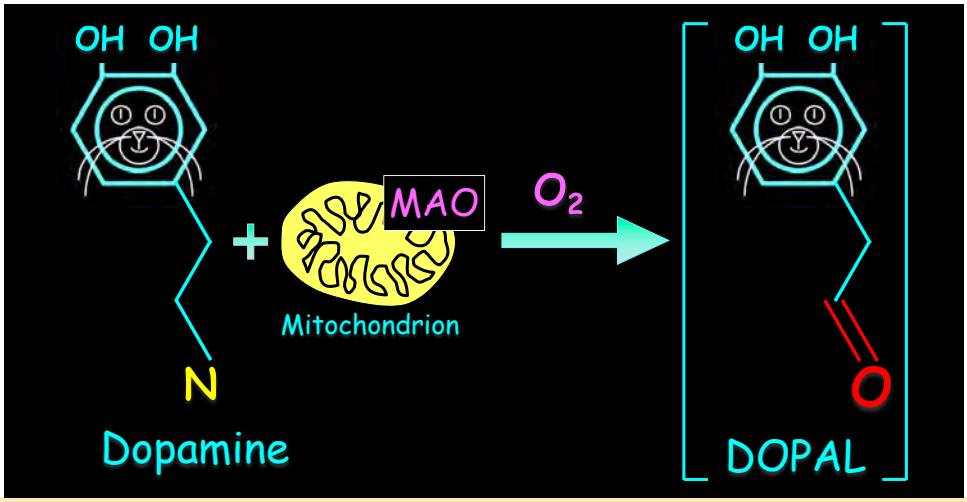


Fig. 91: DA metabolism to DOPAL. *Monoamine oxidase (MAO) acting on dopamine (DA) produces the catecholaldehyde, DOPAL.*

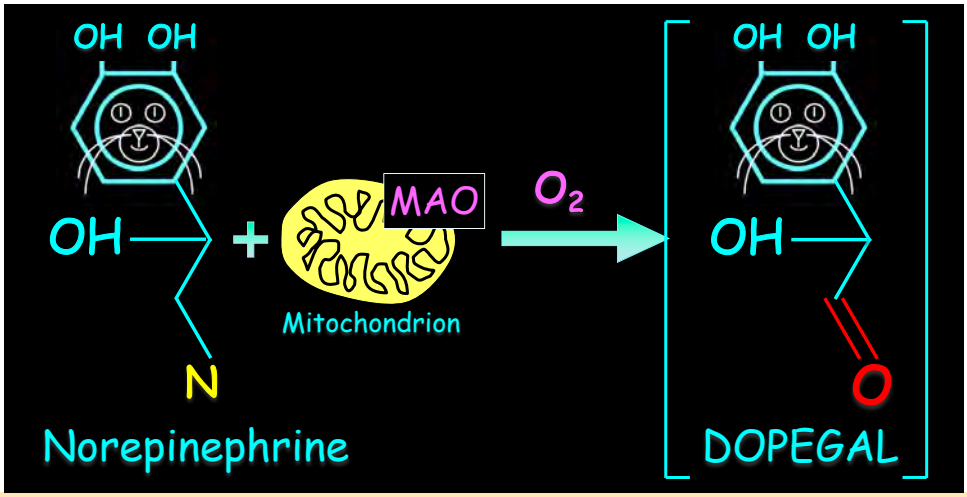


Fig. 92: NE metabolism to DOPEGAL. *The immediate product of monoamine oxidase (MAO) acting on norepinephrine (NE) is the catecholaldehyde, DOPEGAL.*

There are two forms of MAO, MAO-A and MAO-B. The main form in sympathetic nerves is MAO-A. MAO catalyzes the conversion of dopamine to an aldehyde called DOPAL (an abbreviation for 3,4-dihydroxyphenylacetaldehyde). Analogously, MAO catalyzes the conversion of norepinephrine to an aldehyde called DOPEGAL (an abbreviation for 3,4-dihydroxyphenylglycolaldehyde).

As for all aldehydes formed in cells of the body, DOPAL and DOPEGAL are toxic. Their toxicity is the basis for the "catecholaldehyde hypothesis" for the loss of catecholamine-producing neurons that characterizes neurodegenerative diseases such as Parkinson's disease, a topic that is covered in a section later.

Bad Seed

Genetic deficiency of MAO-A causes severe hyperactivity and aggressiveness, in mice and men. I use the phrase "in mice and men" here for a reason. Mice with genetic MAO-A deficiency are impulsively aggressive. A Dutch family with inherited decreased MAO-A activity attained notoriety for antisocial behavior, murder, and violent rape. In this family with "bad seed" from mutation of the MAO-A gene, only males have the disorder, and the disease skips generations.

The genes for MAO-A and MAO-B are located close to each other on the X chromosome. Since males have one X and one Y chromosome, in boys carrying a mutation of the gene encoding MAO-A on their single X chromosome, the disease is expressed. Girls have two X chromosomes; if the same

mutation occurred on one of their two X chromosomes, the other chromosome would still encode MAO-A, and the disease would not be expressed (they would be asymptomatic carriers).

When NOT to attend a wine and cheese party

No discussion of MAO would be complete without wine and cheese.

Red wine and hard cheeses contain large amounts of a chemical called tyramine. Tyramine is an indirectly acting sympathomimetic amine. That is, it doesn't exert effects by itself but increases release of norepinephrine from sympathetic nerves. The released norepinephrine increases the blood pressure and the force of the heartbeat.

Ordinarily, relatively little of ingested tyramine makes its way to the bloodstream because of an effective "gut-blood barrier," which includes a variety of enzymes, one of which is MAO. Patients taking an MAO inhibitor have a relatively permissive gut-blood barrier for dietary substances that normally would be broken down by MAO in the gut or liver. In the setting of MAO inhibition, dietary tyramine can penetrate the gut-blood barrier and reach sympathetic nerves. Once inside the nerves, tyramine in the cytoplasm gets taken up into the vesicles by way of the vesicular monoamine transporter (VMAT), and inside the vesicles tyramine augments leakage of norepinephrine from the vesicles, possibly by alkalinizing the vesicles and decreasing the hydrogen ion gradient required for concentrating norepinephrine in the vesicles.

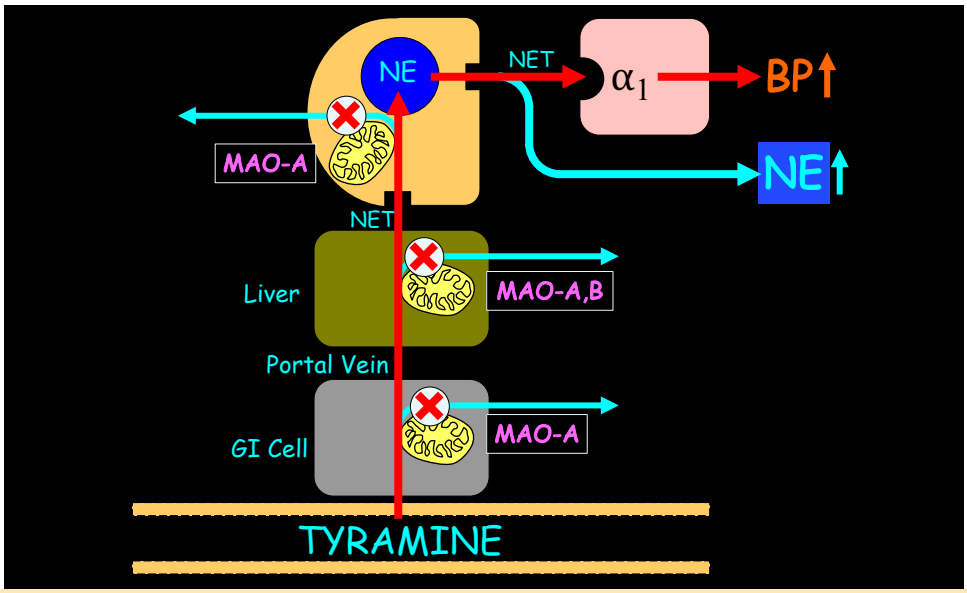


Fig. 93: The "cheese effect." *In the setting of MAO inhibition, tyramine in cheese can displace norepinephrine from sympathetic nerves, resulting in a paroxysmal increase in blood pressure.*

Norepinephrine then builds up in the cytoplasm and can travel backward through the NET to reach the fluid surrounding the cells, or it can exit the cell from vesicles that are fused with the membrane surface and have the "omega sign" opening them to the extracellular fluid. By these mechanisms, norepinephrine is delivered to its receptors on cardiovascular cells, and the blood pressure and the force of the heartbeat increase.

In people taking an MAO inhibitor, such as for depression, ingestion of tyramine can produce a paroxysmal increase in blood pressure or evoke a dangerously abnormal heart rhythm. This is why if you were taking an MAO inhibitor for depression, you wouldn't want to attend a wine and cheese party.

It is thought that the enzymatic gut-blood barrier for tyramine depends mainly on MAO-A. Theoretically, the "cheese effect" would apply only to drugs that inhibit MAO-A or inhibit both forms of MAO. In particular, selegiline (also called l-deprenyl, brand name Eldepryl™) and rasagiline (brand name Azilect™), which are used to treat Parkinson's disease, are relatively selective MAO-B inhibitors; they are much less likely to cause a cheese effect than are drugs that inhibit MAO-A.

DOPAC and DHPG

MAO acting on cytoplasmic dopamine yields DOPAL, and MAO acting on cytoplasmic norepinephrine yields DOPEGAL.

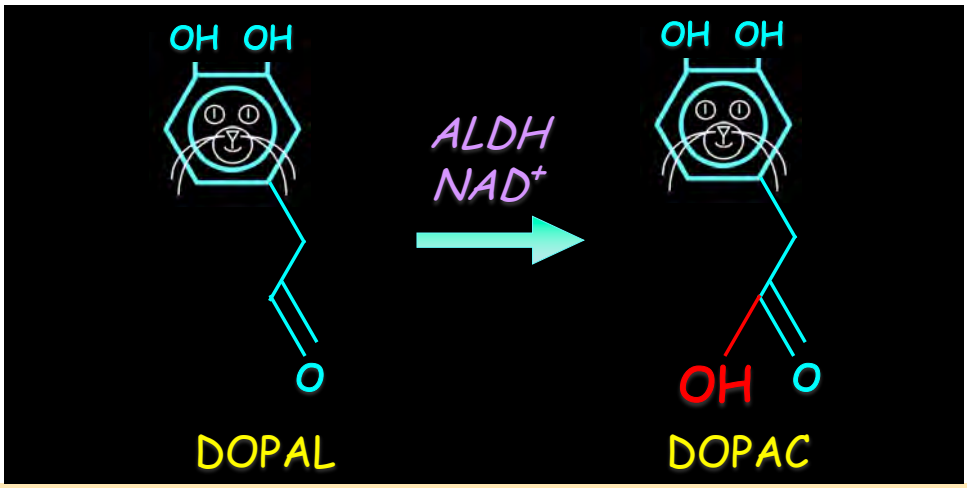


Fig. 94: ALDH & conversion of DOPAL to DOPAC. *The enzyme aldehyde dehydrogenase (ALDH) catalyzes the conversion of DOPAL to DOPAC. NAD^+ is a required co-factor for ALDH.*

Both catecholaldehydes are toxic but normally are detoxified by another metabolic step. The enzyme aldehyde dehydrogenase

(ALDH) converts DOPAL to the acidic catechol, DOPAC (an abbreviation for 3,4-dihydroxyphenylacetic acid). DOPAC is the main intra-neuronal metabolite of dopamine.

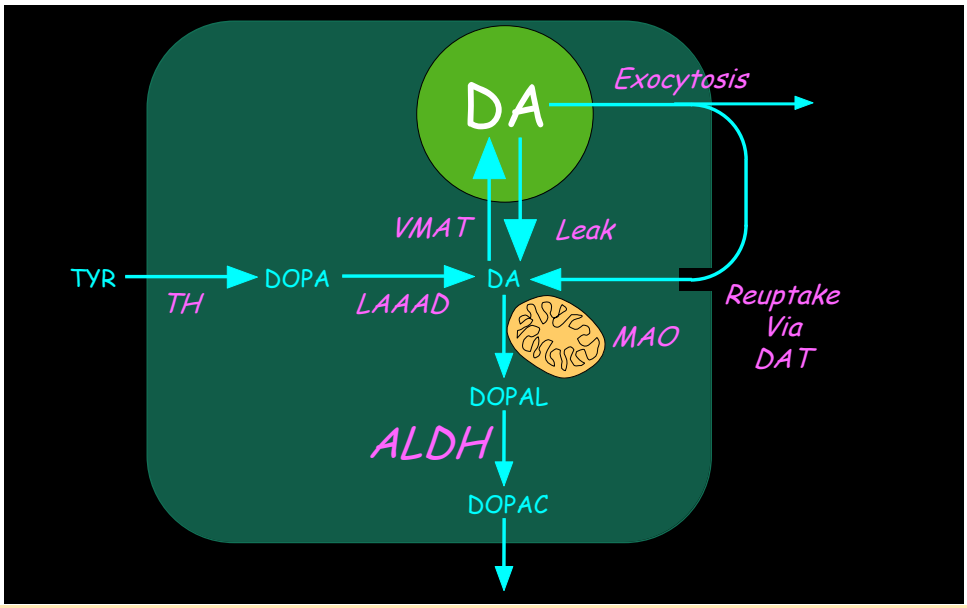


Fig. 95: Role of ALDH in dopamine metabolism. *Aldehyde dehydrogenase (ALDH) catalyzes the conversion of DOPAL to DOPAC, the main intra-neuronal metabolite of dopamine.*

DOPAC is the main intra-neuronal metabolite of dopamine. As an acid, DOPAC is actively extruded from the neuron. ALDH therefore is a key enzyme for keeping DOPAL levels low in the neuronal cytoplasm. In humans there are 19 genes or pseudogenes for ALDH.

The oxidized form of nicotinamide adenine dinucleotide (NAD^+) is a required co-factor for ALDH. NAD^+ is produced in mitochondria as result of the Complex 1 in the mitochondrial electron “bucket brigade” that results in ATP generation. Drugs such as rotenone, which inhibits Complex 1, indirectly inhibit

ALDH activity; a consequence is DOPAL accumulation.

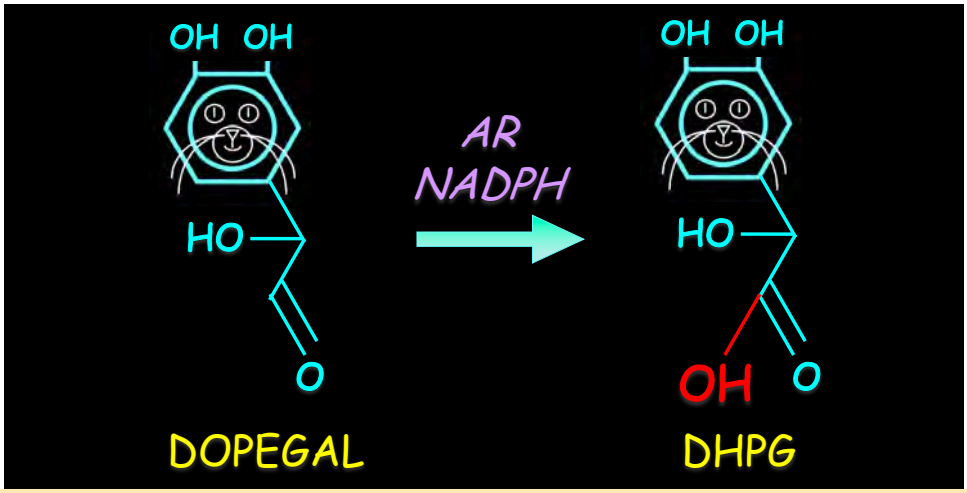


Fig. 96: AR & conversion of DOPEGAL to DHPG. *Aldehyde/aldose reductase (AR) catalyzes the conversion of DOPEGAL to DHPG, the main intra-neuronal metabolite of norepinephrine.*

The enzyme aldehyde reductase (which also acts as aldose reductase) converts the catecholaldehyde 3,4-dihydroxyphenylglycolaldehyde (mercifully abbreviated DOPEGAL) to the catechol glycol, 3,4-dihydroxyphenylglycol (DHPG). There are many enzymes that taken together are ARs.

Just as DOPAC is the main intra-neuronal metabolite of dopamine, DHPG is the main intra-neuronal metabolite of norepinephrine. DHPG is a glycol (somewhat resembling the body sugar, glucose) that easily passes through cell membranes and enters the circulation. Irv Kopin discovered DHPG.

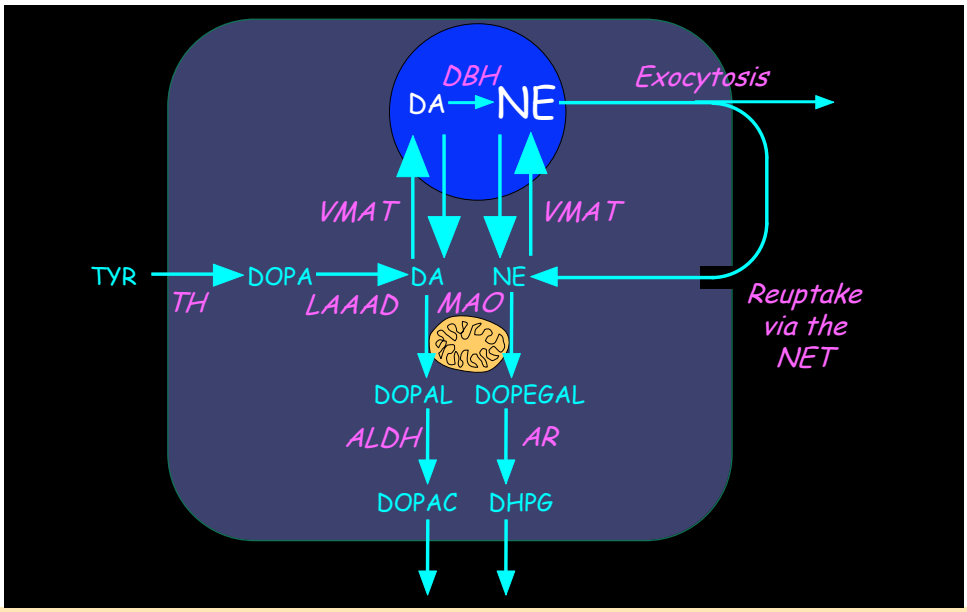


Fig. 97: NE synthesis & neuronal fate. *DOPAC is produced from MAO acting on cytoplasmic dopamine and DHPG from MAO acting on cytoplasmic norepinephrine.*

Fig. 98: Julie Axelrod & Irv Kopin. *(Compare with Fig. 83 from about a quarter century before this photo.) The two intellectual giants were pioneers of catecholamine metabolism. Their zeal for getting the facts right and then trying to understand them by debate come through in this iconic photo.*

A section later emphasizes the clinical utility of measuring norepinephrine and DHPG simultaneously in the assessment of patients with dysautonomias.

The Ends of the Lines

Non-neuronal cells contain the enzyme catechol-O-methyltransferase, or COMT, which Julie Axelrod discovered. COMT transfers a methyl group to DOPAC, with S-adenosyl-methionine (SAMe) serving as the methyl group donor, to form homovanillic acid (HVA). HVA is the main end-product of dopamine metabolism.

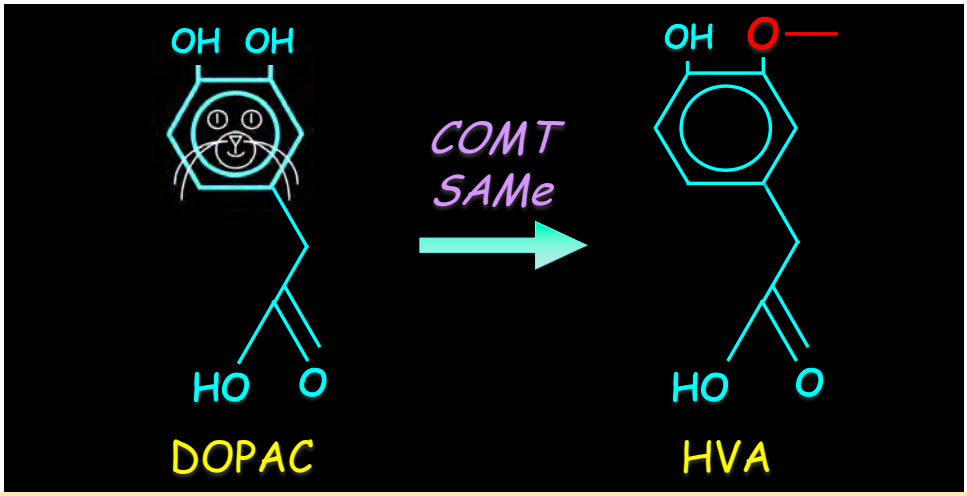


Fig. 99: HVA production from DOPAC. *DOPAC is converted to homovanillic acid (HVA) by the enzyme catechol-O-methyltransferase (COMT).*

There are two main end-products of norepinephrine metabolism—MHPG and VMA. MHPG is an abbreviation for 3-methoxy-4-hydroxyphenylglycol, and VMA is an abbreviation for vanillylmandelic acid. Circulating DHPG is

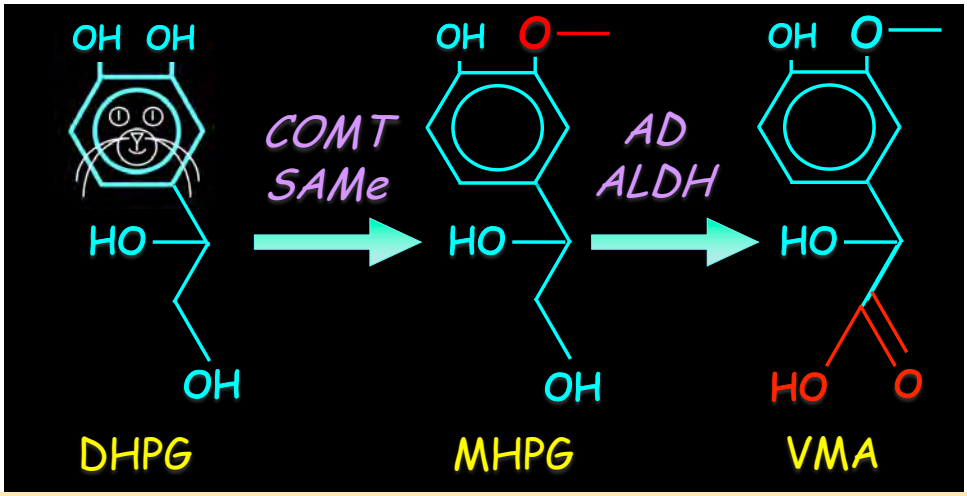


Fig. 100: End-products of norepinephrine metabolism. *DHPG is converted to MHPG via catechol-O-methyltransferase (COMT). In the liver MHPG is converted to vanillylmandelic acid (VMA).*

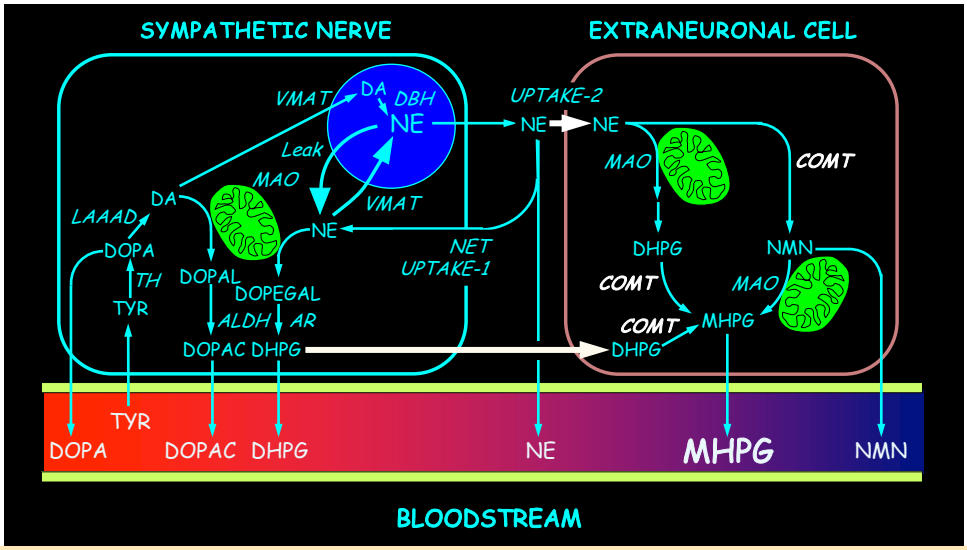


Fig. 101: Overview of NE synthesis & metabolism. *The O-methylated metabolites of NE are produced in non-neuronal cells after uptake of NE and DHPG.*

converted extensively to MHPG by COMT. In the liver much of MHPG is converted to VMA.

Norepinephrine Turnover

The rate of synthesis of norepinephrine in a tissue is normally balanced by the rate of loss of norepinephrine and all its metabolites from the tissue (turnover).

One might think that the main determinant of tissue norepinephrine turnover is exocytotic release with escape of reuptake via the NET.

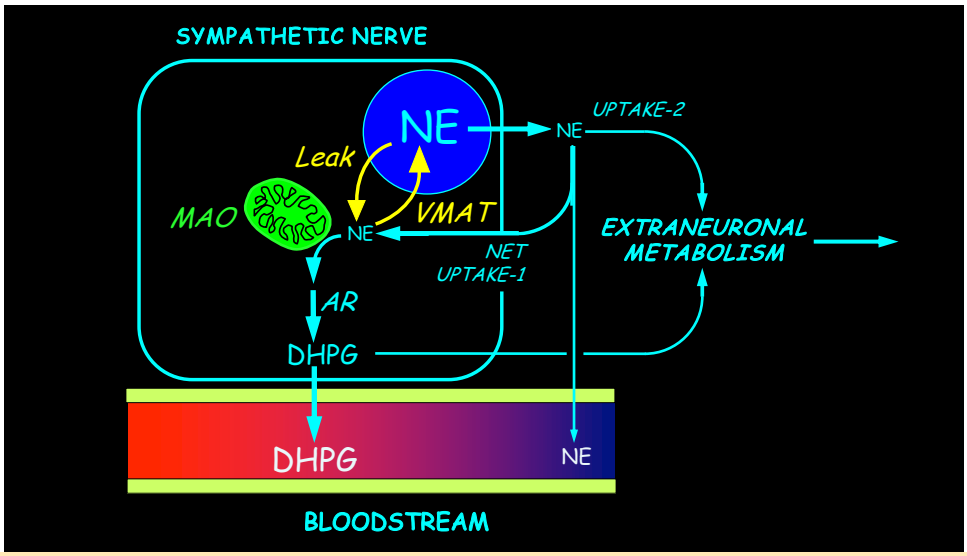


Fig. 102: NE turnover: *Under resting conditions most of tissue norepinephrine (NE) turnover is from net leakage from vesicles into the cytoplasm, followed by enzymatic metabolism to DHPG.*

In fact, under resting conditions most of norepinephrine turnover is from net leakage from vesicles into the cytoplasm. There are two general reasons for this. First, the NET is so efficient in taking released norepinephrine back up into the nerve, relatively little of released norepinephrine escapes

neuronal reuptake.

Second, there is a tremendously high rate of vesicular uptake of NE via the VMAT. There is a correspondingly high rate of passive leakage into the cytoplasm. The enzymatic sequence of MAO and AR acting on cytoplasmic norepinephrine then results in DHPG formation. As a glycol, DHPG readily passes through the cell membrane and is lost from the tissue.

Ingesting alcohol (ethanol) competes with MHPG for alcohol dehydrogenase (AD) in the liver, and this increases the amount of MHPG with respect to VMA (a phenomenon discovered by Irv Kopin).

Adrenomedullary cells express COMT, whereas sympathetic nerves and catecholamine neurons in the central nervous system do not. As a result, adrenaline in the cytoplasm of adrenomedullary cells can be converted to metanephrine, and norepinephrine can be converted to normetanephrine. Because of the ongoing leakage of catecholamines from the vesicles into the cytoplasm, in the adrenomedullary cells metanephrine and normetanephrine are being made all the time, even in the absence of catecholamine release. This explains why plasma levels of metanephrines (unconjugated normetanephrine and metanephrine) are sensitive indices of pheochromocytoma.

Dopamine Surprises

Most of the synthesis and metabolism of dopamine in humans takes place not in the brain or in the autonomic nervous system—in fact not in nerves at all—but in non-neuronal cells

of the gut. The functions and regulation of this non-neuronal dopamine system are poorly understood.

Outside the brain, dopamine appears to be an "autocrine/paracrine" substance, produced in, released from, and acting locally on the same or nearby cells. Concentrations of dopamine in these organs have little to do with local nerves. In evolutionary terms, dopamine systems seem to date from before the time of nerve networks or hormones.

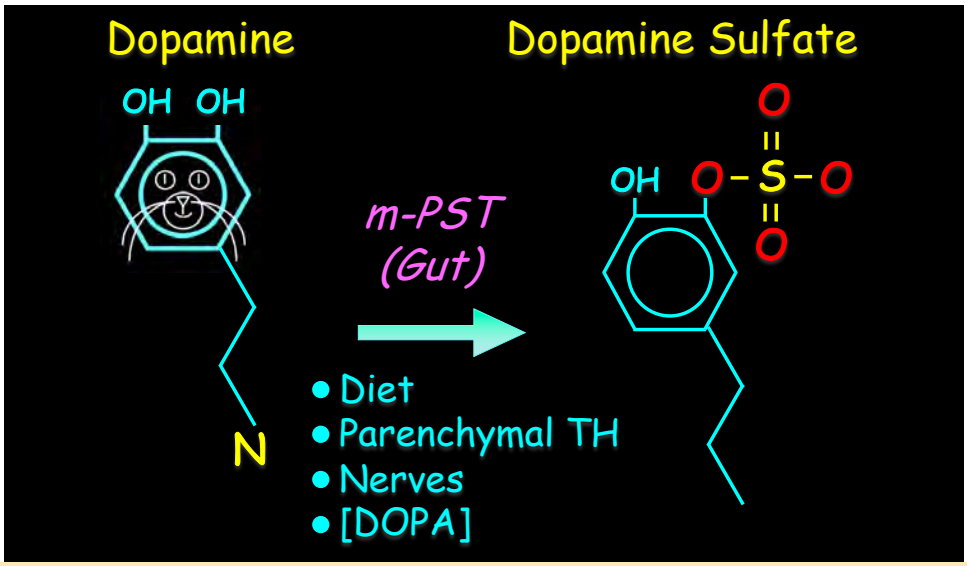


Fig. 103: DA sulfoconjugation. *Most of circulating dopamine is in the form of dopamine sulfate.*

Another surprising fact about dopamine metabolism is that there is a very large amount of DOPAC in the urine—far more than can be accounted for by filtration of DOPAC in the plasma reaching the kidneys. Most of the dopamine, and probably most of the DOPAC, in the urine comes from uptake and decarboxylation of circulating DOPA by non-neuronal cells in the kidneys, in the renal DOPA-dopamine autocrine/paracrine

system.

Virtually all of the dopamine in the plasma exists not in free form but as a conjugated form—dopamine sulfate. The conjugation takes place in the gut via an enzyme called monoamine-preferring phenolsulfotransferase (mPST).

Spontaneous Oxidation

Catecholamines in aqueous solution are extremely susceptible to oxidation. Over the course of hours, a clear solution of dopamine takes on a tan color, and by the next day there is a black powdery precipitate.

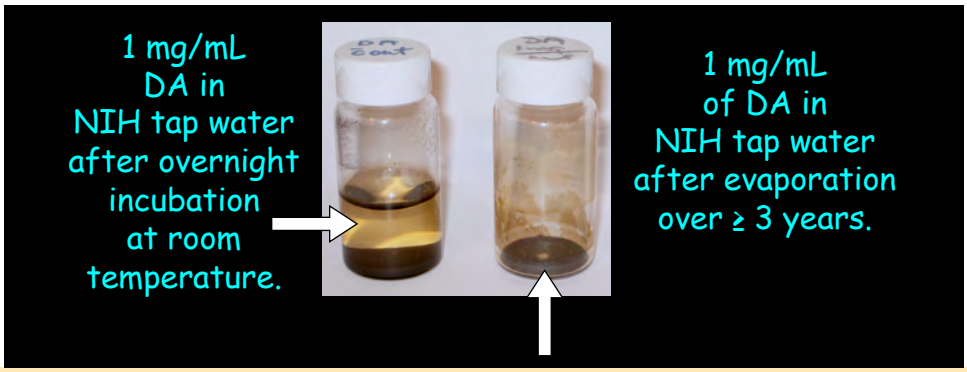


Fig. 104: Oxidation of dissolved dopamine. *Dissolved dopamine oxidizes spontaneously, forming a tan-colored solution and coating any surface with a tan stain. Polymerization of oxidation products of dopamine produces a black powder, melanin.*

This is why a tan color indicates that an EpiPen has expired and should be replaced.

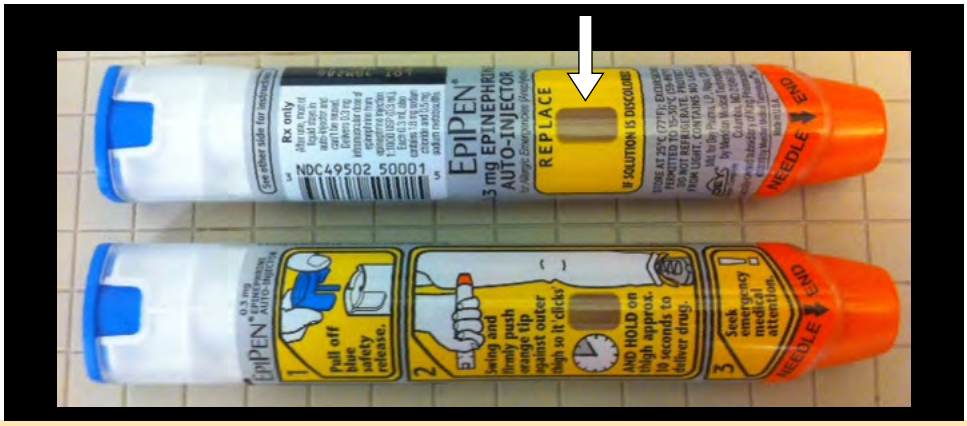


Fig. 105: Expired EpiPen. *The tan color indicates oxidation of the adrenaline, so the EpiPen should be replaced.*

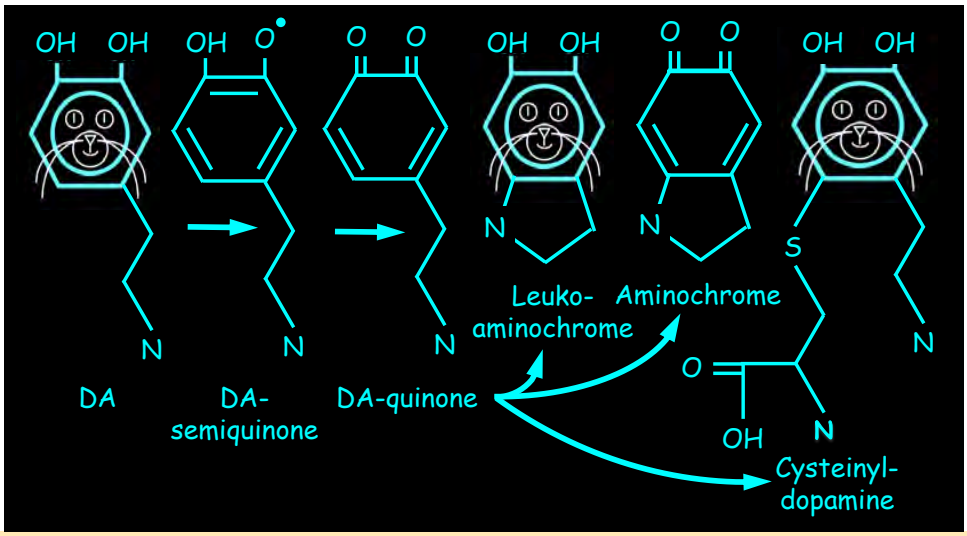


Fig. 106: Dopamine oxidation products. *Dopamine oxidizes spontaneously to dopamine-quinone and then to a variety of oxidation products.*

In general, dopamine in the neuronal cytoplasm has three possible fates. The first and main fate is vesicular uptake, which is mediated by the VMAT. The second is oxidative deamination catalyzed by MAO to form DOPAL, followed by conversion of DOPAL to DOPAC via ALDH.

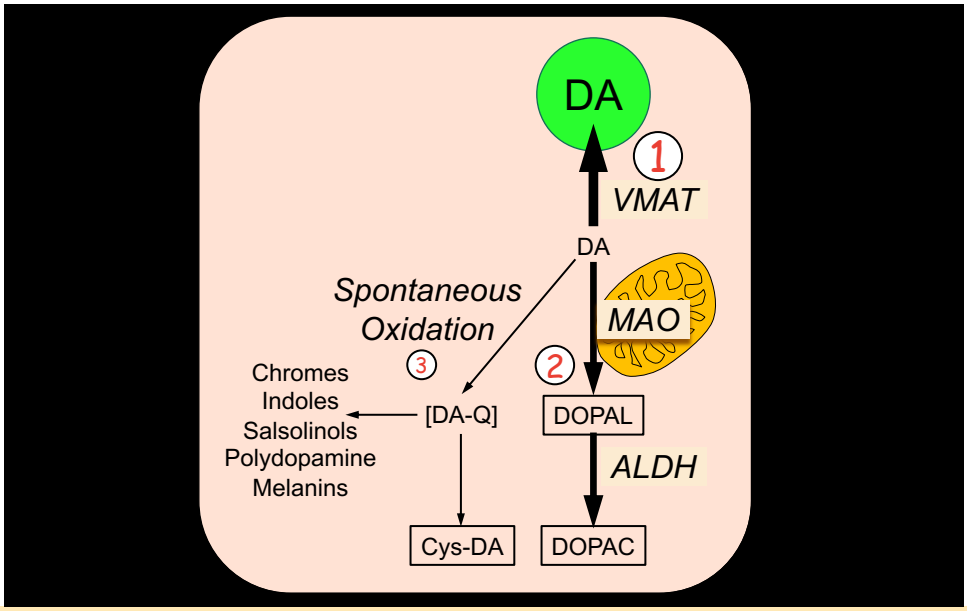


Fig. 107: Three fates of cytoplasmic dopamine. *(1) The main fate of cytoplasmic dopamine (DA) is uptake into vesicles via the vesicular monoamine transporter (VMAT). (2) The second fate is the enzymatic sequence of monoamine oxidase (MAO) and aldehyde dehydrogenase (ALDH). (3) Cytoplasmic DA can oxidize spontaneously to DA-quinone (DA-Q), which leads to a variety of oxidation products. Cytoplasmic DA levels therefore are very low.*

The third fate is spontaneous oxidation to form dopamine semi-quinone and dopamine-quinone (DA-Q) and then chromes, indoles, isoquinolines, and melanins. Given the alternatives of oxidizing spontaneously vs. oxidizing enzymatically, it stands to reason that the enzymatic route to form DOPAL would be preferred. Because of these processes, cytoplasmic DA concentrations are very low.

5-S-Cysteinyldopamine (Cys-DA) is formed from the reaction of dopamine-quinone with the amino acid cysteine (which can

be formed from enzymatic cleavage of the 3-amino acid peptide glutathione). A small amount of Cys-DA is found normally in human cerebrospinal fluid (CSF). CSF-DA levels provide a neurochemical measure of the spontaneous oxidation of DA in the central nervous system.

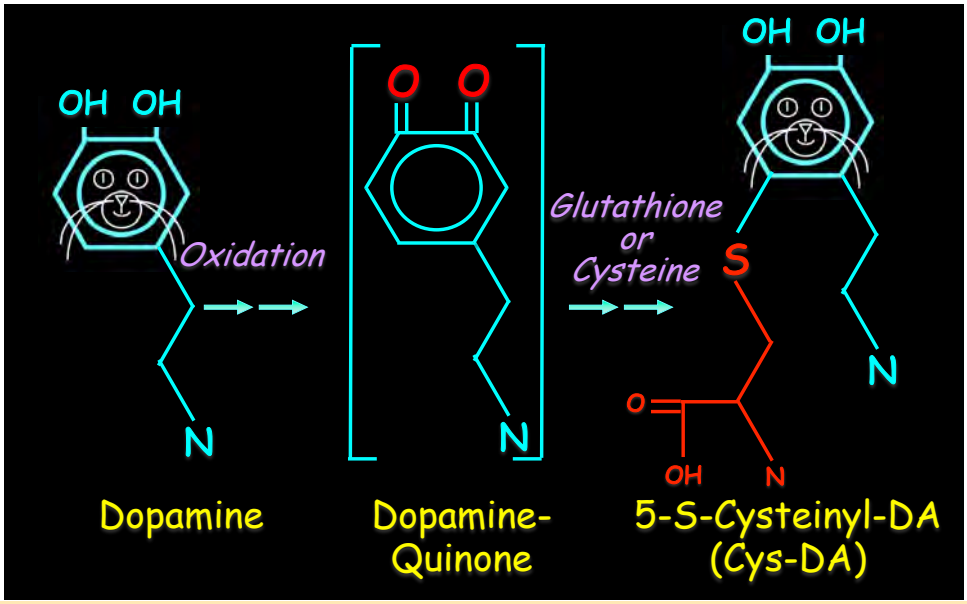


Fig. 108: Cysteinyldopamine. *5-S-Cysteinyldopamine (Cys-DA) is formed from spontaneous oxidation of dopamine, followed by reaction with cysteine (which can be generated from glutathione).*

MELANINS

When catechols such as DOPA and dopamine oxidize spontaneously, they form quinones. DOPA quinone and dopamine quinone are unstable and tend to polymerize to form large compounds called melanins.

Melanin comes from the Greek word for “black.”

Neuromelanin is produced in the cytoplasm from the spontaneous oxidation of dopamine. Loss of black pigment in the substantia nigra (from the Latin for "black substance") is a pathologic hallmark of Parkinson's disease, probably because of the loss of dopaminergic neurons that contain neuromelanin.

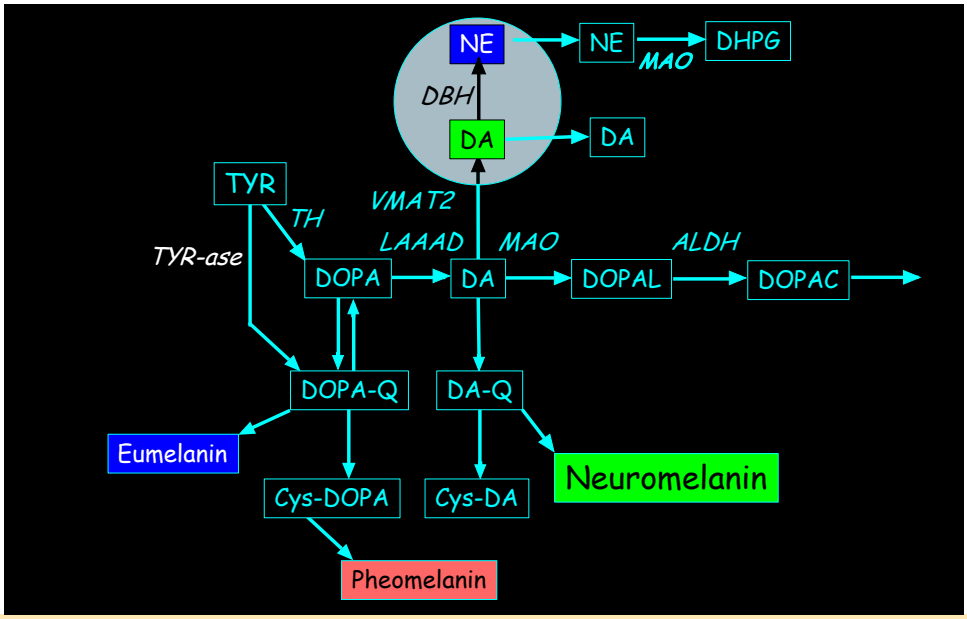


Fig. 109: Melanins. *Melanins are pigmented polymers formed from the oxidation of catechols such as DOPA and dopamine.*

SUMMARY OF CATECHOLAMINE SYNTHESIS & METABOLISM

In summarizing catecholamine synthesis and metabolism there are a few general principles to have in mind.

First, dopamine and norepinephrine have a single source, DOPA.

Second, dopamine is made in the cytoplasm, whereas norepinephrine is made in the vesicles.

Third, released norepinephrine is recycled by uptake into the cytoplasm via the NET followed by uptake into the vesicles via the VMAT.

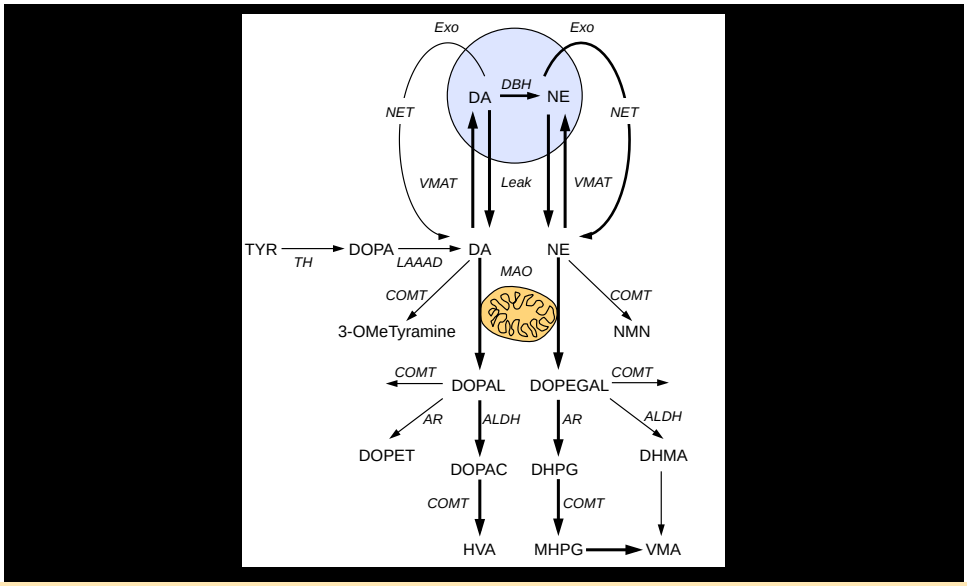


Fig. 110. Overview of catecholamine synthesis and metabolism in the sympathetic noradrenergic system.

Fourth, in healthy people, the main determinant of catecholamine turnover under resting conditions is not release by exocytosis followed by extra-neuronal metabolism but rather vesicular leakage followed by MAO.

Fifth, as depicted in the diagram above, MAO plays a central role in catecholamine metabolism. Virtually all of neuronal catecholamine metabolism occurs via MAO.

Finally, end-products of catecholamine metabolism are formed

in the gut and liver.

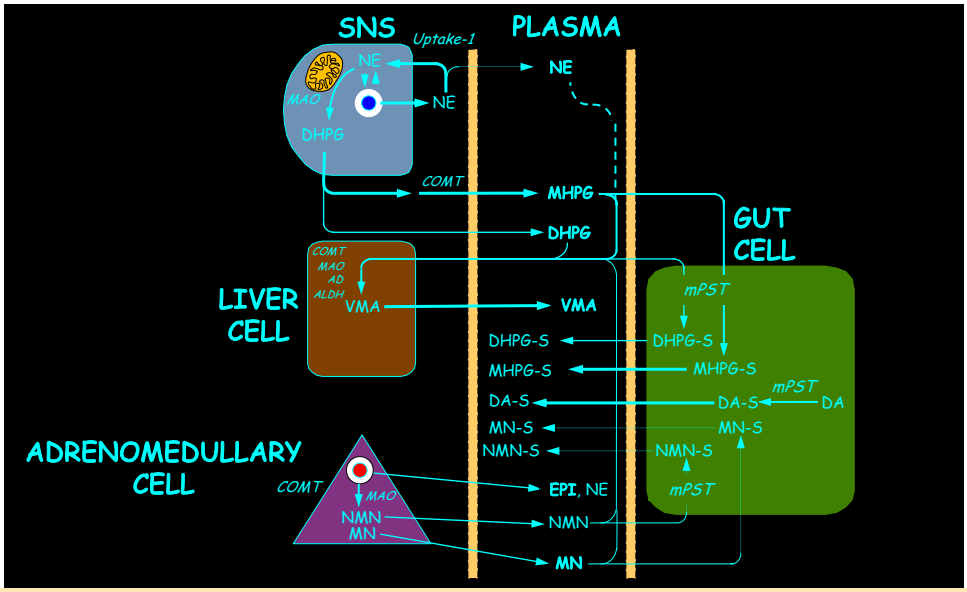


Fig. 111: Overview of plasma catecholamines and their metabolites. *The levels are determined complexly and involve sympathetic nerves, adrenomedullary cells, the liver, and the gut.*

The plasma of healthy people contains an abundance of catechols and catecholamine metabolites. As discussed in a later section, simultaneous measurements of levels of these compounds can provide valuable diagnostic or pathophysiologic information.

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CATECHOLAMINE RECEPTORS

The chemical messengers of the autonomic nervous system exert their effects on body functions by way of receptors and particular "second messengers" in the target organs.

The main chemical messengers of the autonomic nervous system are acetylcholine and the catecholamines norepinephrine and epinephrine. Acetylcholine and norepinephrine are neurotransmitters, whereas epinephrine is a hormone. Dopamine outside the brain probably functions mainly as an autocrine-paracrine substance, although this area is less well understood than the neurotransmitter and hormonal systems.

Receptors are highly specialized molecules embedded in the membranes of the target cells.

The synthesis of these chemical messengers and the processes of their metabolism seem relatively simple compared to the bewildering arrays and locations of the receptors.

Most drugs used to treat dysautonomias work by way of their effects on receptors.

About the same time that U.S. von Euler identified norepinephrine as the neurotransmitter of the sympathetic nervous system (disproving Cannon's notion about adrenaline being the sympathetic neurotransmitter), Raymond P. Ahlquist

proposed an explanation for the impressively large variety of effects of the two rather simple chemicals.

Ahlquist's idea was that catecholamines differentially stimulate specific receptors—called adrenergic receptors or adrenoceptors. In 1948, he suggested that there were two types of adrenoceptors, alpha and beta. Norepinephrine would stimulate alpha adrenoceptors, the synthetic catecholamine isoproterenol would stimulate beta adrenoceptors, and adrenaline would stimulate both types of adrenoceptors.

Numerous studies, using drugs and more recently molecular genetic tools, have by now not only confirmed Ahlquist's suggestion but actually provided the molecular structures of adrenoceptors.

Fig. 112: Brian Kobilka (Nobel Prize, 2012). *Brian Kobilka received a Nobel Prize for identifying the genes encoding beta-adrenoceptors.*

For cloning the genes encoding beta-adrenoceptors and thereby

elucidating their molecular structures, Brian Kobilka shared a Nobel Prize for Chemistry in 2012.

After Ahlquist's suggestion that there were two types of adrenoceptors, alpha and beta, researchers directed their attention to development of novel treatments for diseases based on drugs that block or stimulate adrenoceptors. For the development of beta-adrenoceptor blockers, Sir James Black shared a Nobel Prize in 1988.

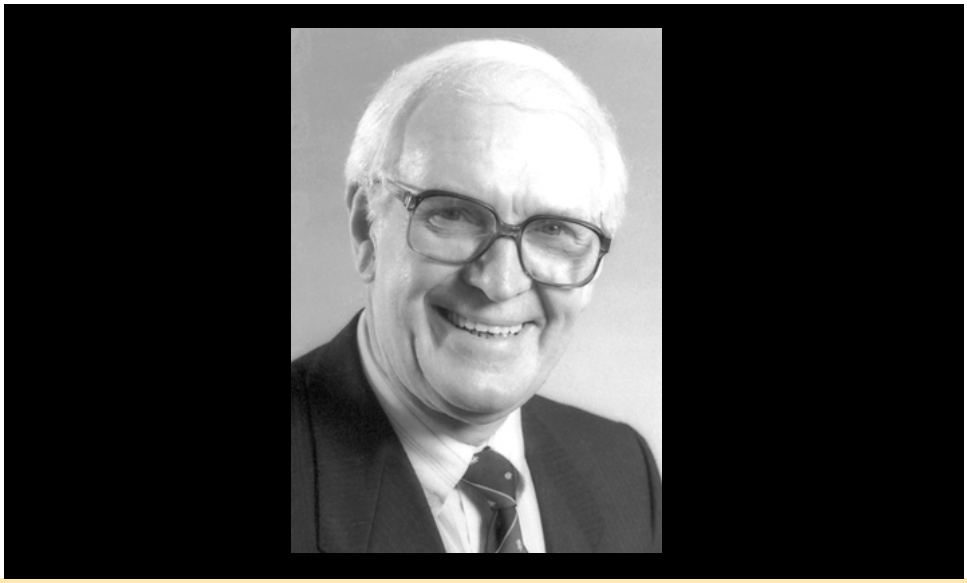


Fig. 113: Sir James W. Black (Nobel Prize, 1988). *Black developed a class of catecholamine receptor blockers—beta-blockers.*

There are 9 different adrenoceptors in humans—α1A, α1B, α1D, α2A, α2B α2C, β1, β2, and β3.

Frau Schwandt's Cold

In the early 1960s, chemists at the German drug company Boehringer-Ingelheim came up with what they thought would be an effective treatment for nasal congestion.

The drug, clonidine, which has an imidazoline chemical structure, constricted blood vessels in a manner similar to phenylephrine, the alpha-1 adrenoceptor agonist sold as NeoSynephrine™, but clonidine had a longer duration of vasoconstrictor action.

In 1962, the secretary to the medical director, a Frau Schwandt, came down with a bad cold, and to relieve her nasal congestion the medical director applied a dilute solution of clonidine to the mucus membranes in her nose.

Soon after, she fell asleep, and she didn't wake up until the next day. Her blood pressure and heart rate also decreased substantially. It was soon realized that clonidine enters the central nervous system, producing sedation and dropping sympathetic noradrenergic system outflows to the blood vessels and heart. The company creatively redirected its marketing strategy, and the drug was developed and is still marketed (as Catapres™) to treat hypertension. The drug has also been used successfully to treat conditions as diverse as alcohol and opiate withdrawal, baroreflex failure, and attention deficit hyperactivity disorder.

It is thought that in humans clonidine works in humans by

stimulating both alpha-2 adrenoceptors and imidazoline receptors.

Ironically, the active ingredient in NeoSynephrine™ 12-hour nose spray is no longer phenylephrine but oxymetazoline, which has an imidazoline structure like clonidine but does not so readily enter the brain.

Adrenaline stimulates all types of adrenoceptors. By way of occupying beta-2 adrenoceptors on vascular smooth muscle cells, adrenaline indirectly increases release of norepinephrine from sympathetic noradrenergic nerves.

Norepinephrine exerts its cardiovascular effects mainly by stimulating alpha-adrenoceptors. It also is an agonist at beta-1 adrenoceptors, but, unlike adrenaline, norepinephrine is a relatively poor agonist at beta-2 adrenoceptors.

Medical textbooks often include imposing-looking charts that list the numerous types and subtypes of adrenoceptors and dopamine receptors. The remarkable array of receptors contrasts with the small family of chemicals that reach those receptors. The multiplicity of receptors for catecholamines generally fits with the notion that natural selection has favored the evolution of multiple effectors.

Adrenoceptors such as beta adrenoceptors in the cell membrane transmit information via specific “G-proteins” (the “G” stands for guanine-nucleotide-regulatory). G-proteins are located near the receptors on the inner portion of the cell membrane.

For the discovery of G-proteins and their significance in

cellular activation by adrenaline, Alfred G. Gilman and Martin Rodbell shared the Nobel Prize in Physiology or Medicine in 1994.

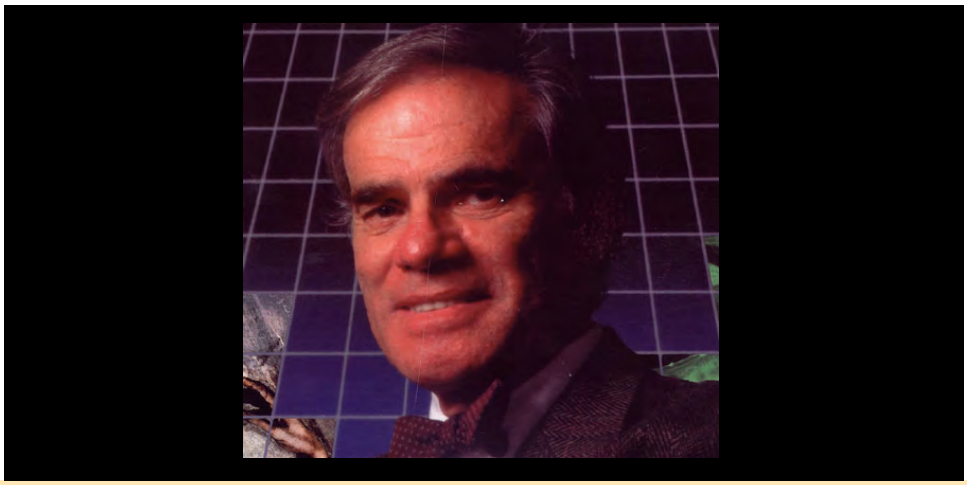


Fig. 114: Martin Rodbell (Nobel Prize 1994). *Rodbell received a Nobel Prize for discovering G-proteins.*

Describing to an audience of colleagues his reaction to the news that he had won a Nobel Prize, as reported in the Washington Post, Gilman quipped, “First, I secreted a hell of a lot of adrenaline and then that reached my adrenergic receptors and they responded via the G-proteins.”

There are a tremendous number of G-protein-coupled receptors (GPCRs). Indeed, a substantial proportion of *all* currently prescribed medications work in one way or another via GPCRs.

Second Messengers

In the liver, adrenaline liberates the vital metabolic fuel, glucose. This is a major way that adrenaline increases blood

glucose levels. The release of glucose by adrenaline takes place partly by stimulating the breakdown of glycogen to form glucose. The breakdown of glycogen, in turn, involves a rather involved cascade of biochemical events. For this cascade to begin requires the formation of a messenger substance, cyclic adenosine monophosphate (cAMP), inside the liver cells.

Fig. 115: Earl W. Sutherland, Jr. (Nobel Prize, 1971). *Sutherland discovered cyclic adenosine monophosphate (cAMP), the first identified "second messenger."*

cAMP was the first identified intracellular messenger, or "second messenger." (The first would be the hormone itself, such as adrenaline). For the discovery of cAMP, E. W. Sutherland received a Nobel Prize in 1971.

A family of chemicals called arrestins help turn off the intra-cellular cascade that activates cells when G-protein-coupled receptors such as beta-adrenoceptors are occupied. Beta-arrestin was one of the first arrestins to be identified ("beta" because this form of arrestin is associated with beta-adrenoceptors).

The first step in the desensitization of the receptors is

Fig. 116: Robert Lefkowitz (Nobel Prize, 2012). *Lefkowitz shared with Brian Kobilka the 2012 Nobel Prize in Chemistry, for isolating beta-adrenoceptors and discovering proteins that desensitize the receptors.*

phosphorylation by a class of chemicals called G-protein coupled receptor kinases (GRKs). The action of a GRK prepares the receptor for binding to arrestin. Arrestin binding to the receptor then blocks further G-protein-mediated signaling and also targets the receptors for displacement from the cell membrane into the cytoplasm.

Robert Lefkowitz received a 2012 Nobel Prize for isolating beta-adrenoceptors and discovering the beta-arrestin and GPCR kinase gene (GRK) families, which desensitize the receptors.

There are two classes of alpha-adrenoceptors, alpha-1 and alpha-2. Each class has 3 types. Adrenaline is an agonist at all

adrenoceptors, including both classes of alpha-adrenoceptors. In general, stimulation of alpha-1 adrenoceptors increases activity of the target cells, whereas stimulation of alpha-2 adrenoceptors

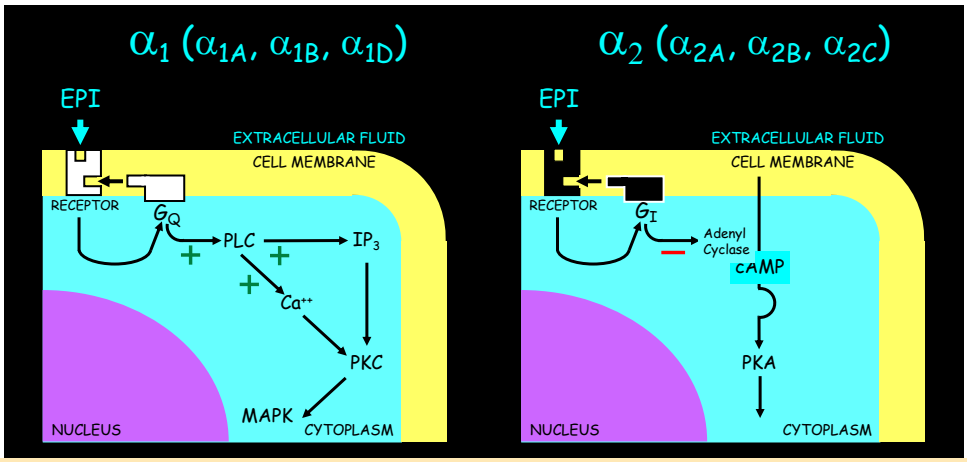


Fig. 117: Alpha-adrenoceptors. *There are two classes of alpha-adrenoceptors, alpha-1 and alpha-2. Each class has 3 types.*

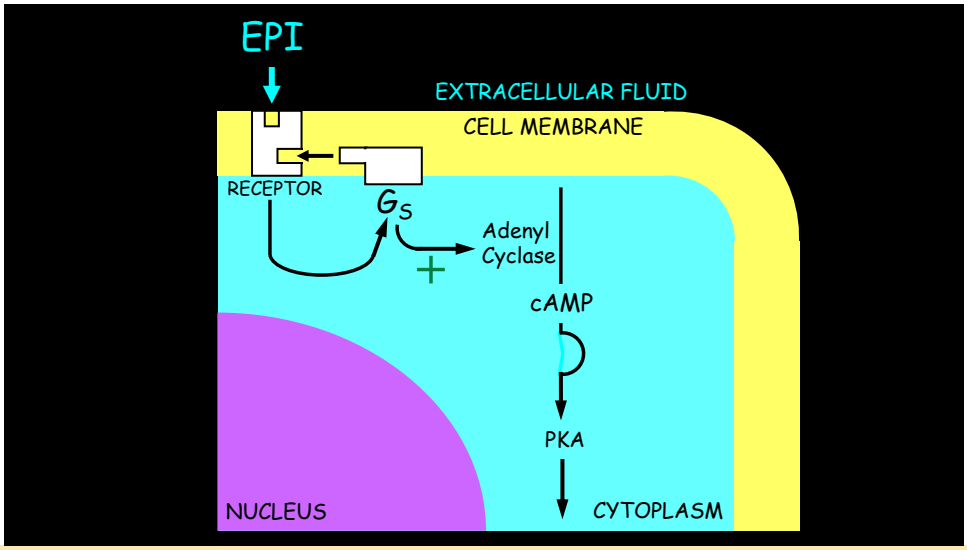


Fig. 118: Beta-adrenoceptors. *There are 3 types of beta-adrenoceptors. All work by way of G-protein coupled receptors and the second messenger cyclic adenosine monophosphate (cAMP).*

decreases activity of the target cells. The GPCRs and second messenger systems are different for alpha-1 vs. alpha-2 adrenoceptors.

There are three types of beta-adrenoceptors, beta-1, beta-2, and beta-3, which are encoded by three different genes. All three types of beta-adrenoceptors use the same second messenger, cAMP.

There are also two classes of dopamine receptors, called "D1-like" and "D2-like." The nomenclature is confusing, as in the D1-like family there are D1 and D5 receptors, and in the D2-like family there are D2, D3, and D4 receptors. The G-proteins differ for the two classes of DA receptors.

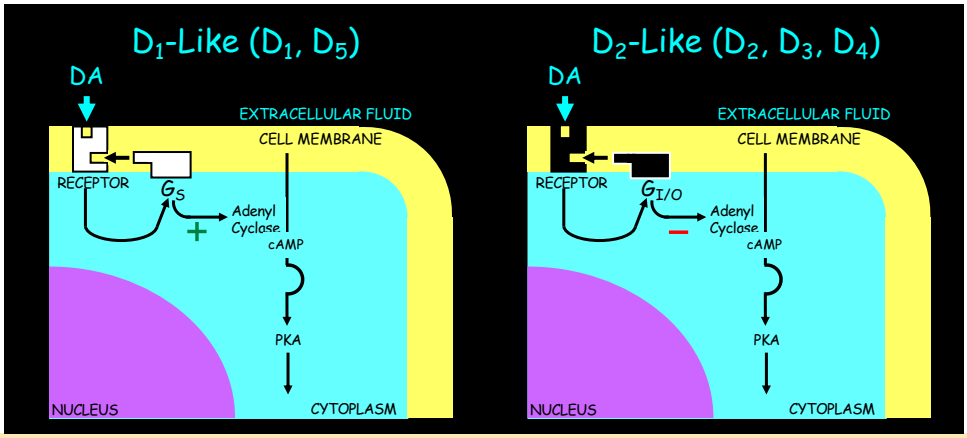


Fig. 119: Dopamine receptors. *As for alpha-adrenoceptors, there are 2 classes of dopamine receptors, the first generally being stimulatory and the second inhibitory.*

Analogously to alpha-adrenoceptors, stimulation of D1-like receptors generally activates the target cells, and stimulation of D2-like receptors generally inhibits the target cells. Occupation of dopamine receptors of either class alters cellular functions by

increasing or decreasing the activity of cAMP-dependent protein kinase A (PKA).

Communication between nerve cells mediated by catecholamines takes place by a relatively slow, diffuse process, called slow synaptic transmission.

The adjective, “slow,” here is of course a relative term. Fast synaptic transmission occurs over the course of about a millisecond or less. The main chemical messenger for fast synaptic transmission is glutamate, the anion of the amino acid glutamic acid.

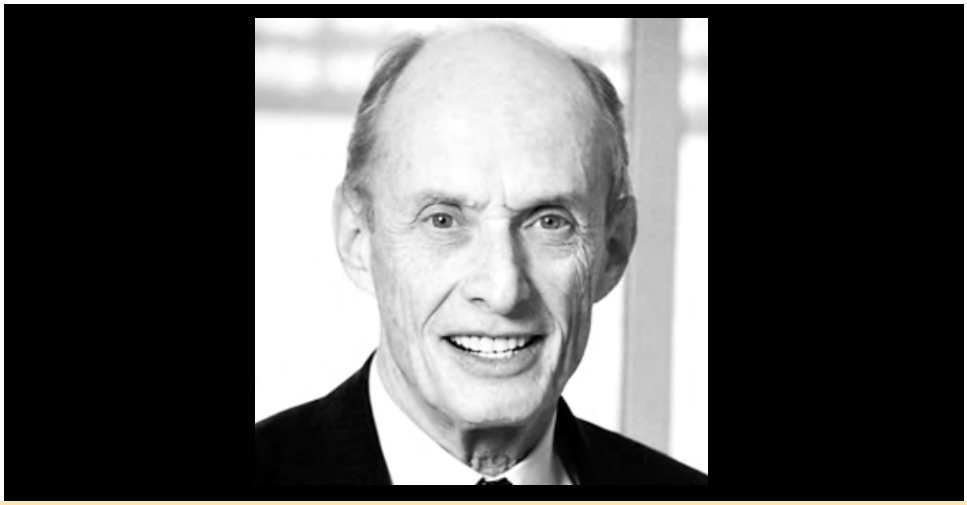


Fig. 120: Paul Greengard (Nobel Prize, 2000). *Greengard received a Nobel Prize for discoveries related to slow synaptic transmission and the role of the protein, cAMP-regulated phosphoprotein with molecular weight 32 kD, or DARPP-32.*

When released by exocytosis, glutamate stimulates ion channels in the membranes of target cells. This allows sodium ion to enter the cells, depolarizing and thereby activating them. Fast

inhibitory synaptic transmission occurs mainly via gamma-aminobutyric acid (GABA), which opens channels for chloride ions, hyperpolarizing and inactivating the target cells.

Slow synaptic transmission is more complex and occurs over the course of several milliseconds to seconds. Dopamine's effects occur via slow synaptic transmission.

Paul Greengard was awarded a Nobel Prize in 2000 for his research related to slow synaptic transmission mediated by dopamine. Greengard discovered a particular phosphoprotein, which he named cAMP-regulated phosphoprotein with molecular weight 32 kD, or DARPP-32.

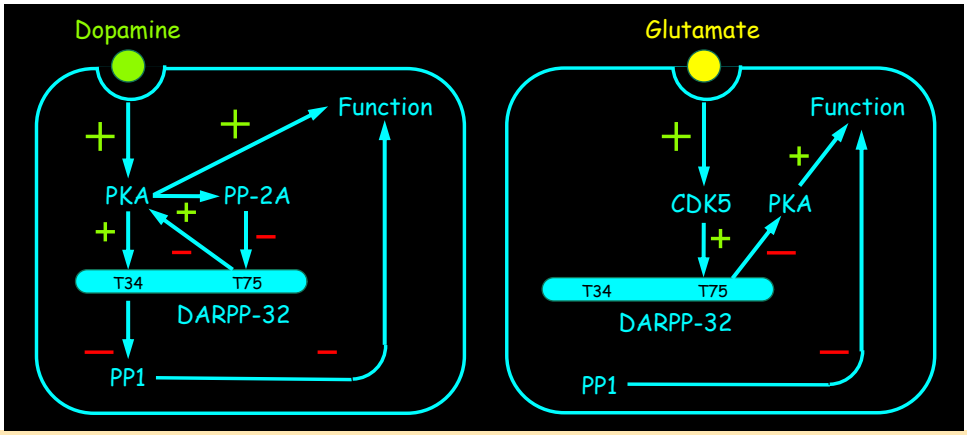


Fig. 121: Dopamine & glutamate signaling through DARPP-32. *This model depicts opposing effects of dopamine and glutamate on striatal function.*

DARPP-32 is highly concentrated in the striatum and the nucleus accumbens, which are the respective terminal fields of dopaminergic neurons of the substantia nigra and ventral tegmental area (VTA) in the midbrain. Animals without DARPP-32 have decreased or even absent biochemical,

pharmacologic, and behavioral responses that involve nigrostriatal or VTA dopaminergic activity.

DARPP-32 plays a key role in the opposing effects of dopamine and glutamate. Manipulation of this balance can help explain how deep brain stimulation improves movement abnormalities in patients with Parkinson's disease.

ACETYLCHOLINE SYNTHESIS

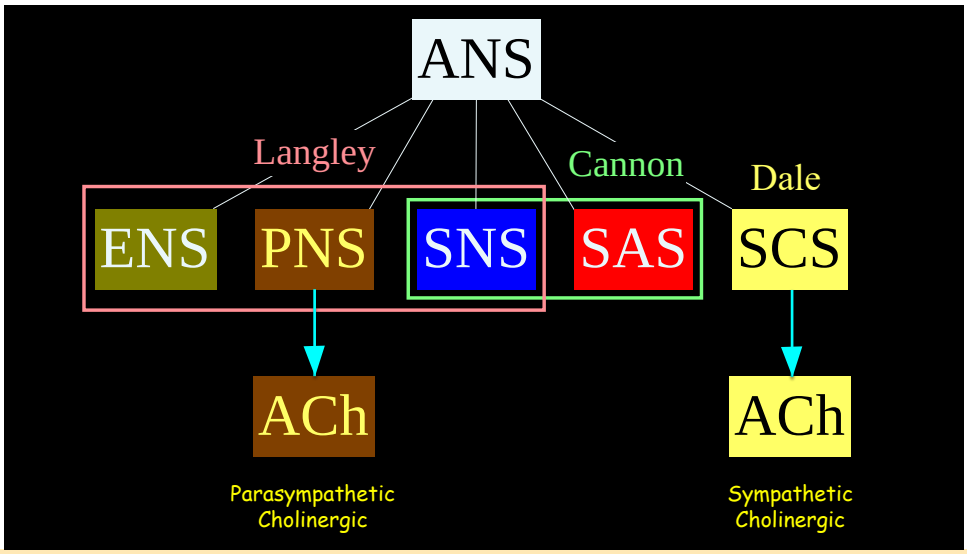


Fig. 122: Cholinergic components of the autonomic nervous system. *In addition, chemical neurotransmission in all autonomic ganglia is by way of acetylcholine.*

Acetylcholine is the main chemical messenger of two components of the autonomic nervous system, the parasympathetic nervous system (PNS) and the sympathetic cholinergic system (SCS). Chemical neurotransmission in all autonomic ganglia is by way of acetylcholine.

Acetylcholine is important for "vegetative" activities like salivating, digesting, and getting rid of waste.

Acetylcholine released from parasympathetic nerves produces many effects in the body, including increasing the tone of the urinary bladder and bowel, increasing gastric acid secretion, stimulating salivation and tear production, and decreasing the rate and force of the heartbeat. Acetylcholine released from sympathetic cholinergic nerves evokes sweating.

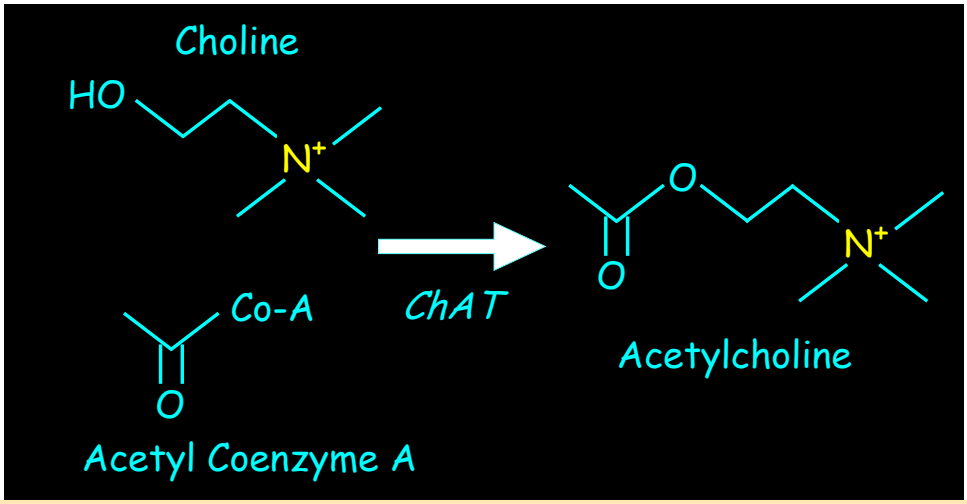


Fig. 123: Acetylcholine synthesis. *Acetylcholine is formed from the quaternary ammonium compound choline and acetyl coenzyme A. Choline acetyltransferase (ChAT) catalyzes the reaction.*

Acetylcholine (ACh) is produced from the action of the enzyme, choline acetyltransferase (ChAT), on choline and acetyl coenzyme A in the neuronal cytoplasm. ChAT catalyzes the transfer of the acetate ion from acetyl coenzyme A to choline.

In the body probably the main role of acetyl coenzyme A is in the Krebs cycle, providing the acetyl group that is oxidized for energy production. Oxidation of the acetyl group yields carbon dioxide, water, and energy that is captured in the form of 11 adenosine triphosphate (ATP) molecules and one guanosine triphosphate (GTP) molecule per acetyl group.

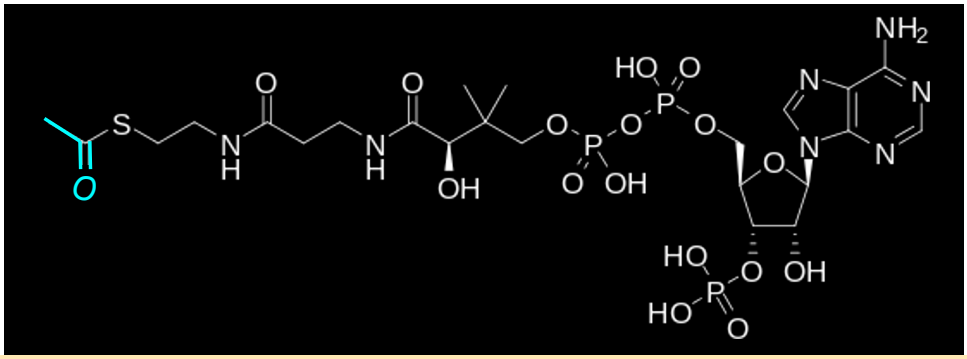


Fig. 124: Acetyl coenzyme A. *Acetylcholine is formed by the enzyme choline acetyltransferase transferring the terminal acetyl group (in aqua) from acetyl coenzyme A to choline.*

As for other neurotransmitters, ACh formed in the neuronal cytoplasm is actively taken up into vesicles by a transporter, in this case the vesicular acetylcholine transporter, or VAChT. The gene encoding the VAChT molecule is called the solute carrier family 18, member 3 gene, or *SLC18A3* gene). *SLC18A3* is located within the first intron (a non-coding region) of the gene that encodes ChAT. This aspect of the genomic structure of ChAT is unique compared to genes encoding synthetic enzymes for other neurotransmitters.

The vesicular uptake of ACh depends on a proton pump, which pumps protons into the vesicles. As the protons leak from the vesicles back into the cytoplasm, ACh enters the vesicles via

the VAChT.

Because ACh is required for neuromuscular transmission, blockade of the VAChT causes skeletal muscle paralysis.

After release of acetylcholine by exocytosis into the extracellular fluid, the transmitter can bind to specific receptors on target cells, but it is also rapidly broken down by the enzyme acetylcholinesterase (AChE), which regenerates the acetate and choline. Because of the rapid breakdown of acetylcholine by

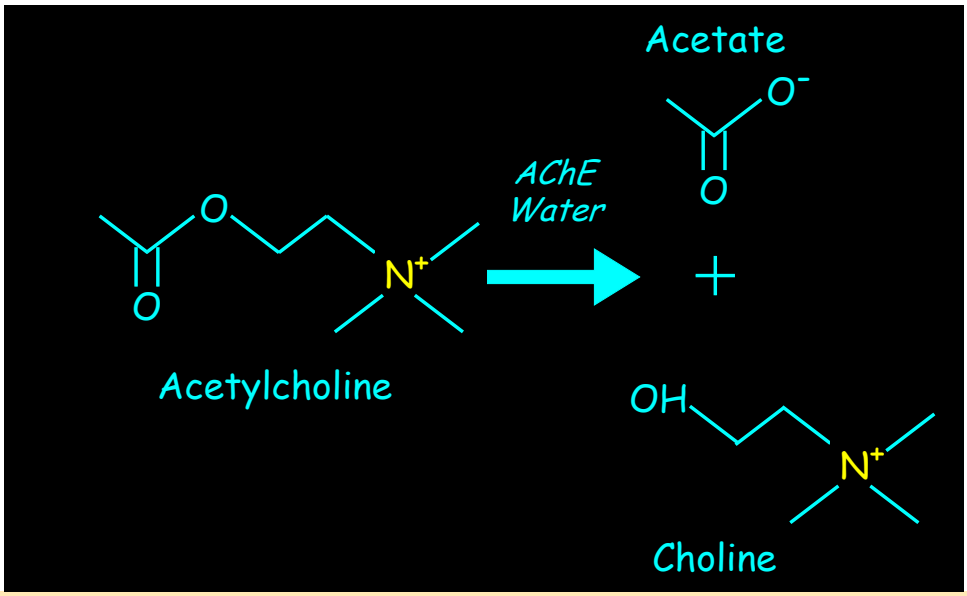


Fig. 125: Acetylcholine breakdown. *Acetylcholine breakdown is by way of acetylcholinesterase (AChE) in the extracellular fluid.*

AChE, it is impossible to monitor activity of the cholinergic neurons by measuring levels of acetylcholine in body fluids such as plasma or urine.

ACETYLCHOLINE RECEPTORS

The neurotransmitter in all the autonomic ganglia is acetylcholine. Acetylcholine binds to nicotinic receptors ($^{+}$N in Fig.126) on the cell bodies of the post-ganglionic nerves. Acetylcholine is also the chemical messenger released from the post-ganglionic parasympathetic nerve terminals in target organs. The receptors in target organs such as the heart, gut, and sweat glands are muscarinic ($^{+}$M). The receptors on skeletal muscle cells are nicotinic.

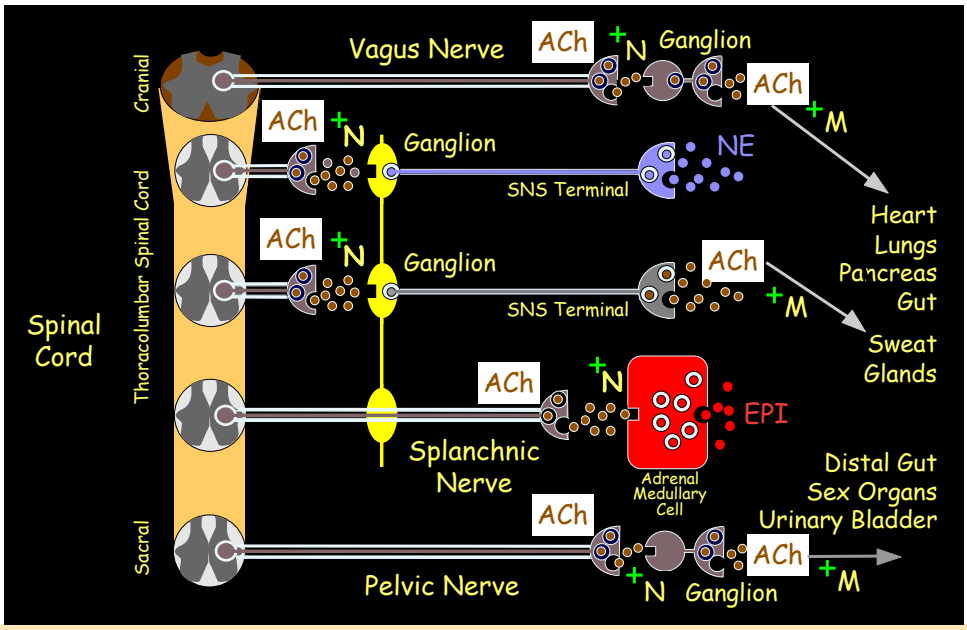


Fig. 126: Acetylcholine & its receptors. *Ganglionic transmission occurs via acetylcholine (ACh) binding to nicotinic receptors on post-ganglionic neurons or adrenomedullary chromaffin cells.*

Tobacco and Mushrooms

The history of acetylcholine receptors begins with John Newport Langley—the same Langley who coined the terms "autonomic nervous system" and "parasympathetic nervous system." In 1905 Langley proposed that skeletal muscle expresses "a substance that combines with nicotine and curare…receives the stimulus and transmits it." He referred to a "receptive substance" in the muscle.
There are two classes of receptors for acetylcholine—nicotinic and muscarinic. These names are derived from the drugs nicotine, which is made in tobacco plants, and muscarine, which is made in certain types of mushrooms.

The chemical structures of nicotine and muscarine differ, but they both are small organic molecules that contain prominent nitrogen atoms.

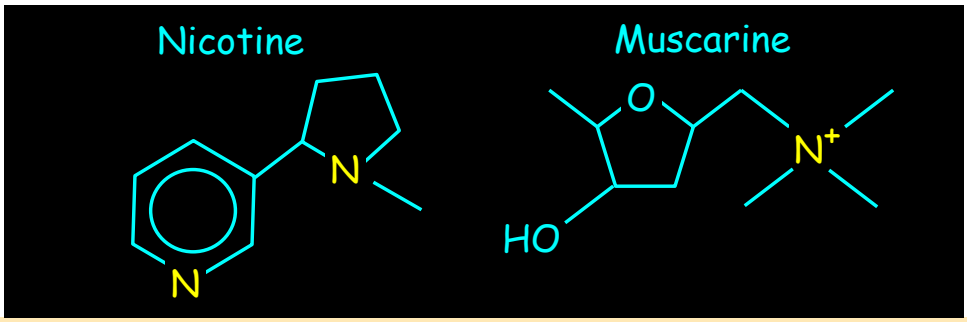


Fig. 127: Nicotine & muscarine.

Nicotinic Receptors

Nicotine is the classic stimulator of the neuronal nicotinic receptor—the first type of neurotransmitter receptor to be identified.

Nicotinic receptors are called "ionotropic," because when they are occupied by acetylcholine they allow ions to enter the cell from the extracellular fluid. By letting in sodium ions the cells lose some of their charge (i.e., they depolarize), and the depolarization then enables calcium ions to enter. Calcium ion builds up in the cell through the channel itself or via induced calcium release from intracellular stores. It is the buildup of ionized calcium in the cytoplasm that activates the cell.
There are numerous types and sub-types of nicotinic receptors.

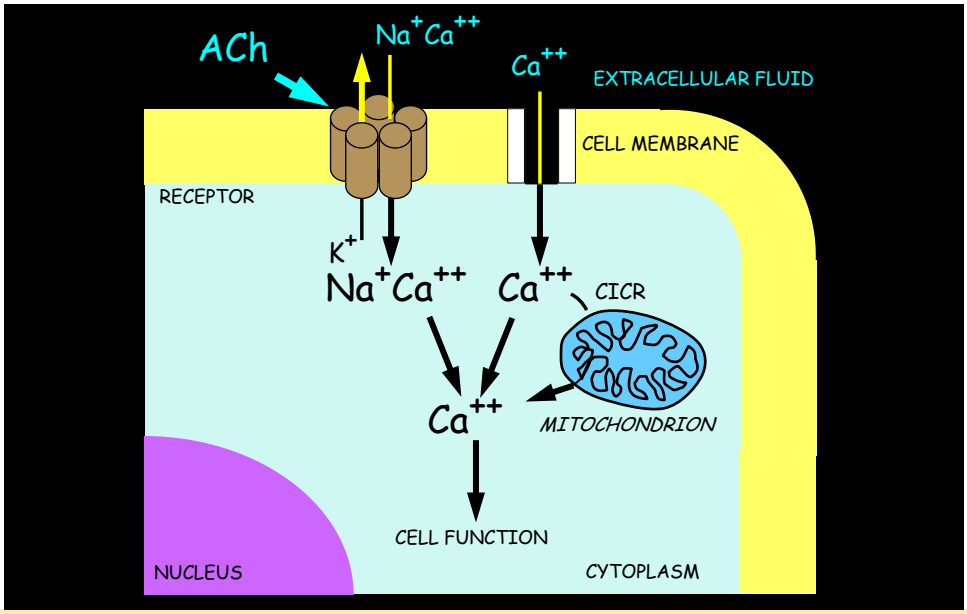


Fig. 128: Nicotinic receptors. *Nicotinic receptors are "ionotropic," in that they stimulate the cell by allowing ions to enter the cell. Nicotinic receptors have a pentameric structure that surrounds a channel through which ions can pass.*

All have 5 component parts—i.e., they are pentamers. For instance, a common arrangement in the sympathetic ganglia is a pentamer that has 2 alpha-3 subunits and 3 beta-4 subunits.

The constituents of the nicotinic receptor mediating skeletal muscle neurotransmission differ from those of the nicotinic receptor mediating ganglionic neurotransmission. This is why ganglion blockade with a neuronal nicotinic receptor blocker does not cause paralysis.

IT'S A GIRL!

Stimulation of nicotinic receptors on adrenal medullary cells rapidly evokes adrenaline release. Here is an anecdote to help remember this fact.

When my brother and sister-in-law had their youngest daughter, they gave me an "It's a Girl!" cigar. I've never been a tobacco smoker, but given the occasion I thought I should smoke it. My wife wouldn't let me smoke in the house, so I decided to take a stroll in the neighborhood around our long block. I lit up and started a leisurely walk, and I was puffing away proudly with my chin high and hands clasped behind my back when about half way around the block I suddenly came to the realization that I was about to die.

My heart was racing, I broke out in a sweat, I gasped for breath, I began to tremble, and I experienced what in medical circles is called the "feeling of impending doom." I made it home and flung myself on the couch in our family room. From my pallor, sweating, hyperventilation, and tremulous speech, everyone was immediately concerned and wanted to know what was wrong. I gasped, "It's that damned It's a Girl! cigar."

In non-smokers, the nicotine in tobacco smoke releases adrenaline, producing fast pulse rate, sweating, pallor, hyperventilation, and a "feeling of impending doom."

All these symptoms and signs were due to release of adrenaline from my adrenal glands after occupation of nicotinic receptors on my adrenomedullary cells.

Muscarinic Receptors

Muscarinic receptors for acetylcholine are expressed in virtually all the organs of the body, including the heart, gut, sweat glands, urinary bladder, and lungs. Probably the most noticeable effect of muscarinic receptor stimulation is gastrointestinal upset, nausea, and vomiting.

A chemical found in some mushrooms was the basis for naming one class of acetylcholine receptors—muscarinic.

Of the five types of muscarinic receptors, the M2 type is the main form in the heart. Stimulation of the M2 receptors in the heart decreases the rate and force of heart contraction, via two processes.

First, occupation of M2 receptors on the heart muscle cells inhibits the cells' activities via decreasing generation of the second messenger cyclic AMP and augmenting the entry of potassium ion into the cells. Second, stimulation of M2

receptors on cardiac sympathetic nerves inhibits norepinephrine release for a given amount of post-ganglionic sympathetic nerve traffic.

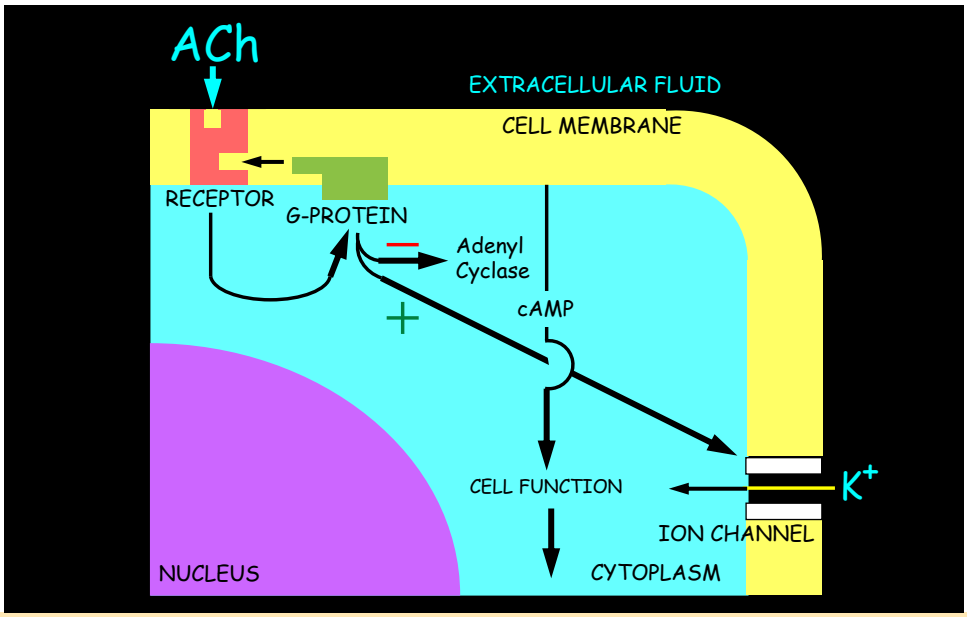


Fig. 129: Muscarinic receptor. *There are 5 types of muscarinic receptors. Muscarinic receptors are called "metabotropic," because they alter cell function via production of second messengers.*

Another cholinergic signaling system mediates relaxation of blood vessels independently of muscarinic receptors. This system involves production of the gas, nitric oxide (NO).

NO is generated in different types of cells. In this case we are dealing with NO production within the endothelial cells that line the innermost walls of blood vessels. NO diffuses from the endothelial cells to nearby smooth muscle cells, causing the smooth muscle cells to relax.

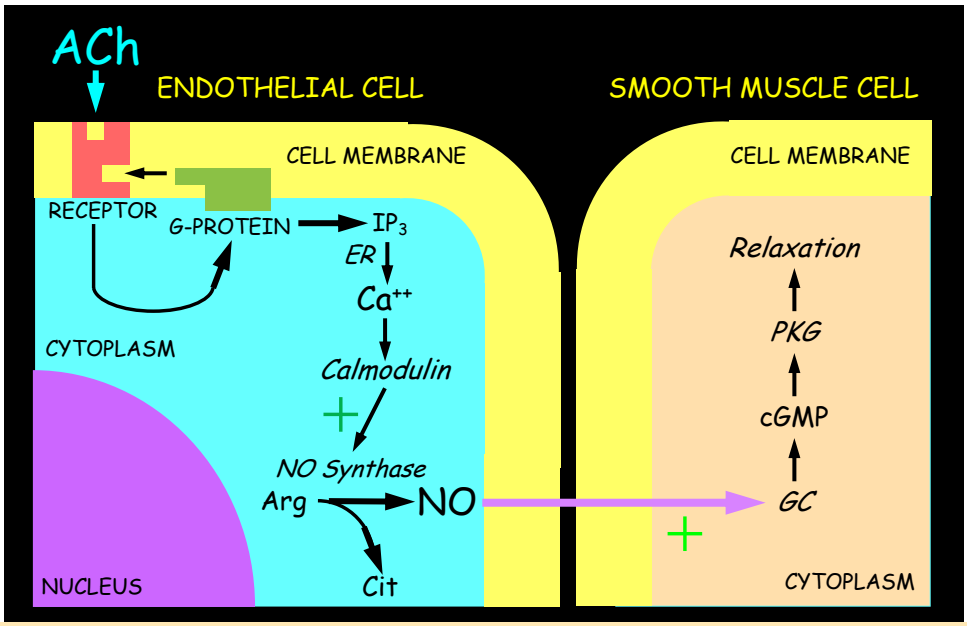


Fig. 130: Acetylcholine & nitric oxide (NO). *The NO signaling system mediates vascular smooth muscle relaxation in response to acetylcholine.*

The acetylcholine/NO mechanism plays an important role in the relaxation of local blood vessels in the corpora cavernosa that enables blood to engorge the penis during erection. When this pair of sponge-like structures fill with blood, their expansion interferes with venous return of blood in the shaft, and the penis stiffens.

MAGIC MUSHROOMS 101

When I was a junior resident in internal medicine in Seattle, one night when I was working in an emergency room a group of students came in, all looking acutely ill. They had ingested what they thought were psychedelic (psilocybin) “magic” mushrooms.

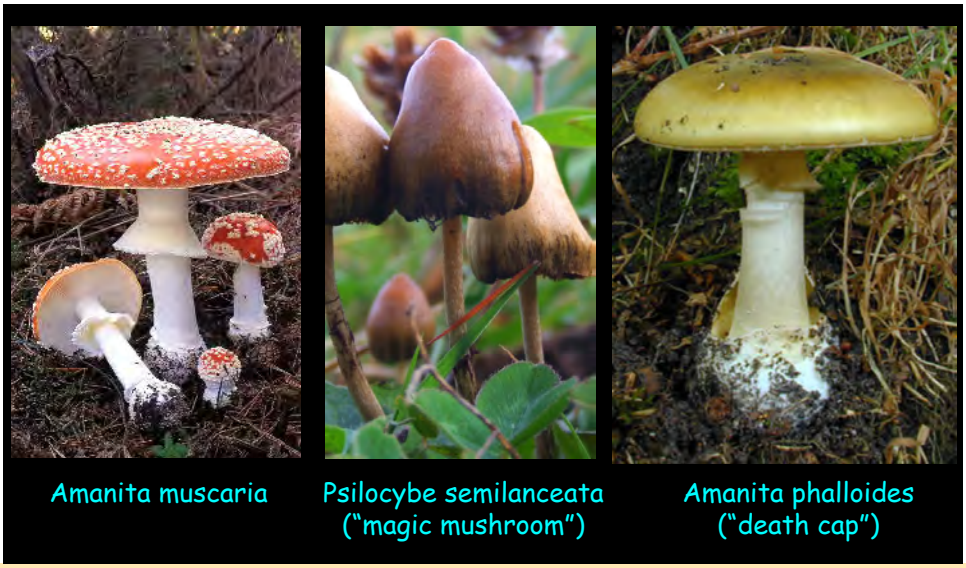


Fig. 131: Mushrooms. *These 3 mushroom species are relevant to the autonomic nervous system, in different ways.*

It hadn't taken long before they'd realized they'd made a bad mistake. They all were retching and vomiting. In the vomitus were mushroom parts. At the time, on the faculty of the University of Washington was Dr. Daniel Stuntz, a professor of botany who was a world-renowned authority on mushrooms. We called him up, and he came to the emergency room. I remember him looking stereotypically professorial in a cardigan sweater, which contrasted with our medical white jackets.

Dr. Stuntz identified the matter in the students' vomitus as coming from a variety of poisonous mushroom called *amanita phalloides*, also known somewhat more graphically as "death cap." The retching and vomiting in these students was the result of muscarinic toxicity.

Dr. Stuntz truly was an expert on the subject. Several years previously he had discovered a new species of the psychedelic

mushroom *Psilocybe* on the UW campus. This species was later named *Psilocybe stuntzii* in his honor.

PRETTY WOMAN

According to tradition, Italian women used to instill in their eyes a product of the root of a plant in the genus *Atropa,* out of the belief that the drug-induced dilation of the pupils would make them more attractive.

Blockade of effects of the parasympathetic nervous system on the pupils causes the pupils to dilate.

The extract came to be called "belladonna," meaning "pretty woman," and the full taxonomic name of the plant is *Atropa belladonna.*

Fig. 132: Atropine & mydriasis. *Atropine, derived from the plant,* Atropa belladonna, *dilates the pupils.*

A less appealing appellation for the same plant is "deadly nightshade." Every part of the plant is poisonous, and atropine

overdose can be lethal. Atropine overdose manifests with dry mouth, dry eyes, pupillary dilation, lack of sweating, loss of gastrointestinal and urinary bladder tone, rapid heart rate, delirium, and coma. The word, Atropa, is derived from the *Atropos*, one of the Fates in Greek mythology. *Atropos* held the shears that could cut the thread of human life.

Troops at risk of exposure to organophosphorus nerve gases such as sarin are issued atropine auto-injectors. By blocking muscarinic receptors atropine can interfere with toxic effects of nerve gas-induced blockade of acetylcholinesterase (AChE). AChE blockade floods cholinergic receptors with acetylcholine and causes death by asphyxia due to the inability to regulate respiratory muscles.

During the 1991 Persian Gulf war, which was precipitated when Saddam Hussein's Iraqi troops invaded Kuwait, "scud" tactical ballistic missiles were fired on civilian neighborhoods in Tel Aviv, Israel. Many of the casualties were people who had injected atropine into themselves for what they thought was a nerve gas attack.

NEUROTROPHIC FACTORS

Release of norepinephrine in response to traffic in sympathetic nerves depends on the existence of functional sympathetic nerve terminals. The development and continued existence of sympathetic nerves in an organ depend in turn on a continuous supply of a nerve growth factor.

The discovery of nerve growth factor (NGF) arose importantly

from studies of sprouting of nerve filaments from sympathetic ganglia cells. For describing the first known neurotrophic factor, Stanley Cohen and Rita Levi-Montalcini shared a Nobel Prize in 1986.

Since the discovery of NGF a variety of other neurotrophic factors have been described, such as glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF).

Fig. 133: Rita Levi-Montalcini (Nobel Prize, 1986). *Levi-Montalcini and Stanley Cohen shared a Nobel prize for the discovery of nerve growth factor, which sympathetic nerves require.*

According to the "neurotrophic factor hypothesis," neuronal survival requires target-derived factors. The neurotrophic factors themselves, membrane receptors for the factors, or second messengers produced by neurotrophic receptor occupation are transmitted retrogradely in the axons to the neuronal cell bodies, promoting neuronal growth, axonal sprouting, and survival. Experimental data about NGF fit with

the neurotrophic factor hypothesis. For instance, after injection of a radiolabeled NGF into axon terminals radioactivity is detected in neuronal cell bodies.

HOMEOSTASIS, STRESS, AND CENTRAL ANS REGULATION

CLAUDE BERNARD AND THE "INNER WORLD"

Understanding the roles of the autonomic nervous system in health and disease begins with the teachings and demonstrations of the 19th century French physiologist Claude Bernard. Bernard is widely regarded as the father of modern physiology.

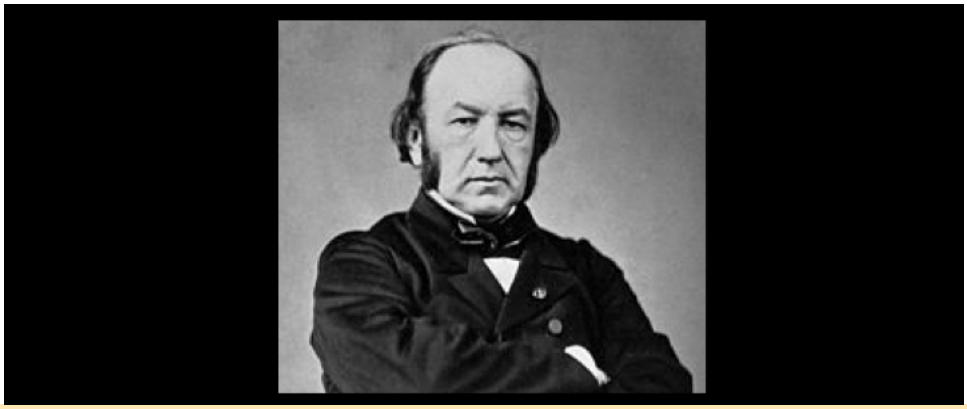


Fig. 134: Claude Bernard. *Bernard, who introduced the idea of the internal environment, the* milieu intérieur, *is regarded as the father of modern physiology.*

Bernard introduced the idea of the “inner world” inside the body—what he called the *milieu intérieur*. He theorized that a constant fluid environment bathes all the body’s cells.

Bernard's conception evolved over several years. Near the end of his life, in about 1876, he postulated something even more profound. The body *maintains* the constant internal environment by myriad, continual, compensatory reactions. These compensatory reactions tend to restore a state of equilibrium in response to any outside changes and in so doing

enable independence of the organism from the vicissitudes of the external environment.

Bernard therefore not only introduced the notion of an apparently constant inner world but also a *purpose* for body processes.

> Claude Bernard wrote, "The constancy of the internal environment is the condition for free and independent life…All the vital mechanisms, however varied they might be, always have one purpose, that of maintaining the integrity of the conditions of life within the internal environment."

This view may seem obvious now, but it was revolutionary in the history of medical ideas.

Bernard's idea may be diagrammed as follows.

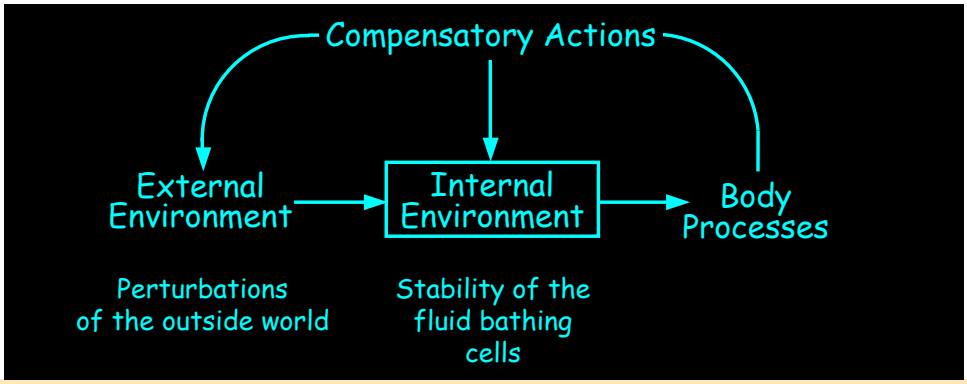


Fig. 135: Maintaining the inner world. *Claude Bernard taught that the purpose of body processes is to maintain the constancy of the internal environment.*

The diagram in Fig.136 introduces the idea of a negative feedback loop.

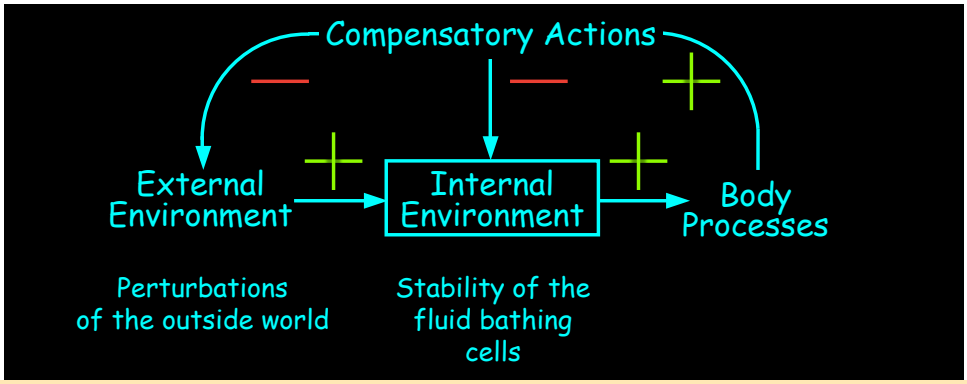


Fig. 136: Negative feedback loops. *(+) signs indicate stimulatory and (-) signs inhibitory effects. Loops with single (-) signs maintain stability.*

The (+) signs in Fig. 136 indicate stimulatory effects, and the (-) signs indicate inhibitory effects. Loops with single (-) signs maintain stability. A perturbation of the outside world has an effect on the internal environment, but the internal environmental changes evokes effects on body processes that act compensatorily on the external or internal environments.

For instance, you could be caught in a blast of cold air, which which would tend to decrease your core temperature. By way of a somatic body process, locomotion, you would seek a warmer place, and by way of an autonomic body process, activation of the sympathetic noradrenergic system (SNS), you would constrict blood vessels in the skin, which decreases heat loss and conserves body heat.

It can be shown mathematically that in any system containing a negative feedback loop, the level of the monitored variable (in

this case core temperature) reaches a stable, plateau level.

Bernard's visionary concept of the stability of the internal environment attracted little attention until Walter B. Cannon proposed his theory of homeostasis.

CANNON'S "HOMEOSTASIS"

Fig. 137: Walter B. Cannon, the father of homeostasis. *Cannon's theory followed directly on Bernard's* milieu intérieur.

Cannon coined the word, "homeostasis." He used this term to describe the overall stability of the various constituents of body fluids and of core temperature that make up the body's inner world. The full description of this new concept was based on the results of Cannon's own studies and those reported in the two decades preceding his 1929 review, "Organization for Physiological Homeostasis."

In that review he acknowledged the importance of Bernard's "fixity of the *milieu intérieur*" and quoted Haldane's comment, "No more pregnant sentence was ever framed by a physiologist."

Walter B. Cannon invented the word, "homeostasis." By this term he was referring to the stability of the inner world of the body. Energy-consuming processes are required to maintain homeostasis.

Cannon taught that core temperature, blood levels of oxygen and glucose, concentrations of red blood cells in the bloodstream, amounts of electrolytes, and many more "variables" of the body don't vary by much; they are kept within ranges.

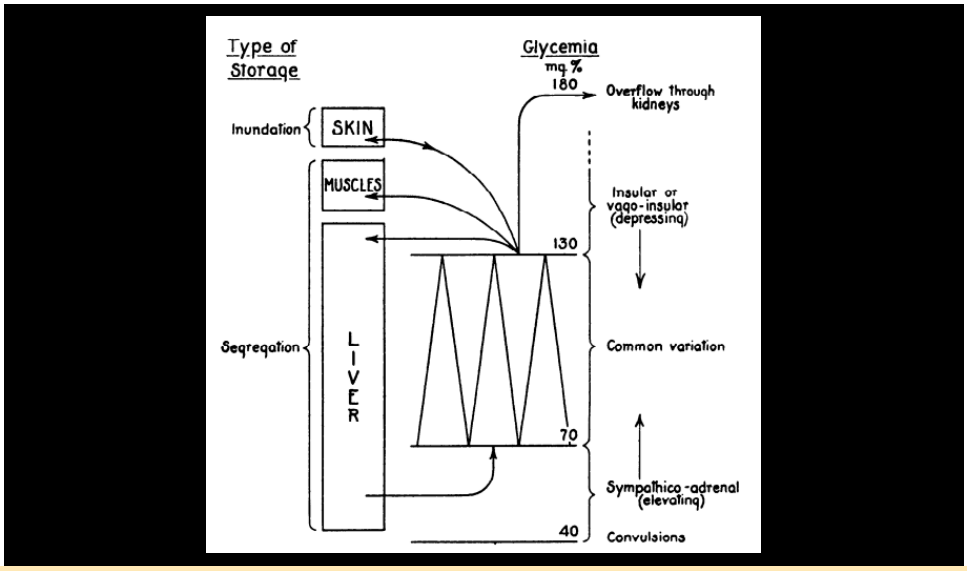


Fig. 138: Blood glucose regulation according to Cannon. *Note the roles of "sympathico-adrenal" activation and "vago-insular" inhibition in keeping blood glucose within bounds.*

Cannon's classic presentation of his theory in 1929 in Physiological Reviews contains the diagram in Fig. 138. According to Cannon, the blood glucose level ("glycemia") is kept within bounds, because when the glucose level goes down the "sympathico-adrenal" system (in this book called the sympathetic adrenergic system, or SAS) is activated, and this increases the glucose level via the stimulatory effects of high circulating adrenaline levels on the liver, releasing glucose into the bloodstream. When the glucose level goes down the vago-insular system (in this book the parasympathetic nervous system, or PNS) is activated, and this decreases the glucose level via the stimulatory effects of acetylcholine on insulin secretion by the pancreas, augmenting cellular uptake of circulating glucose.

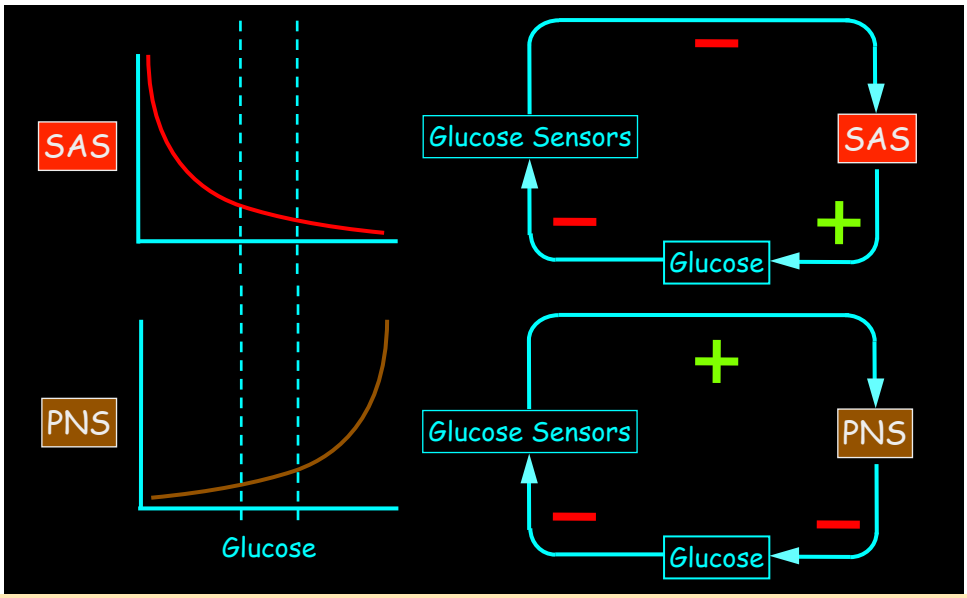


Fig. 139: Autonomic regulation of blood glucose. *Blood glucose is kept within bounds by altered states of activity of two components of the autonomic nervous system. Cannon referred to them as the "sympathico-adrenal system" and the "vago-insular system."*

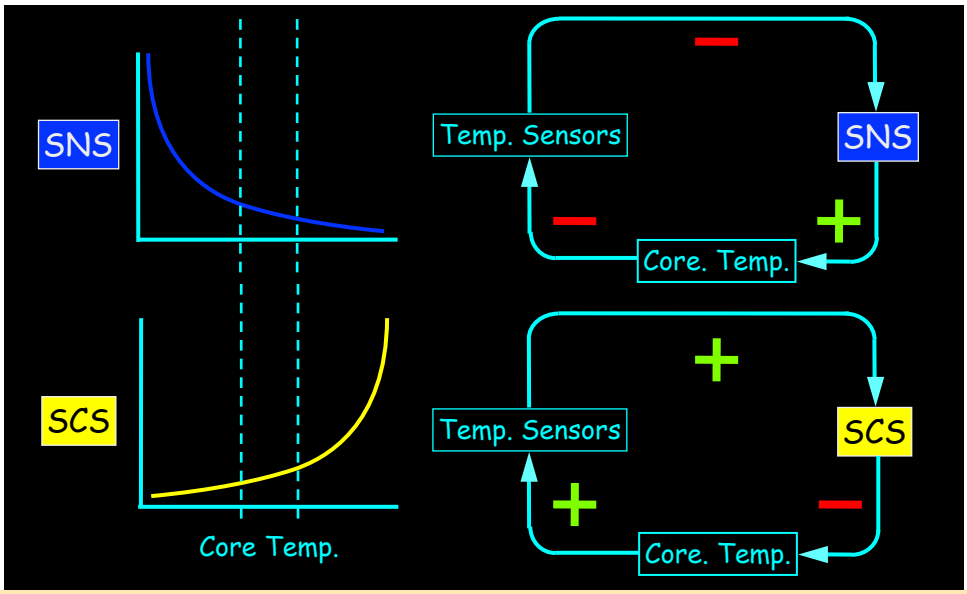


Fig. 140: Temperature regulation by the ANS: *A drop in core temperature evokes SNS activation, which decreases blood flow to the skin, and an increase in core temperature evokes SCS activation, which increases sweating.*

Similar sorts of diagrams can be drawn for homeostasis of core temperature via the SNS and SAS (activation of which tends to increase temperature by decreasing blood flow to the skin, thereby decreasing evaporative heat loss) and SCS (activation of which tends to decrease temperature by augmenting sweating and thereby increasing evaporative heat loss).

An Amazing Cooking Experiment

On January 23, 1774, the amazing ability of the human body to maintain core temperature by evaporative heat loss was demonstrated experimentally for the first time. Five men, including Dr. Charles Blagden, who was 26 years old at the time, entered a room-sized chamber that was heated

progressively with dry air. Eventually the temperature exceeded that of boiling water. An egg in the chamber roasted solid. The temperature of Blagden's exhaled breath was relatively cool compared with the external temperature in the room. He noted, "Whenever we breathed on a thermometer the quicksilver sank several degrees." Three weeks later, Blagden reported his observations to the Royal Society of London, which published his report in its Proceedings in 1775.

Fig. 141: Sir Charles Blagden (1748-1820). *Blagden demonstrated the tremendous power of the autonomic nervous system in enabling toleration of extreme external heat.*

In the heat chamber Blagden eventually began to experience anxiety. His pulse rate increased dramatically, and he decided to end the experiment. He wrote, that at 260 degrees "I sweated, but not very profusely. For seven minutes my breathing continued perfectly good; but after that time I began to feel an oppression in my lungs, attended with a sense of anxiety; which gradually increasing for the space of a minute, I thought it most prudent to put an end to the experiment, and immediately left

the room. My pulse, counted as soon as I came into the cool air, was found to beat at the rate of 144 pulsations in a minute, which is more than double its ordinary quickness."

One may speculate that Blagden's anxiety, which ended his amazing cooking experiment, was associated with a high adrenaline level in his bloodstream. Adrenaline both constricts blood vessels in the skin and increases production of metabolic heat (calorigenesis). The combination could have interfered with Blagden's ability to maintain core temperature within bounds by evaporative heat loss.

Blagden subsequently had an illustrious career as a chemist. His notion of a chemical reaction was a founding concept of modern chemistry. He also discovered that adding a solute such as table salt to water decreases the freezing temperature of the solution. This has been called Blagden's law.

Cannon's Denervated Heart Preparation

How did Cannon demonstrate that stressors such as hypoglycemia and hypothermia evoke release of adrenaline into the bloodstream? Beginning in about 1919 and over the next two decades, he exploited a clever experimental setup to identify and quantify adrenaline release. He would surgically excise the nerves supplying the heart of a laboratory animal such as a dog or cat. Then he would subject the animal to a stressor and record the heart rate response.

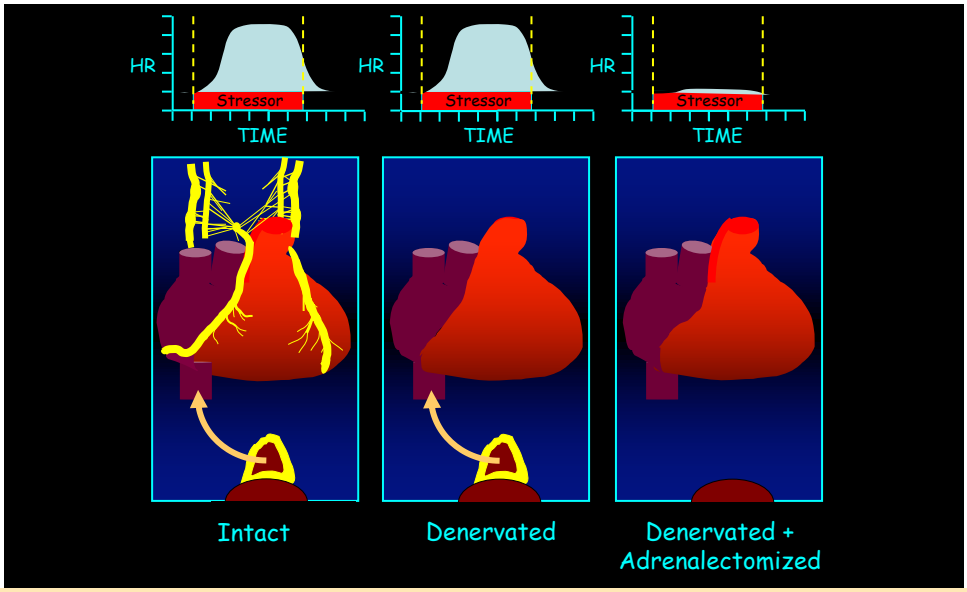


Fig. 142: Cannon's denervated heart preparation. *Walter B. Cannon used an ingenious denervated heart preparation to measure adrenaline release in response to different stressors.*

With the nerves to the heart removed, he could conclude that if the heart rate increased in response to the perturbation, then the increase in heart rate resulted from the actions of a hormone. He would then compare the results in an animal with intact adrenal glands to those in an animal from which he had removed the adrenal glands or tied off the blood vessels of the glands. From the difference in the heart rate responses of the two animals, he could infer that the hormone responsible for the increase in heart rate came from the adrenal glands. The amount of increase in the heart rate provided a measure of the amount of hormone released—what today would be called a "biomarker."

FROM TELEOLOGY TO HOMEOSTATS

Teleology is a doctrine that explains phenomena in terms of

their purpose, goal, or end. The word comes for the Greek, *telos*, meaning "end," and logos, meaning "reason."

Claude Bernard wrote, "All the vital mechanisms, however varied they might be, always have one *purpose,* that of maintaining the integrity of the conditions of life within the internal environment." (I've added the italics to emphasize Bernard's teleological thinking here.) Similarly, Walter B. Cannon wrote, "My first article of belief is based on the observation, almost universally confirmed in present knowledge, that what happens in our bodies is directed toward a *useful end.*" These are teleological statements.

Teleology has had a checkered past in science. Physics and chemistry discarded teleology centuries ago, but it remains an unsettled aspect of biology. As indicated by the quotes above, integrative physiologists often think teleologically. When they ponder the *function* of a body process, they have in mind the purpose of that process. In contrast, when systems biologists think about the function of a body process, they have in mind the *mechanism.*

In integrative physiology, homeostasis is a key goal driving body processes. In systems biology, however, homeostasis seems to be little more than a mechanistic fact emerging from the operations of complex networks.

In the integrative physiology model depicted on the right in Fig. 143, there is a negative feedback loop that keeps levels of the regulated variable within bounds. The items in blue are measurable; the items in green are not. There is a "regulator" that provides an algorithm for responding to a homeostatic

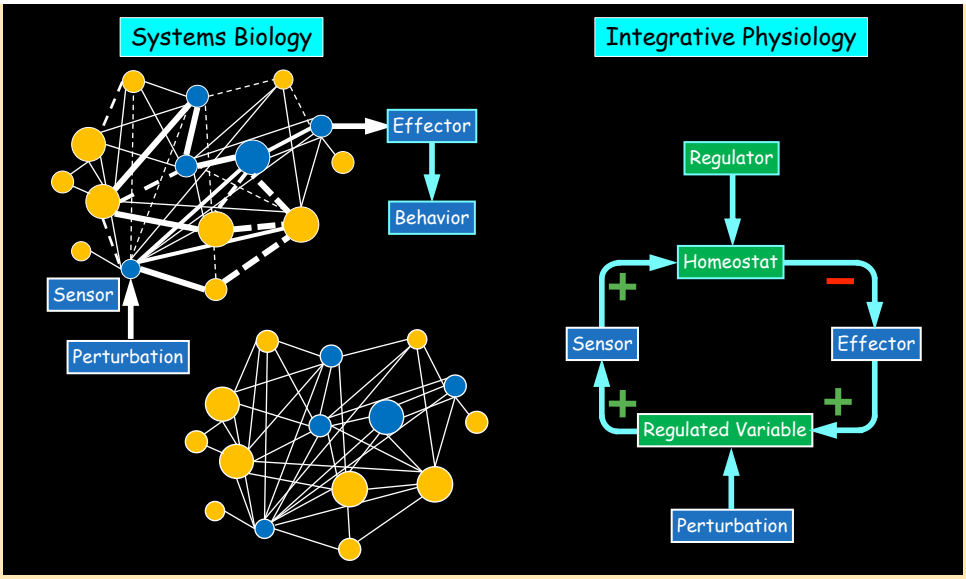


Fig. 143: Systems biologic and integrative physiological models. *Both types of model "explain" responses of an effector (e.g., a component of the autonomic nervous system) upon exposure of an organism to a biological perturbation. The items in blue are measurable; the items in green are not.*

comparator, a "homeostat." Information about a "regulated variable" (e.g., core temperature) reaches the homeostat, which compares the sensed information with the algorithm for responding, and the discrepancy (error signal) determines the state of activity of an effector (e.g., the sympathetic noradrenergic system).

In the systems biology model depicted on the left in Fig. 143, homeostasis is an emergent phenomenon resulting from a pattern of activation (thick solid lines) and inhibition (thick dashed lines) among positive (solid lines) and negative relationships (dashed lines) embedded in a network. Homeostasis is not a goal; it is simply a fact.

The evolutionary biologist Ernst Mayr argued for the existence of "teleonomic" activities, goal-directed behaviors or processes where the goal-directedness depends on the operation of a *program*.

Fig. 144: Ernst Mayr (1904-2005). *Mayr proposed the existence of teleonomic programs that lead behaviors or biologic processes toward goals.*

The program contains not only the blueprint of the goal but also the instructions about how to use the information of the blueprint.

It is not difficult to conceptualize that genes, gene expression, transcription factors, epigenetic modifiers, etc., serve as the bases for programs upon which natural selection can operate. A potential resolution of the dialectic between integrative physiology and systems biology may come from viewing homeostasis from the perspective of evolution. "Darwinian medicine" avoids teleological purposiveness and transcends pure mechanism by incorporating adaptiveness in evolution.

This is one of the ideas for the future presented at the end of this book.

Homeostats

Students learning about regulation of homeostasis of internal variables are often taught by analogy with a thermostat that regulates the interior temperature of a house. The thermostat compares the temperature that is set with the temperature that is sensed. When the discrepancy is sufficiently large, the thermostat directs changes in activities of the effector, such as a furnace, which reduces the discrepancy. The level of the monitored variable, in this case the inside temperature, eventually reaches a stable value. The plateau level may not actually be the set temperature, because this would depend on factors such as the power of the furnace and efficiency of the insulation. Eventually, the inside temperature is held between what is sensed and what is set.

Homeostats are metaphorical comparators that work like thermostats.

For a given perturbation, the more rapid, sensitive, and powerful the control by negative feedback, the smaller the fluctuations in levels of the monitored variable. When a system regulated by negative feedback is exposed to a fluctuating outside influence, the swings in the levels of the monitored variable are smaller than in the absence of negative feedback.

Combined heating and cooling systems, each controlled by a

single thermostat that can turn on either the furnace or the air conditioner, constitute a thermostatic system.

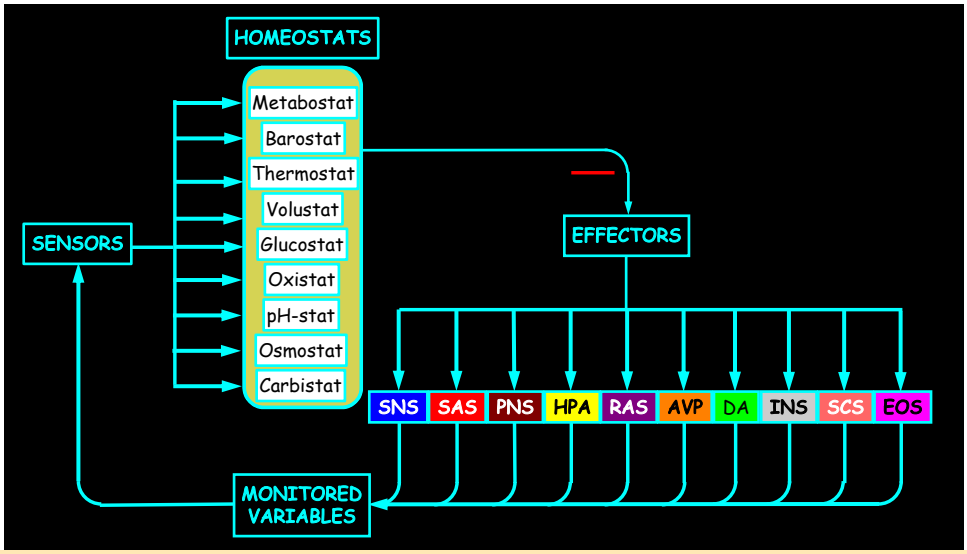


Fig. 145: Multiple homeostats and effectors. *The monitored variables are regulated by negative feedback.*

One can think of a multitude of internal homeostatic systems, each with its own "homeostat"—a "barostat" for regulating blood pressure, a "thermostat" for regulating core temperature, a "glucostat" for regulating blood glucose levels, an "osmostat" for regulating serum osmolality, and so forth.

This of course introduces a problem: homeostats, regulators, and regulated variables are all ideas. We are dealing here with metaphors. They cannot be observed directly. Their existence cannot be disproven, which makes them weak scientifically.

It doesn't take long before things seem to get out of hand. How about an "immune-stat" for the overall state of immunity, a "metabostat" for basal metabolic rate, a "volustat" for

extracellular fluid volume, a “nocistat” for the feeling of pain—even a “psychostat” for the sense of mental equilibrium?

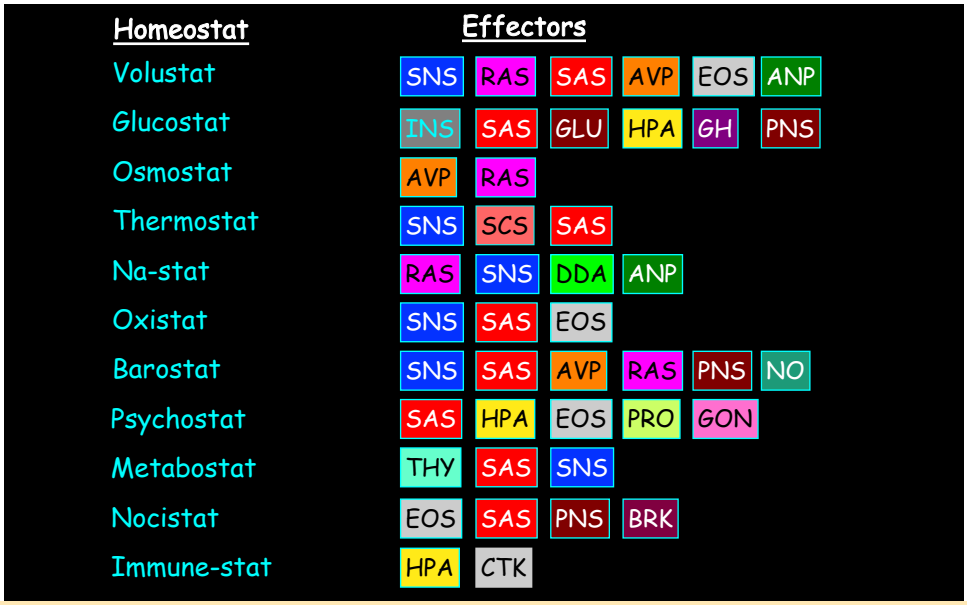


Fig. 146: Many putative homeostats and effectors. *A key disadvantage of the homeostat idea is that no evidence has accrued for the existence of physiological homeostatic comparators.*

Nevertheless, thinking in terms of homeostatic systems can yield valuable insights and organizing concepts, such as stress and allostasis, which are covered later in this section.

Biocybernetics

During a stay in Walter B. Cannon’s laboratory, the Mexican physician Arturo Rosenblueth became acquainted with Norbert Wiener and Julian Bigelow, who at the time (wartime in the early 1940s) were working on a servo-mechanism-based rangefinder for anti-aircraft guns. Their machine was

"intelligent," in that it could predict the trajectory of an airplane based on the previous trajectories ("memory"); however, when researchers tried to correct the machine for friction, it developed uncontrollable swings in motion.

Wiener asked Rosenblueth, who had become a neurologist, if there were neurological disorders manifesting similar signs. Rosenblueth described the difficulty of patients with cerebellar injury in drinking a glass of water, due to uncontrolled, oscillatory amplification of voluntary movements. From the similarity of the neurological disorder to malfunction of the rangefinder they realized that both required "a closed loop (negative feedback) allowing the evaluation of the effects of one's actions and adaptation of future conduct based on past performance."

Fig. 147: Arturo Rosenblueth, Norbert Wiener, & Julian Bigelow. *In 1943 the three proposed a definition of a teleological behavior.*

The authors conceived of the idea that control systems in machines could be designed to simulate the nervous system by

negative feedback and to self-regulate using the results of earlier activity to improve the likelihood of attaining the goal. Conversely, examination of the requirements for ideal control might provide directions in research about how the nervous system is designed to gain control of physiological variables via negative feedback and memory.

In a famous essay published in 1943 Rosenblueth, Wiener, and Julian Bigelow tackled the matter of teleology in neurobiology (Fig. 148). They argued that a behavior can be active or passive; if it is active, it can be purposeful or non-purposeful (random); and if it is purposeful it can be feedback-regulated or not feedback-regulated. A behavior is teleological if it is purposeful and feedback-regulated.

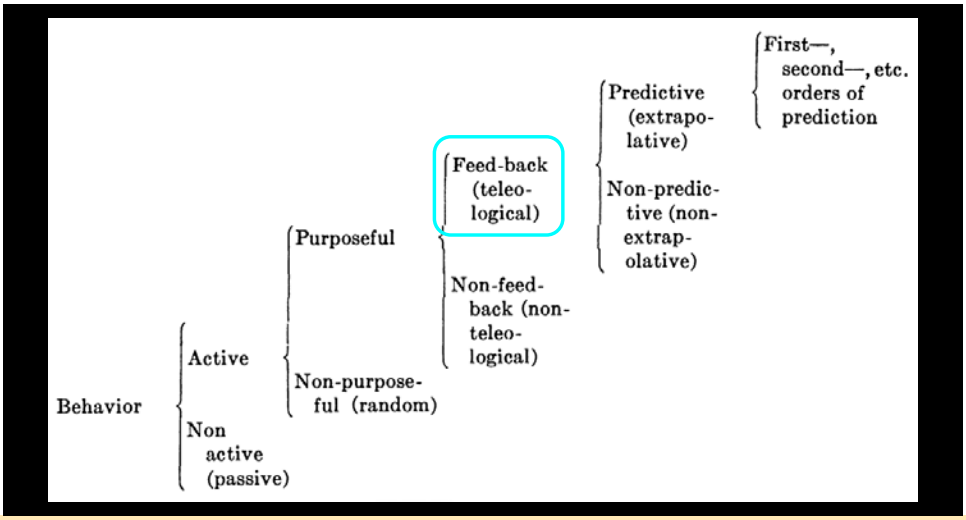


Fig. 148: Rosenblueth, Wiener, & Bigelow's concept of a teleological behavior. *A teleological behavior has a purpose (goal) and is guided by feedback.*

Teleology was not taken to imply "final causes" and was viewed as synonymous with purpose controlled by feedback.

Finally—and provocatively—they argued that the "broad classes of behavior are the same in machines as in living organisms," regardless of the complexity of the behavior.

In a book published in 1948 Wiener introduced the term, "cybernetics." He thought his theory of control systems would be applicable to a wide variety of disciplines, including biology—"biocybernetics." Wiener distinguished two forms of biocybernetics, medical biocybernetics and neurocybernetics. In medical biocybernetics, "homeostasis is the main consideration," whereas neurocybernetics mainly involves "the pathways of actions via sense-organs, neurons and effectors," although he pointed out that "there is no sharp distinction between the two fields."

THREE ROUTES TO HOMEOSTASIS

This section develops the idea that homeostasis does not result from negative feedback alone. Instead three types of process maintain homeostasis. The first and most well known is error control by negative feedback regulation. The second is feed-forward regulation, which is the most challenging from a theoretical point of view. The third is buffering.

Fig. 149 shows the relationships of reflexive error control via negative feedback (red), buffering (tan), and anticipatory regulation (blue). The anticipatory control mechanisms can be instinctive (solid lines) or conditioned (dashed lines). A disturbance can arouse anticipatory instinctive responses by pathways involving awareness (conscious or unconscious); and an associated conditioned stimulus can arouse anticipatory

responses by pathways involving awareness and conditioned learning. A disturbance is sensed by interoceptors (e.g., gastrointestinal hemorrhage) or exteroceptors (e.g., touching a hot iron), while a conditioned stimulus is sensed by exteroceptors.

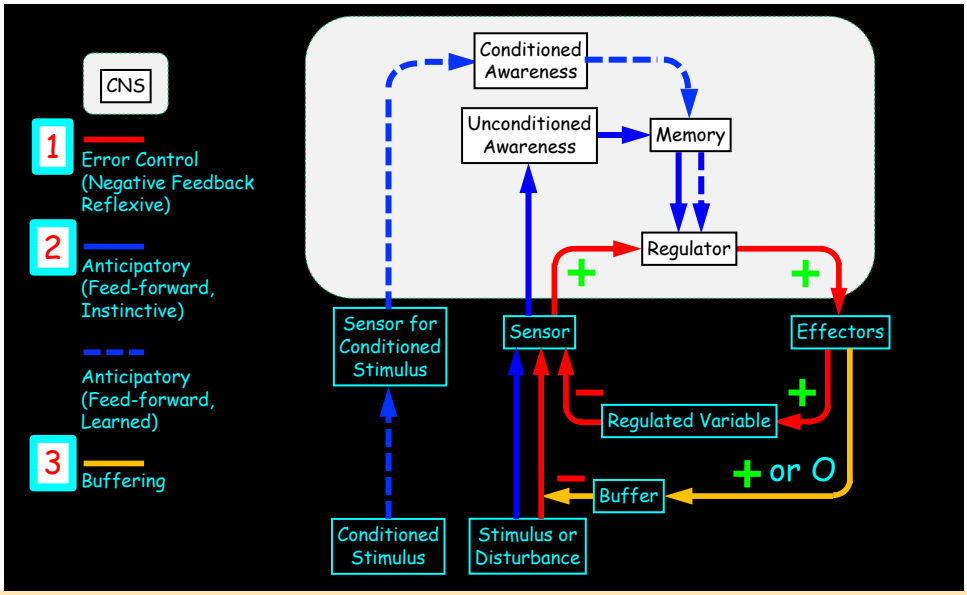


Fig. 149: Three ways homeostasis happens. *One can conceptualize three mechanisms of homeostasis—error control (negative feedback), anticipatory (feed-forward), and buffering. Anticipatory regulation can be instinctive or learned.*

Examples of behavioral responses to buffer the cold include huddling, seeking shelter, hibernation, and bird migration. Humans can also don appropriate clothing, which is applying a buffer. Thus, buffering can be energy-dependent or energy-independent. In the Figure, the + or 0 refers to buffering that depends on or occurs independently of effector activation.

The following sections go into more detail about the three ways homeostasis is maintained.

Error-Controlled (Reflexive) Regulation

Reflexive regulation by negative feedback (error control) is a key mechanism for maintaining physiological homeostasis and is a founding principle of integrative physiology and autonomic medicine. Perhaps surprisingly, Cannon did not formally include negative feedback regulation in his theory of homeostasis.

Negative feedback regulation is a founding principle of autonomic medicine.

Probably the first researcher to emphasize physiological regulation by negative feedback was the Russian physiologist, Pyotr K. Anokhin (1898-1974) in the mid-1930s.

Anokhin's "theory of functional systems" involved feedback of two types, the first similar to homeostasis for regulation of internal variables such as blood pressure and glucose and the second for regulation of behavioral responses based on feedback from environmental signals.

In a retrospective about Anokhin's theory, his disciple K.V. Sudakov wrote, "Any deviation of the parameter from the level required for normal life of the organism immediately elicits (through feedback mechanisms or reverse afferentation after Anokhin), a sequence of processes that develop in central and peripheral tissues in order to restore the optimal level of the given result." One appreciates readily the equivalence of "reverse afferentation" and negative feedback.

In a physiological negative feedback loop, when a perturbation alters levels of a monitored variable, the activity of an effector changes in a way that counters the effects of the perturbation. As we have seen, a negative feedback loop has one (or an odd number) of negative relationships in the cycle. When a variable is regulated by a negative feedback loop, in response to a constant perturbation the level of the regulated variable reaches a steady-state value—homeostasis.

Examples of negative feedback regulation abound in autonomic medicine. For instance, insulin-induced hypoglycemia, via a complex network of peripheral and central mechanisms, evokes marked sympathetic adrenergic system (SAS) activation and adrenomedullary secretion of epinephrine (EPI), which releases glucose into the bloodstream. Performance of the Valsalva maneuver, which decreases venous return to the heart and consequently decreases cardiac stroke volume, reflexively increases skeletal muscle SNS traffic and total peripheral vascular resistance, attenuating the fall in blood pressure. Intravenous injection of cold saline evokes increases in both SNS and SAS and outflows, resulting in cutaneous vasoconstriction and calorigenesis that blunt the fall in core temperature. Standing up (orthostasis) decreases venous return to the heart, and this rapidly increases SNS outflow via low-pressure and arterial baroreceptors.

Anticipatory (Feed-Forward) Regulation

Regulation by negative feedback is essentially reactive. In contrast, feed-forward regulation is mediated by anticipatory adjustments in physiological systems based on awareness of a

previously experienced or instinctively recognized signal, preceding any change in the level of the regulated variable itself.

Feed-forward regulation is more efficient than negative feedback regulation, because it diminishes or eliminates the need for homeostatic adjustments. An example is vagal mediation of the "cephalic phase" of insulin release prior to eating, in *anticipation* of an increase in blood glucose. Another is the pattern of sympathetically mediated hemodynamic changes from "central command" in *anticipation* of exercise.

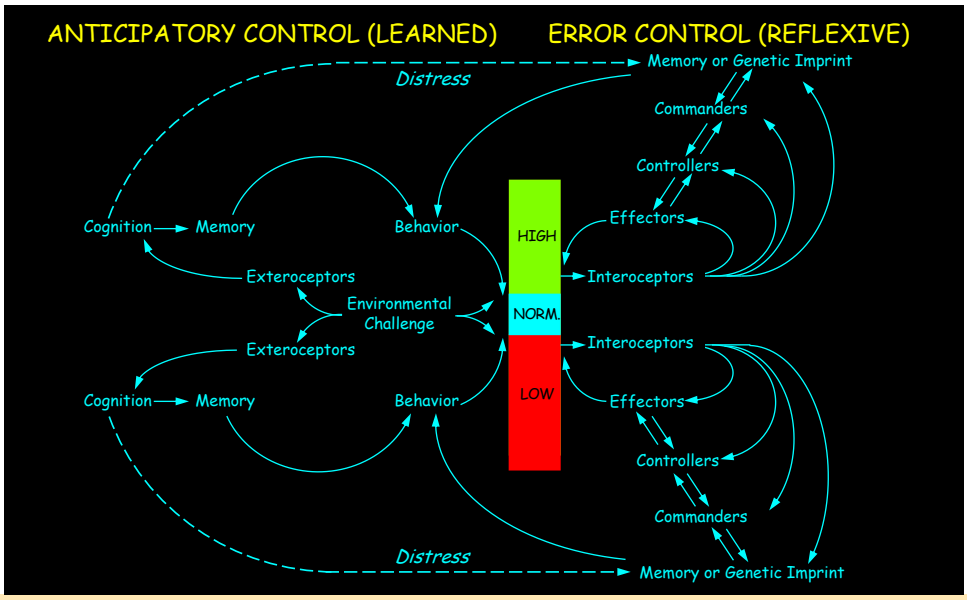


Fig. 150: Anticipatory control vs. error control. *Under ordinary circumstances, levels of regulated variables are kept within bounds by anticipatory (learned) control. When this gives way, error-controlled (reflexive) negative feedback regulation comes into play. Being reactive, error-controlled regulation is associated with greater variability of the monitored variable.*

Cannon was referring to feed-forward mechanisms when he

noted that internal changes during emotional turmoil *prepare* the organism for extreme muscular exertion.

Fig. 150 depicts regulation by anticipatory control vs. error control. Anticipatory control usually is learned and is mediated by or associated with externally observable behaviors (i.e., the somatic nervous system). In contrast, error control is reflexive, mediated by effectors such as components of the autonomic nervous system, and may not be associated with externally observable behaviors.

Under normal circumstances, in response to anticipation of environmental challenges (e.g., going out into the cold outdoors) levels of regulated variables are kept within bounds mainly by anticipatory behaviors (e.g., donning a jacket), the elicitation of which depend on input from exteroceptors (e.g., visual input), perception of the meaning of the input (e.g., awareness that snow is falling), and memory (when snow falls, the temperature is cold). The behavior prevents exposure to the environmental challenge from actually altering levels of the regulated variable, the core temperature.

When anticipatory, learned behaviors to deal with cold exposure are insufficient and an actual change in the level of core temperature occurs, the situation evokes reflexive increases in sympathetic noradrenergic and adrenergic outflows, which by cutaneous vasoconstriction and calorigenesis help maintain core temperature. The reflexive responses may include certain externally observable behaviors, such as shivering, piloerection, and folding the arms. In distress, awareness and memory result not only in behaviors (e.g., flight) but also in changes in reflexive regulation (dashed

lines).

Buffering

A third, relatively recently conceptualized mechanism for maintaining homeostasis is “buffering.” Buffering is a means of diminishing the intensity of an external disturbance, thereby reducing the required use of reflexive homeostatic mechanisms. Just as insulation in the walls of a house diminishes the requirement of internal adjustment by a furnace in cold weather, many mammals have fur, which creates a layer of motionless air as an insulator above the skin. Other examples of genetically determined insulation include blubber in whales and closely packed feathers in birds. The barrier to heat loss can be enhanced during more severe cold exposure by reflexive bristling of the hair, mediated by sympathetic nerves; this increases the depth of the layer of motionless air.

In addition to these inherited and acquired forms of buffering, countercurrent heat exchange is a relatively common, efficient mechanism in animals that limits heat loss through the surfaces of the body exposed to an extremely cold environment (polar regions or ice cold water). The preservation of heat is the result of differences in the temperature in closely adjacent arterial and venous blood vessels. Heat from arterial blood warms the cold venous blood returning from the cold surface, diminishing heat loss from the surfaces exposed to the cold. This arrangement occurs in the feet of penguins standing on ice and of wading birds in cold water, the paws of the arctic fox, and the tongue of the whale filtering plankton in cold water. The heat transfer between the countercurrent flows depends on the difference in

the temperatures and does not require energy other than that required to maintain the flows.

A somewhat more complex countercurrent system in some species has evolved that cools the brain during exposure to high environmental temperatures. This involves two sequential heat transfers. During inhalation, particularly during panting, moisture evaporation cools the nasal mucosa. A second heat transfer occurs when the cooler venous blood from the nasal mucosa flows into the pterygoid plexus surrounding the carotid *rete* (from the Latin for "meshwork") in a sinus at the base of the brain. Here there is a countercurrent transfer of heat from the warm arterial blood, which flows in the direction opposite to the cooler mucosal venous blood. The cooled arterial blood enters the circle of Willis and is delivered to the brain during exposure to a hot environment. This countercurrent exchange mechanism has been described in sheep, cats, and other species.

Humans do not have a carotid *rete*. In the course of human evolution, perhaps evaporative heat loss from naked skin became so efficient for controlling core temperature that a separate brain cooling mechanism became unnecessary. It has been hypothesized that the diversity in human craniofacial features (e.g., nostril size) in different geographical regions reflects different advantages of mechanisms for selective brain cooling in hot environments. Instead of brain cooling, however, it may be that in a warm, humid climate having a wide nose allows more air to be inhaled with less effort, whereas in a cool, dry climate this could more irritating than helpful, and having narrow nostrils might help warm the inhaled air.

ROLES OF THE BRAIN IN HOMEOSTASIS

In higher organisms, maintaining homeostasis depends on complex coordination by the brain. Just as the brain receives information from sense organs about and determines our interactions with the outside world, the brain also receives information from internal sensors and acts on that information to regulate the inner world. For most of our lives the brain tracks many monitored variables by way of internal sensory information and acts on that information to maintain levels of monitored variables by modulating numerous effectors that work in parallel.

Marthe Vogt was a pioneer of catecholamine neurochemistry in the brain.

Fig. 151: Marthe Vogt. *Vogt proposed that norepinephrine is a neurotransmitter in the brain.*

She was already a prominent neuroscientist and pharmacologist when she escaped Nazi Germany for England to work with Sir Henry Dale. In 1936 they published the first report that acetylcholine is a neurotransmitter at skeletal neuromuscular junctions. It was partly for this discovery that Dale shared a Nobel Prize with Otto Loewi the same year.

In 1954 Vogt noted large regional differences in concentrations of norepinephrine (at the time still termed "sympathin," following Cannon's concept) in the brain. This heterogeneity could not be explained by norepinephrine in blood vessel walls and suggested that norepinephrine may be a neurotransmitter. Vogt's proposal proved to be correct.

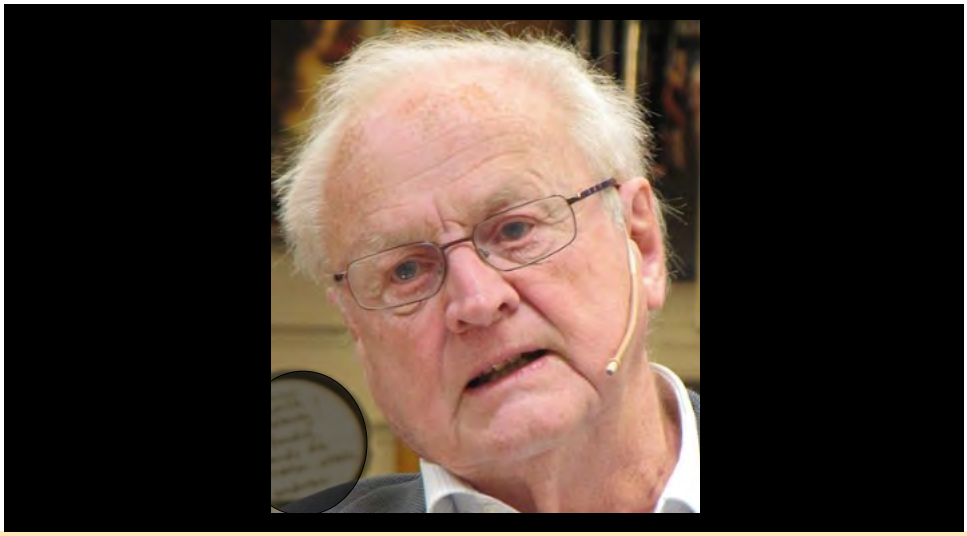


Fig. 152: Arvid Carlsson (Nobel Prize, 2000). *Carlsson discovered that dopamine is a neurotransmitter in the brain.*

Until about the 1950s, dopamine had been assumed not to have any specific function in the body beyond serving as a chemical intermediary in the production of adrenaline and norepinephrine.

The Swedish physiologist Arvid Carlsson discovered that dopamine in the brain acts as a neurotransmitter in its own right and is of great importance in regulation of movement. This discovery led to Carlsson's sharing a Nobel Prize with Julie Axelrod in 1970. Carlsson also demonstrated that effective drugs to treat schizophrenia work by blocking dopamine receptors in the brain.

Two other Swedish researchers, Annica Dahlstrom and Kjell Fuxe, subsequently described catecholamine pathways and centers that were distinct from traditional neuroanatomic tracts and nuclei.

Over the next half century, catecholaminergic neurochemical pathways in the brain were described in detail. Adding to the richness of this diversity, Tomas Hökfelt reported evidence for co-storage of peptides with catecholamines in brainstem neurons, and Geoffrey Burnstock introduced the concept of purinergic autonomic nerves. The field of "chemical coding" based on co-transmission in the brain and periphery continues to evolve.

Catecholamines in the brain are found in two norepinephrine and three dopamine pathways and in specific clusters of brainstem and hypothalamic neurons. Different functions of dopamine have been proposed in its three chemical pathways.

The nigrostriatal system is the main source of dopamine in the brain and the main determinant of dopamine effects on movement. Nerve fibers in this system travel from pigmented cells in the substantia nigra ("black substance") in the midbrain portion of the brainstem to much larger structures toward the

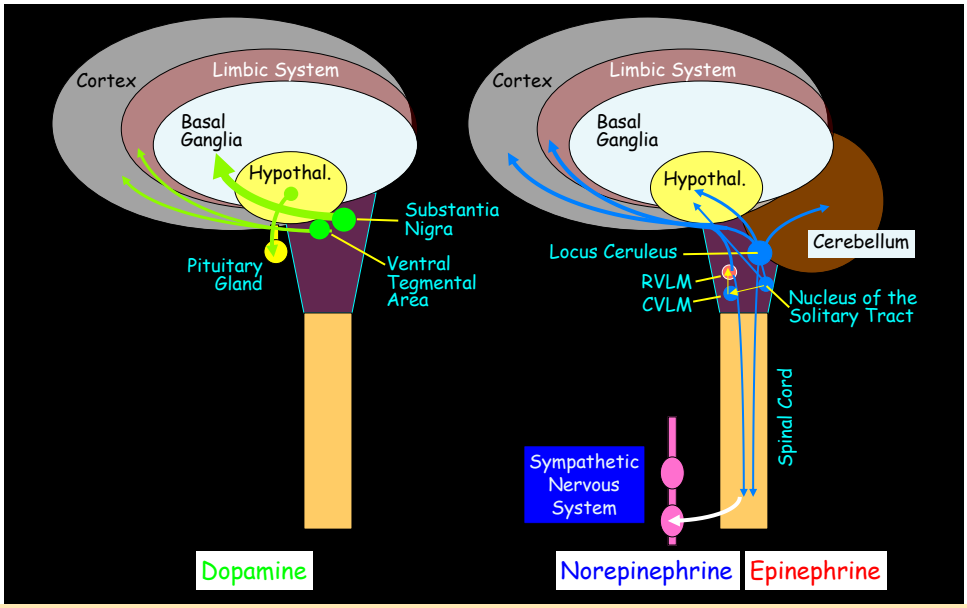


Fig. 153: Central neural catecholamine pathways.

middle front of the brain. These structures are collectively called the "basal ganglia."

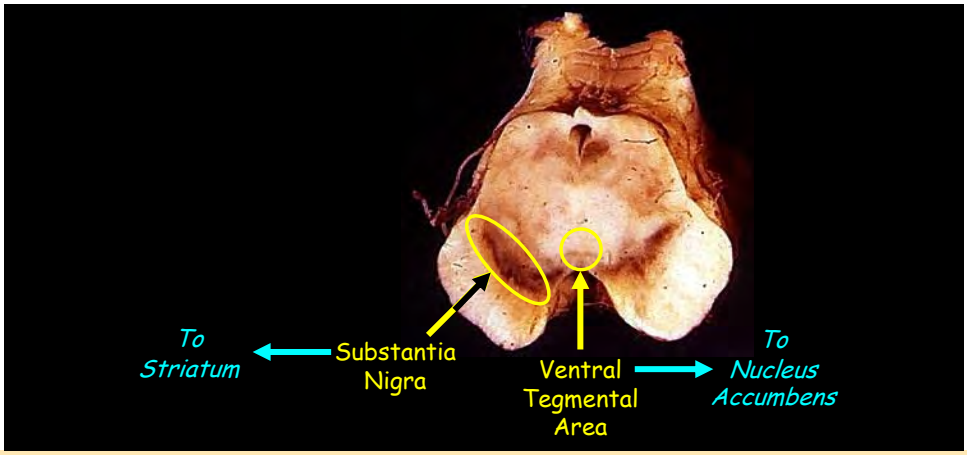


Fig. 154: Midbrain dopaminergic centers. *Dopamine-containing neurons are abundant in the substantia nigra and ventral tegmental area.*

The nomenclature for the components of the basal ganglia can

be confusing. The basal ganglia include the caudate ("tail-like") nucleus and lenticular ("lens-like") nucleus. The lenticular nucleus, in turn, consists of the putamen and globus pallidus. The corpus striatum, often simply called the striatum, consists of the caudate and putamen. One would think the striatum and globus pallidus would be synonymous with the basal ganglia, but some authorities include other components in the basal ganglia.

Loss of dopamine in the striatum (especially the putamen) produces the movement disorder that defines Parkinson's disease.

The mesolimbic (or mesocortical or mesolimbocortical) system sends dopamine fibers from the ventral tegmental area (VTA) in the midbrain to the nucleus accumbens and then to other parts of the limbic system, such as the hippocampus and amygdala, and to parts of the cortex, such as the anterior cingulate cortex and pre-frontal cortex. It is thought that this system is dysfunctional in schizophrenia, because many effective drugs for schizophrenia appear to work by blocking the effects of dopamine in this system. In the mesolimbic system, dopamine seems to increase locomotion and positive reinforcement, not so much due to pleasurable reward sensations as due to an enabling action that decreases the threshold for initiating responses. Functional alterations of the mesolimbic system are associated with all known forms of addiction.

The tuberoinfundibular (or tuberohypophyseal) system delivers dopamine from cells in the hypothalamus to the pituitary gland. Dopamine in the pituitary gland inhibits production of

prolactin. In postpartum women who don't want to breast-feed, a single injection of bromocriptine, which stimulates dopamine receptors, prevents lactation.

Complete destruction of all dopamine systems in the brain produces a syndrome of decreased movement, inattention, decreased food intake, and decreased fluid intake and gives the appearance of generalized behavioral unresponsiveness. This "dopamine deficiency syndrome" applies to all voluntary acts requiring motivation, sustained alertness, and receptiveness to sensory input. Animals deficient in dopamine fail to initiate coordinated movements and fail to orient to sensory stimuli. Motivated behaviors are not eliminated, but the arousal threshold appears to be increased before the behaviors are elicited. Most of the research in this area has depended on administration of a neurotoxin to produce chemical destruction of dopamine cells and terminals; however, the same neurotoxin also destroys noradrenergic cells and terminals.

Increased occupation of dopamine receptors in the brain, such as produced by DOPA, amphetamines, or drugs that stimulate dopamine receptors directly, produces hyperactivity, stereotyped involuntary movements, agitation, psychosis, and risk taking. Patients with Parkinson's disease who take dopamine receptor stimulants can have a surprisingly high frequency of an unusual but related side effect—gambling.

Norepinephrine also is an established neurotransmitter in the brain, although little is known about what exactly it does in humans. Based on studies in animals, rather than acting as a direct inhibitor or stimulator of neuronal function, norepinephrine seems to modify responsiveness to other inputs.

Activation of the locus ceruleus, the brainstem source of most of the norepinephrine in the brain, biases attention toward novel, rapidly changing signals from sense organs monitoring both the outside and inner worlds. Norepinephrine in the locus ceruleus system may therefore play a role in vigilance behavior and in registration of distressing events in long-term memory.

A descending pathway from brainstem norepinephrine-producing neurons down the spinal cord seems to contribute to "stress-induced analgesia." If you've ever played in an athletic competition involving repeated bouts of running and noticed painful foot blisters after the game is over, you know what stress-induced analgesia is.

Lower in the brainstem, norepinephrine-producing cells participate in neurocirculatory reflexes. Most of the evidence for such a role comes from studies of the baroreflex in laboratory animals. Norepinephrine-producing cells are abundant in the nucleus of the solitary tract (NTS), which is the site of termination of input from the baroreceptors to the brain. From the NTS, nerve fibers branch widely as they ascend to higher levels of the central nervous system, such as the hypothalamus and amygdala. Conversely, as part of coordinated behavioral, emotional, and autonomic nervous system responses, descending pathway traffic in fibers from higher centers to the NTS can "reset the barostat" and redefine "normal" blood pressure. A loss of norepinephrine-producing cells in the NTS can help explain why some neurodegenerative diseases feature extreme swings of blood pressure.

Despite the fact that both dopamine and norepinephrine are known neurotransmitters in the brain, and despite the apparent

involvement of dopamine systems and norepinephrine systems in responses to a variety of environmental and internal inputs, interactions between dopamine systems and norepinephrine systems have received relatively little research attention, especially in humans.

The rostral ventrolateral medulla (RVLM) includes neurons called C1 neurons that contain the enzyme PNMT, which catalyzes the conversion of norepinephrine to adrenaline. C1 neurons therefore are thought to be adrenergic. RVLM neurons are a major source of descending projections to the sympathetic pre-ganglionic neurons in the intermediolateral columns of the spinal cord. They also project rostrally to the paraventricular nucleus of the hypothalamus. According to one view, the C1 neurons are the "body's EMTs" because of their involvement with emergency responses to pain, infection, blood loss, hypoxia, and hypoglycemia—analogous to the sympathetic adrenergic system in the periphery.

The generally accepted view from the 1950s until the 1970s was that the summed activity of diffusely interconnected fibers of the "reticular activating system" in the brainstem randomly generated autonomic outflows, as if there were an impenetrable neuronal thicket that intervened between interoceptive input and autonomic output from the brain.

Several developments forced abandonment of this concept. Most interoceptive inputs to the brain were found to terminate in a specific cluster of cells in the dorsomedial medulla, the nucleus of the solitary tract (NTS). Another small collection of neurons in the rostral ventrolateral medulla (RVLM) was found to be a major source of descending

projections to the sympathetic pre-ganglionic neurons in the lateral horns of the spinal cord. Tract tracing experiments showed that ascending and descending information between the lower brainstem and higher centers travels in extensively branching ("arborized") fibers among relatively few clusters of neural cells, rather than in a diffuse reticular system. Neurophysiological studies demonstrated that pre-ganglionic sympathetic neurons discharge rhythmically, the rhythmic discharges depending importantly on lower brainstem networks including coupled oscillators that inherently generate the rhythm—a pacemaker for sympathoneural outflow.

The findings of Dahlstrom and Fuxe demonstrating specific catecholaminergic pathways led to fundamentally new ideas about functional connections in the brain and ushered in the era of "chemical neuroanatomy."

The Central Autonomic Network

Several cortical, subcortical, and brainstem centers in a network participate in regulation of outflows to the autonomic nervous system. This has been called the "central autonomic network." The central autonomic network is diagrammed in Fig. 155.

Cortical centers include the prefrontal cortex, anterior cingulate cortex, and insular cortex. Subcortical centers include the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus.

Brainstem centers include the peri-aqueductal gray (PAG) region in the midbrain, the parabrachial nucleus (PBN) at the

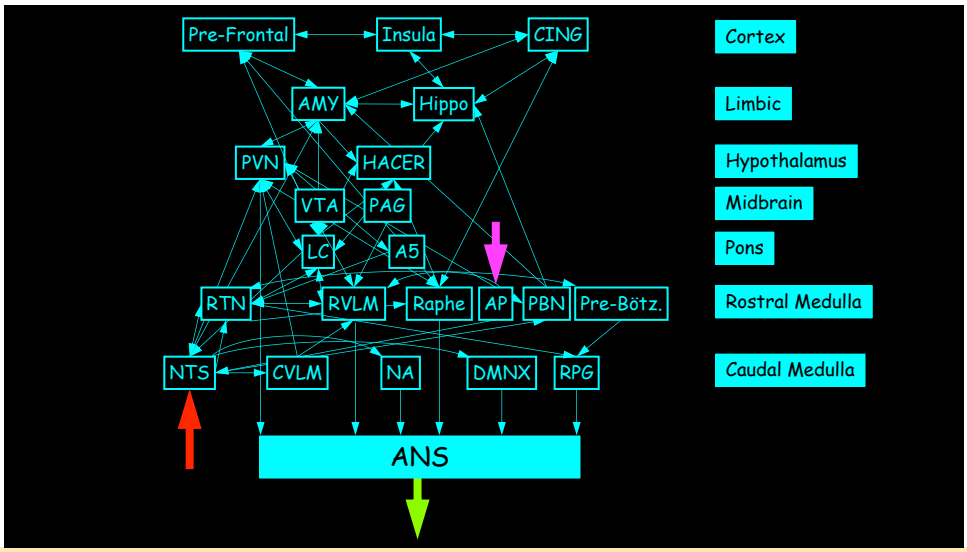


Fig. 155: The central autonomic network. *The central autonomic network is a complex anatomically defined meshwork relating clusters of neurons in the brainstem, limbic system, and cortex. The main inputs are via nerves that reach the nucleus of the solitary tract (NTS, red arrow) and circulating substances that reach circumventricular areas where there is a penetrable blood-brain barrier such as the area postrema (AP, magenta arrow). Autonomic outflows are regulated in a differentiated manner, although in the diagram the autonomic nervous system (ANS, green arrow) is depicted as a unitary entity.*

junction of the midbrain and pons, the locus ceruleus (LC) in the dorsal pons, and the raphe nuclei, rostral ventrolateral medulla (RVLM), caudal ventrolateral medulla (CVLM), dorsal motor nucleus of the vagus (DMNX), nucleus ambiguus (NA), and the nucleus of the solitary tract (NTS) in the medulla.

The central autonomic network is organized not only in neuroanatomic terms but also in neurochemical terms and

includes systems for each of the body's three catecholamines. This is diagrammed in Fig. 156.

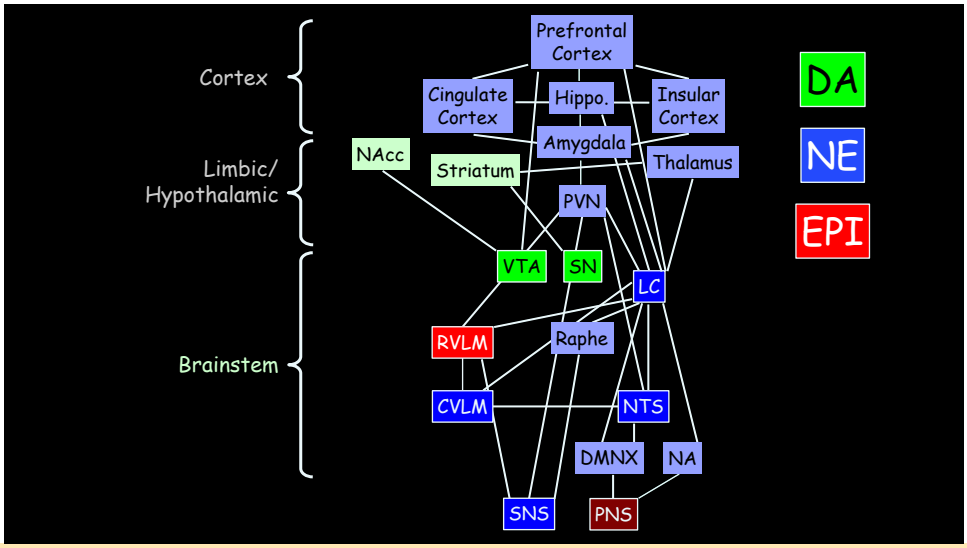


Fig. 156: Catecholamines and the central autonomic network. *Catecholaminergic centers defined neurochemically are related to anatomic locations in the central autonomic network.*

The locus ceruleus in the pons supplies noradrenergic fibers to most higher centers in the brain (an exception is the hypothalamus, which receives noradrenergic fibers from medullary noradrenergic neurons). Dopaminergic fibers in the brain emanate mainly from the substantia nigra and ventral tegmental area in the midbrain. The nigral neurons richly innervate the striatum (caudate and putamen), and the nigrostriatal system is important in initiation of movement. The ventral tegmental neurons innervate the nucleus accumbens, and the nucleus accumbens is important for motivation, pleasure, reward, and reinforcement learning and therefore in addiction.

Epinephrine-synthesizing neurons in the rostral ventrolateral medulla project in the intermediolateral columns of the spinal cord to the sympathetic pre-ganglionic neurons.

In most of the brain epinephrine is not normally detected. It is possible that in distressing situations evoking substantial adrenomedullary secretion, epinephrine can increase blood pressure sufficiently that it interferes with its own blood-brain barrier and enters the brain.

In 1883, Ivan Pavlov reported his studies showing that the "centrifugal nerves of the heart" accelerated and augmented heart contraction. The nerves were traced to their source in the lateral horns of the spinal cord.

At about the same time, other investigators noted the indirect, reflexive cardiovascular effects of stimulating neural pathways traveling to the brain. In 1836, Sir Astley Cooper showed that occluding the common carotid arteries increased blood pressure and heart rate, and in 1900 Siciliano proposed that a signal to the brain comes from the region where the carotid artery splits into the internal and external carotid arteries.

In 1923, Heinrich Hering found that mechanical stimulation of the wall of the carotid sinus, a small area of dilatation in the region of the carotid bifurcation, produced marked decreases in heart rate and blood pressure—and the "baroreflex" was born. The carotid sinus nerve (also called "Hering's nerve") travels in the glossopharyngeal nerve (the ninth cranial nerve) to the lower brainstem.

After Hering's discovery of the carotid sinus nerve, the Belgian

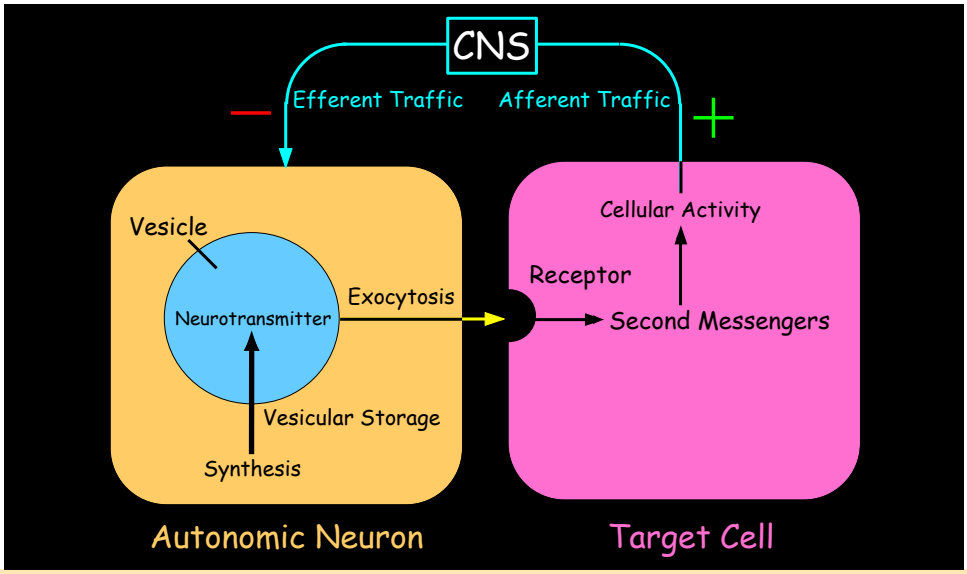


Fig. 157: "Long-distance" regulation of the ANS. *Afferent information to the brain and efferent ANS outflows complete "long-distance" negative feedback loops. Compare with the chemical messaging diagram in Fig. 66.*

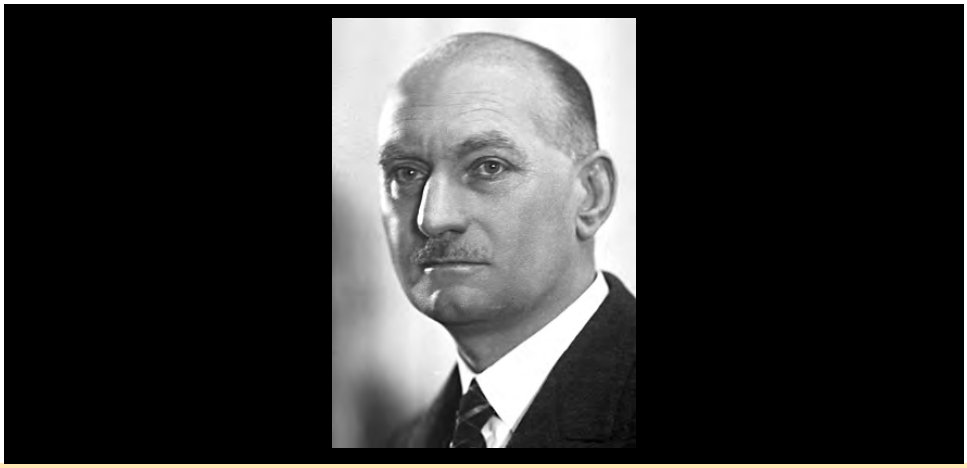


Fig. 158: Corneille Heymans (Nobel Prize, 1938). *Heymans received a Nobel Prize for his studies of reflexes regulating breathing and blood pressure.*

physiologist Corneille Heymans (along with his father, J. F. Heymans) studied reflexive regulation of breathing based on

afferent input to the respiratory center in the brainstem from the carotid sinus region.

The experiments exploited an extraordinary preparation developed by the senior Heymans that made it possible to keep alive the completely isolated head of a dog by perfusion of blood from another dog, while the body was also kept alive with the help of artificial respiration. This meant that the only communication between the head and the rest of the body was provided by the nerves.

Heymans showed that when the lungs expand, inspiration reflexively ceases, and when the lungs are collapsed, inspiration reflexively is stimulated (the Hering-Breuer reflex).

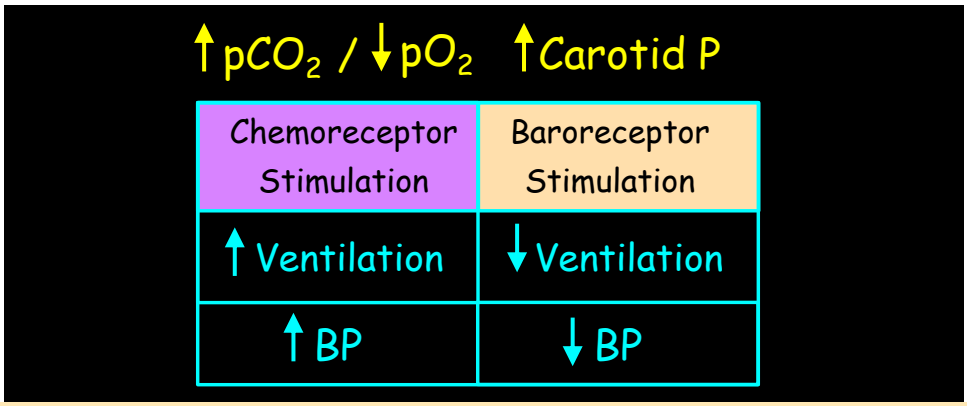


Fig. 159: Heymans's chemoreflex and baroreflex. *This 2 X 2 table summarizes Heymans's findings about the chemoreflex and baroreflex.*

If the tension of carbon dioxide in the arterial blood to the head increased, or the oxygen tension decreased, ventilation increased reflexively (the chemoreflex). Heymans also demonstrated that high blood pressure at the carotid sinus

reflexively relaxes blood vessels and decreases the heart rate (the arterial baroreflex). And he proposed that the carotid sinus baroreflex reflexively modifies adrenomedullary secretion. For this work Heymans received a Nobel Prize in 1938.

Heymans's findings can be depicted by a two-by-two table, in which increasing carbon dioxide tension or decreasing oxygen tension in the carotid arterial blood not only reflexively increases respiration, via chemoreceptors in the carotid body, but also constricts blood vessels and increases heart rate; and increasing carotid arterial pressure not only relaxes blood vessels and slows heart rate but also decreases respiration, via carotid sinus stretching and baroreceptor stimulation.

How Not to Treat Sleep Apnea

The homeostat idea helps conceptualize clinical phenomena in autonomic medicine. Consider the following case of a patient who was referred for evaluation of autonomically-mediated hypertension. He had "complex" sleep apnea, meaning that his condition worsened rather than improved with continuous positive airway pressure (CPAP).

The complex sleep apnea included Cheyne-Stokes respiration (rhythmic cycles of hyperventilation and apnea during sleep), and he had learned that in patients with heart failure CO_2 inhalation abolishes Cheyne-Stokes respiration. He brought with him and used during his hospitalization at the NIH Clinical Center a modified CPAP device that administered CO_2 via the mask. He had also been diagnosed with a form of renal tubular acidosis and panic/anxiety.

The directly recorded brachial systolic blood pressure was dangerously high at about 250 mmHg. There were very high arterial plasma levels of norepinephrine and adrenaline, and baroreflex-cardiovagal gain was near zero.

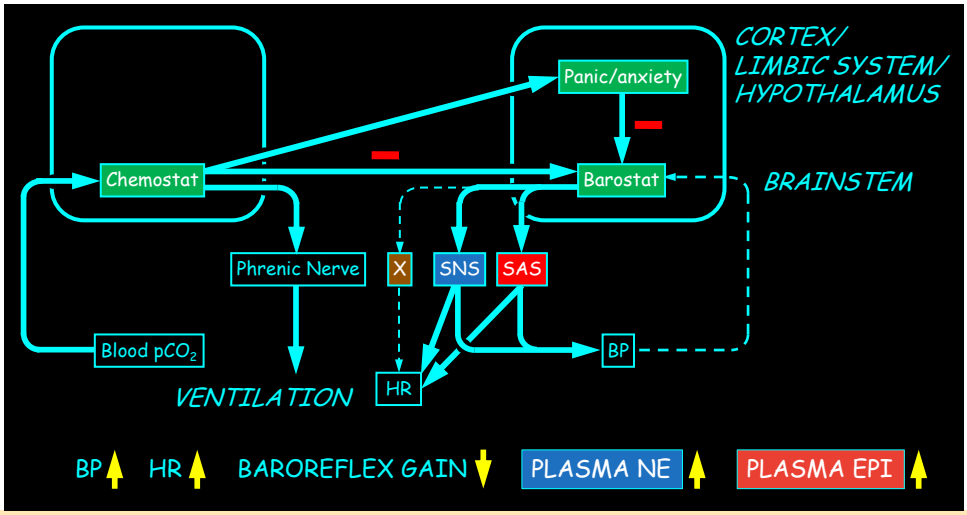


Fig. 160: An unusual case of sleep apnea. *The patient intentionally inhaled carbon dioxide in his CPAP mask. Chemoreflex stimulation blocked the barostat and evoked panic/anxiety, releasing the SNS and SAS from baroreflex restraint and causing paroxysmal hypertension.*

Analysis of the case was as follows. Inhaling CO_2 produces a metabolic acidosis by reacting with body water to generate carbonic acid. The patient's chemostat sensed the hypercarbia and metabolic acidosis, and this released the sympathetic noradrenergic and adrenergic systems from barostatic restraint, blocked the cardiovagal limb of the baroreflex, and evoked a panicky feeling. High sodium bicarbonate intake likely exacerbated the hypertension.

The most effective therapy for this patient's profound dysautonomia was education. (The sections on clinical management later in this book emphasize that education is the most effective, safest treatment for dysautonomias.) He was counseled not to inhale CO_2 via his CPAP device and to stop taking sodium bicarbonate.

Cortical Restraint and the Hypothalamus

Cannon studied not only peripheral autonomic systems but also sites in the brain that regulate them. In the 1920s he noted that removal of the cerebral cortices evoked rage behavior, accompanied by high blood glucose levels. Decorticated adrenalectomized animals exhibited the same behavior, but without hyperglycemia. These findings fit with cortical restraint of primitive emotional behaviors and of emotion-associated adrenaline release. Cannon's student, Philip Bard, obtained evidence that physiological concomitants of primitive emotions originate in the hypothalamus.

In the 1920s and 1930s the Swiss physiologist Walter Rudolf Hess focused on the functional organization of the hypothalamus with respect to the regulation of parasympathetic and sympathetic outflows.

Hess showed that stimulation of the same hypothalamic sites that altered functions of internal organs via sympathetic outflows (pupillary dilation, hair bristling, and tachycardia) also evoked particular behaviors that seemed to be directed outwards towards the environment ("ergotropic" effects). In contrast, stimulation of other sites evoked slow heart rate, salivation,

pupillary constriction, vomiting, urination, and defecation, consistent with generalized parasympathetic activation. These autonomic effects also were associated with particular behaviors (e.g., postural change associated with defecation).

Fig. 161: Walter Rudolf Hess (Nobel Prize, 1949). *Hess received a Nobel Prize for discoveries about the role of the hypothalamus in controlling functions of internal organs.*

Hess viewed these changes as protection against a kind of internal overloading ("trophotropic"). The sympathetic-ergotropic and parasympathetic-trophotropic areas operated as if they were in a dynamic state of equilibrium. For this work Hess received a Nobel Prize in 1949.

BAROREFLEXES

Cannon never referred to homeostasis of any cardiovascular variables. Since his time, however, regulation blood pressure by negative feedback has become a major topic of research in autonomic medicine.

Homeostasis in the cardiovascular system is a prominent topic in autonomic medicine.

The Sleeper Hold

My grandmother and I used to watch professional wrestling on TV. Propped in bed, she would cheer on her hero, Antonino Rocca, the barefoot master of the flying dropkick, and hiss at Skull Murphy, whose specialty was butting opponents senseless with his bald, vaselined head.

In professional wrestling you can win by three smacks on the tarp by the referee, by disqualification, or by submission. In particular, in the "sleeper hold," the attacker suddenly and unexpectedly circles the victim and wraps hands around the victim's neck, as if to choke from behind; but instead of choking the victim, the attacker vigorously massages both sides of the opponent's neck below the angles of the jaw. After several seconds of this massaging, the opponent slumps to the mat unconscious, and by submission that ends the bout.

Over the years I came to question the veracity of professional wrestling, but I do think there is some truth to the sleeper hold.

The story of the sleeper hold teaches that one of the most important examples of negative feedback regulation mediated by the autonomic nervous system is the arterial baroreflex.

Specialized distortion receptors called baroreceptors lie in the carotid sinus, in the crotch of the "Y" where the common

carotid arteries, the main arteries delivering blood to the head, fork in the upper neck. When the blood pressure increases, the wall of the carotid sinus on each side of the neck expands, and this stimulates the baroreceptors in the artery walls.

Nerve traffic to the brain then increases in the carotid sinus nerves and reaches a particular cluster of cells in the lower brainstem—the nucleus of the solitary tract, or NTS. Activation of the NTS cells leads to a rapid, reflexive fall in pulse rate, relaxation of blood vessels, and a less forceful heartbeat. The blood pressure and consequently the blood flow to the brainstem decreases, and the victim loses consciousness.

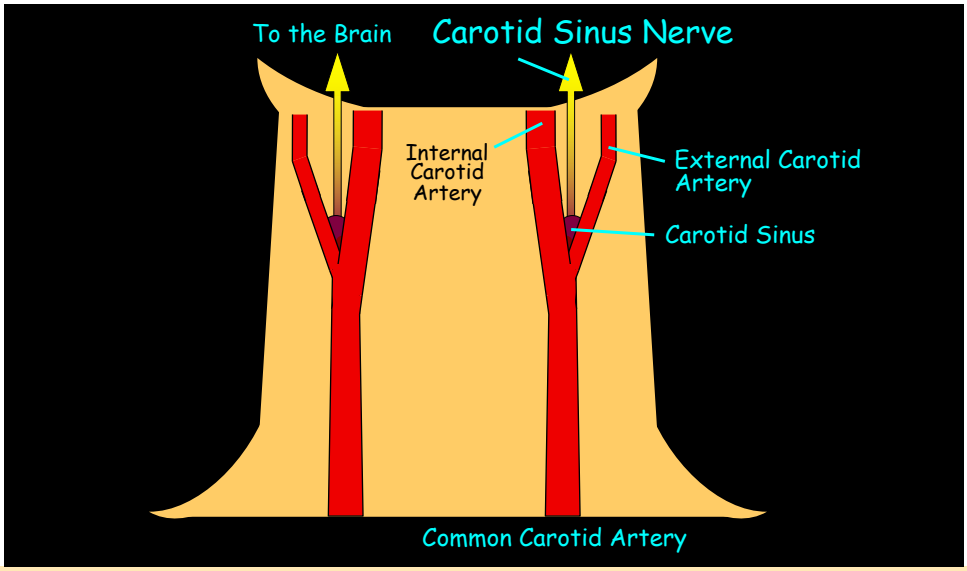


Fig. 162: The carotid sinus baroreflex. *In humans distortion sensors—"baroreceptors"—in the walls of the carotid sinuses send afferent nerve traffic to the brainstem. The efferent limb of the reflex includes altered traffic in autonomic nerves.*

Stimulation of the carotid sinus baroreceptors reflexively decreases sympathetic noradrenergic system (SNS) outflows.

This tends to relax the blood vessels and to decrease the force of the heartbeat.

At about the same time, parasympathetic nervous system (PNS) outflow to the heart via the vagus nerve increases. This also tends to decrease the rate and force of heart contraction. The net effect is to bring the blood pressure down.

It is a teleological idea that in the body there is a reflex that keeps blood pressure in check by negative feedback regulation of the autonomic nervous system. No one really knows the "purpose" of the baroreflex.

The notion that the goal or purpose of the baroreflex is to regulate blood pressure is a teleological idea.

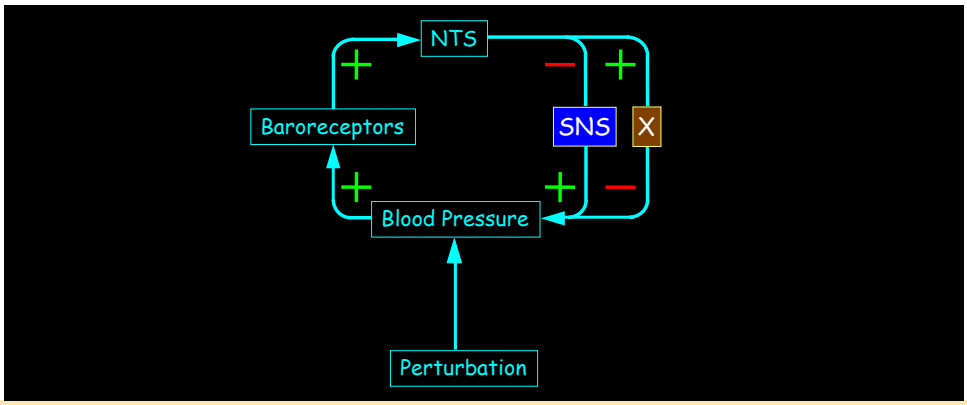


Fig. 163: The SNS and vagus in the baroreflex. *Arterial baroreceptor activation produces opposite effects on sympathetic noradrenergic system (SNS) and parasympathetic vagal outflows. The vagus in the tenth cranial nerve. Note the baroreflex includes 2 negative feedback loops, 1 involving the SNS and the other involving the vagus. The initial brainstem site of input is the nucleus of the solitary tract (NTS).*

The arterial baroreflex involves several other effectors in addition to the SNS and PNS. A sustained decrease in blood pressure releases the arginine vasopressin (AVP) and renin-angiotensin-aldosterone (RAS) systems from baroreceptor restraint. When blood pressure is low enough to become consciously experienced and evokes distress, adrenaline is released.

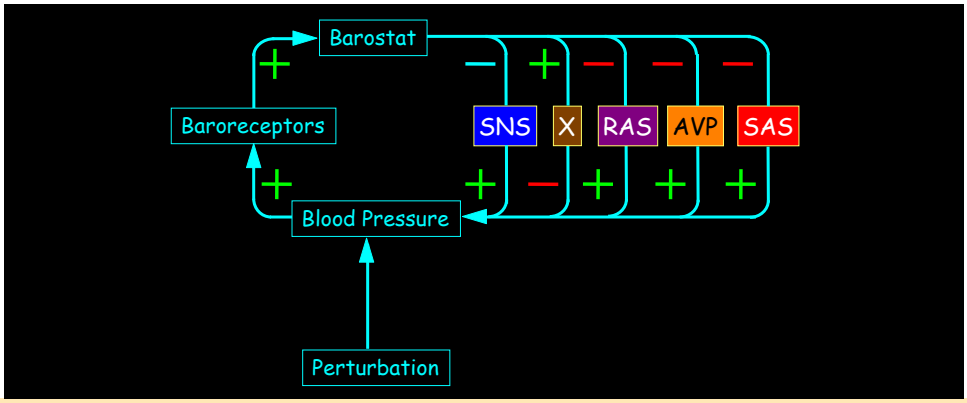


Fig. 164: Multiple baroreflex effectors. *The arterial baroreflex involves multiple effectors, including components of the autonomic nervous system.*

A key sign of arterial baroreflex failure is blood pressure lability.

Patients with arterial baroreflex failure sometimes have hypertension (chronic high blood pressure) or orthostatic hypotension (a fall in blood pressure when standing), but they always have labile blood pressure.

So far we have only considered the “arterial baroreflex.” When

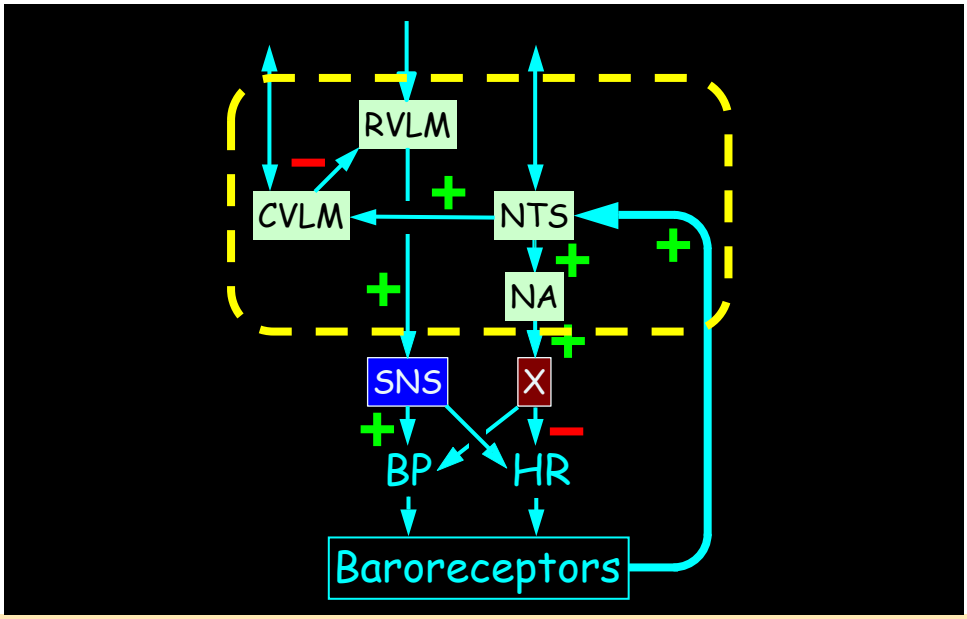


Fig. 165: Medullary components of the "barostat." *The arterial "barostat," delineated by the yellow dashed line, includes clusters of neurons in the nucleus of the solitary tract (NTS), caudal rostrolateral medulla (CVLM), rostral ventrolateral medulla (RVLM), and nucleus ambiguus (NA). The NA is thought to be the major source of cardiac parasympathetic outflow via the vagus nerve (X, for tenth cranial nerve), and the RVLM is the major source of sympathetic noradrenergic system (SNS) outflows to the heart and blood vessels.*

a person stands up there is a decrease in venous return to the heart, and after a few seconds this is translated into a decrease in systemic blood pressure. The decrease in arterial pressure, such as at the carotid sinus, is the source of input to the brain in the arterial baroreflex. There are also distortion sensors in low pressure regions such as the atria and pulmonary veins. These "low-pressure baroreceptors" also send afferent nerve fibers to the NTS in the medulla, arousing reflexive changes in outflows in multiple effectors. The "purpose" of the low-pressure

baroreceptors is a guess, just as is the purpose of the high-pressure baroreceptors. In the schema shown in Fig. 166, the low-pressure baroreceptors are depicted as involved with regulation of extracellular fluid volume or blood volume; the corresponding homeostat is the "volustat."

As complex as the schema in Fig. 166 is, bear in mind that the homeostats ("barostat" and "volustat") and corresponding regulators are only metaphors for complex pathways in the central autonomic network.

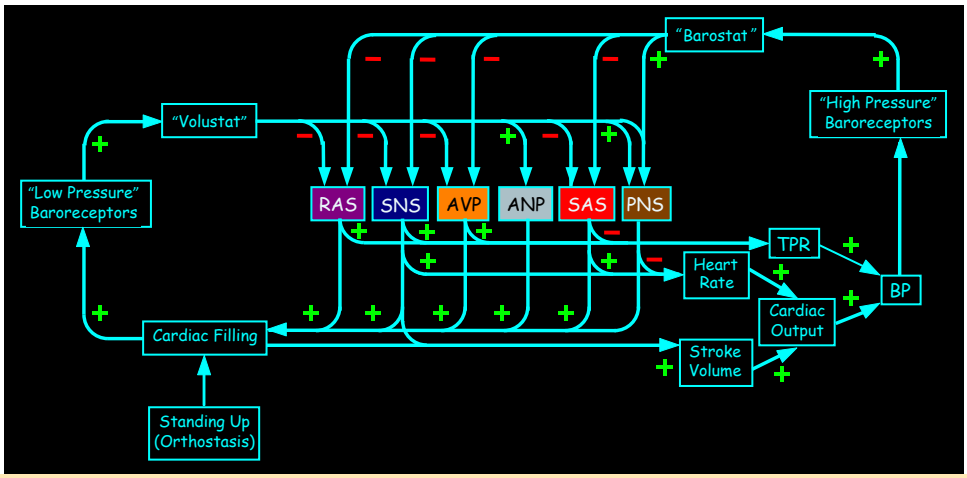


Fig. 166: "Simply" standing up. *Assuming the upright posture (orthostasis) affects complex networks that include high-pressure baroreceptors involved with regulation of systemic blood pressure (the arterial "barostat") and low-pressure baroreceptors involved with regulation of extracellular fluid or blood volume (the "volustat").*

Homeostasis without Homeostats

Although it may be tempting to postulate that there are multiple

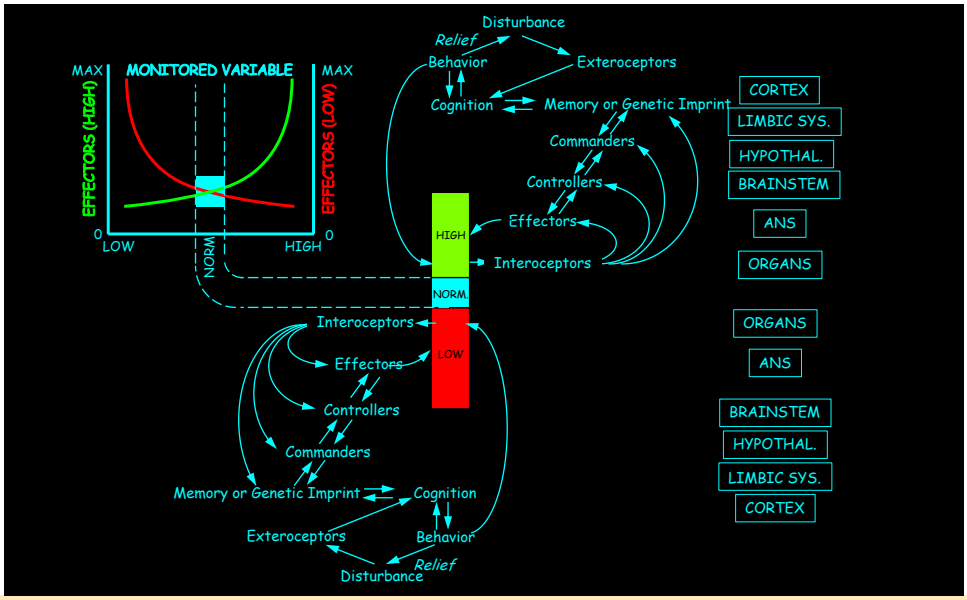


Fig. 167: Homeostasis without homeostats. *At each level of the neuraxis there are feedback loops. Homeostasis of a monitored variable here is attained by complementary actions of two effectors, green responding to increases and red to decreases. Changes in the level of the monitored variable beyond a limit evokes effects at multiple levels of the neuraxis, and the level of the monitored variable is kept within bounds without a comparator (i.e., a homeostat). There are multiple input-output relationships at ascending strata in the neuraxis, from the target organ to lower brainstem "controller" sites mediating reflexes, to upper brainstem/hypothalamic "commander" sites mediating patterned instinctive responses, to limbic sites involving emotional memory and classically conditioned learning, to cortical sites involving social consciousness, restraint of lower centers, instrumentally conditioned learning, and interactions with the environment.*

internal homeostatic systems, each with its own "homeostat"—a "barostat" for regulating blood pressure, a "thermostat" for regulating core temperature, a "glucostat" for regulating blood

glucose levels, an “osmostat” for regulating serum osmolality, and so forth—no comparator has been identified for any regulated internal variable.

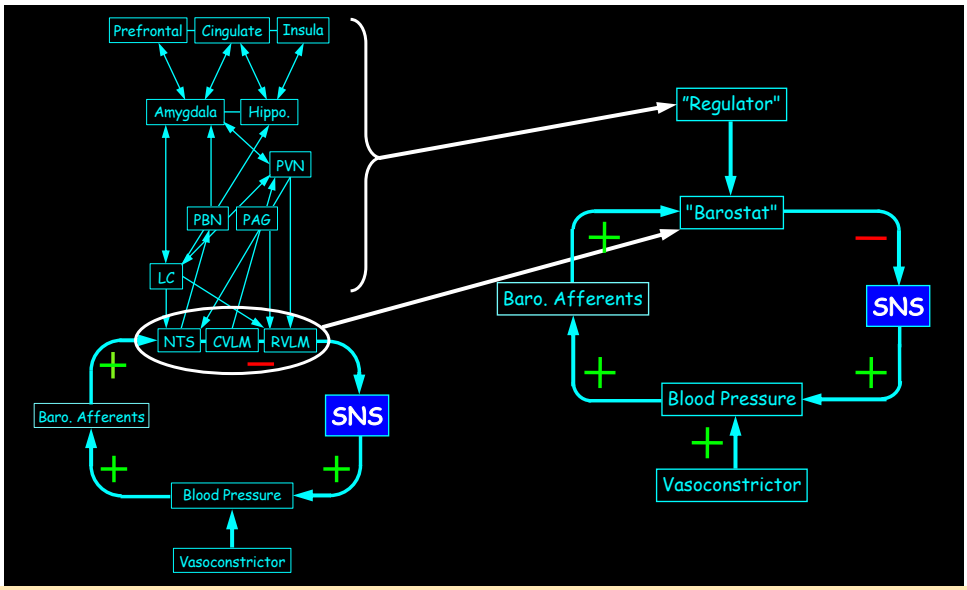


Fig. 168: The barostat as a metaphor. *The “barostat” is a homeostat determining autonomic outflows (e.g., the sympathetic noradrenergic system, SNS) in response to a perturbation of blood pressure (here an increase in pressure from infusion of a vasoconstrictor drug). The barostat and the “regulator” controlling its functions are concepts. The barostat is a metaphor for clusters of neurons in the nucleus of the solitary tract (NTS), caudal ventrolateral medulla (CVLM), and rostral ventrolateral medulla (RVLM). The regulator corresponds to numerous interacting neuron clusters in the central autonomic network. Even the blood pressure here is a concept, in that no one knows if blood pressure is actually the “regulated variable” in the baroreflex.*

Instead there hierarchies of input-output relationships at different levels of the neuraxis.

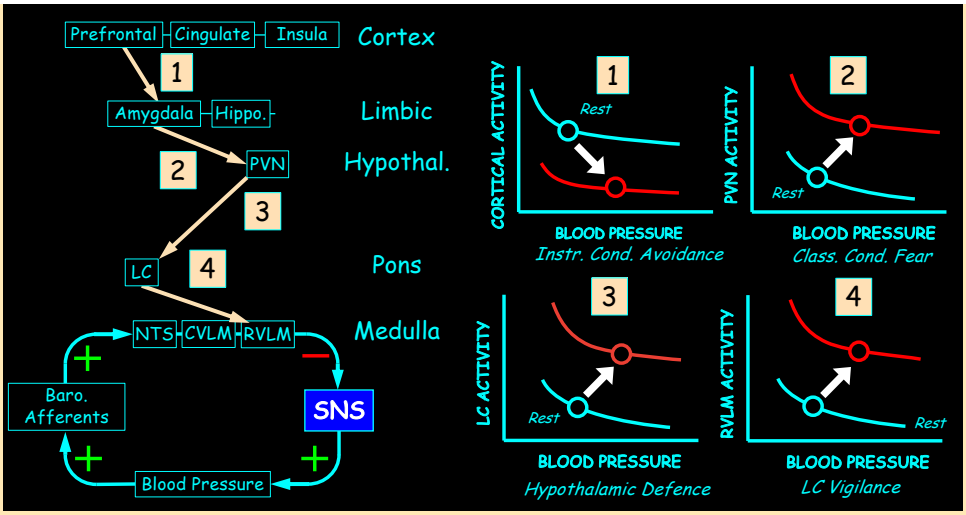


Fig. 169: Homeostasis of blood pressure without homeostats. *In this model blood pressure homeostasis is the product of continual adjustments within hierarchies of input-output relationships. (1) Outer cortical centers involved with instrumentally conditioned behaviors, executive functions, and social restraints modulate the inner cortical limbic system. (2) Limbic system components participating in classically conditioned responses modulate the paraventricular nucleus (PVN) and other hypothalamic neuronal clusters evoking primitive emotional behaviors. (3) The PVN modulates pontine locus ceruleus (LC) noradrenergic neurons that participate in vigilance. (4) LC noradrenergic neurons modulate medullary centers determining descending outflows to sympathetic pre-ganglionic neurons.*

The network is dauntingly complex; however, taken together, the overall functioning of this network corresponds to a regulator for a homeostat—a "barostat." The barostat in Fig. 168 is a homeostat determining reflexive responses of components of the autonomic nervous system (represented here by the SNS) to a perturbation of blood pressure (here an increase in pressure due to infusion of a vasoconstrictor). The

barostat is a metaphor for the clusters of neurons in the nucleus of the solitary tract (NTS), caudal ventrolateral medulla (CVLM), and rostral ventrolateral medulla (RVLM).

The "regulator" corresponds to numerous interacting neuron clusters in the central autonomic network that provide an algorithm for functioning of the barostat.

The notion of hierarchies of input-output relationships maintaining homeostasis without homeostats is illustrated for blood pressure regulation by the SNS in Fig. 169, temperature regulation in Figs. 170 and 171 and glucose regulation in Fig. 172 (compare with Cannon's concept about glucose homeostasis in Fig. 143).

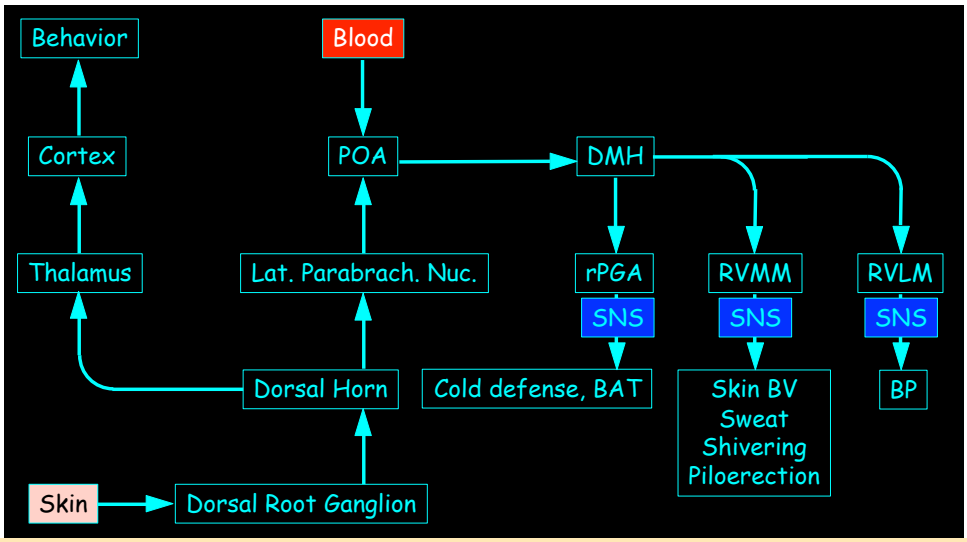


Fig. 170: Thermoregulatory centers. *Afferent information comes from skin temperature sensors and from the temperature of the arterial blood sensed in the preoptic area (POA).*

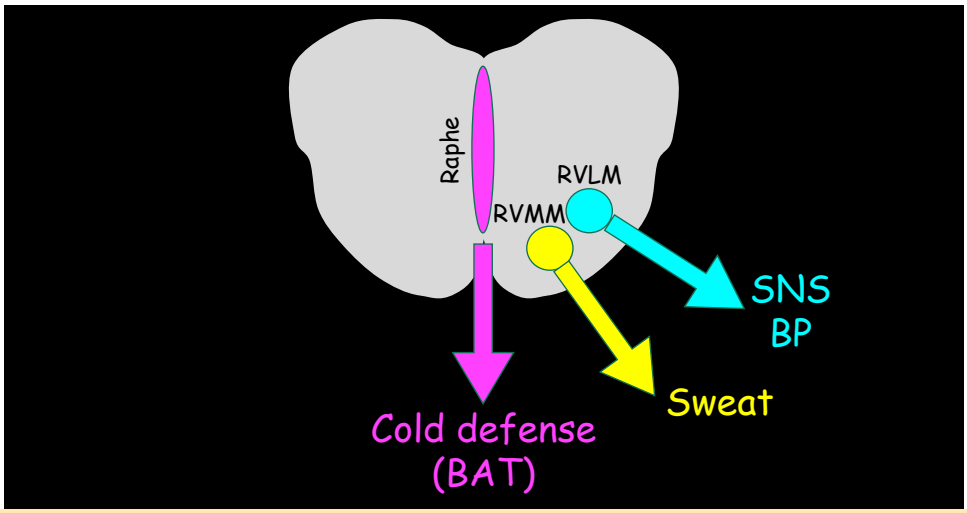


Fig. 171: Medullary thermoregulatory centers. *Raphe serotonergic centers defend against cold via brown adipose tissue (BAT). Rostral ventromedial medulla (RVMM) neurons regulate sweating. The sympathetic noradrenergic system (SNS) and other blood pressure regulating systems determine delivery of blood to the skin surface.*

The American neuropsychologist Antonio Damasio has conceptualized that afferent information to the brain comes from sense organs conveying signals from outside the body and also comes from inside the body in the form of signals ascending in the central nervous system from brainstem neurotransmitter nuclei, muscles and joints, visceral organs, and the circulation (e.g., hormones, cytokines). Stimuli reaching limbic/hypothalamic centers result not only in ascending signals to the outer cortex but also in descending signals to muscles in the face and limbs, the autonomic nervous system, brainstem neurotransmitter nuclei, and the endocrine and immune systems.

Damasio's model resolves a long-standing debate in

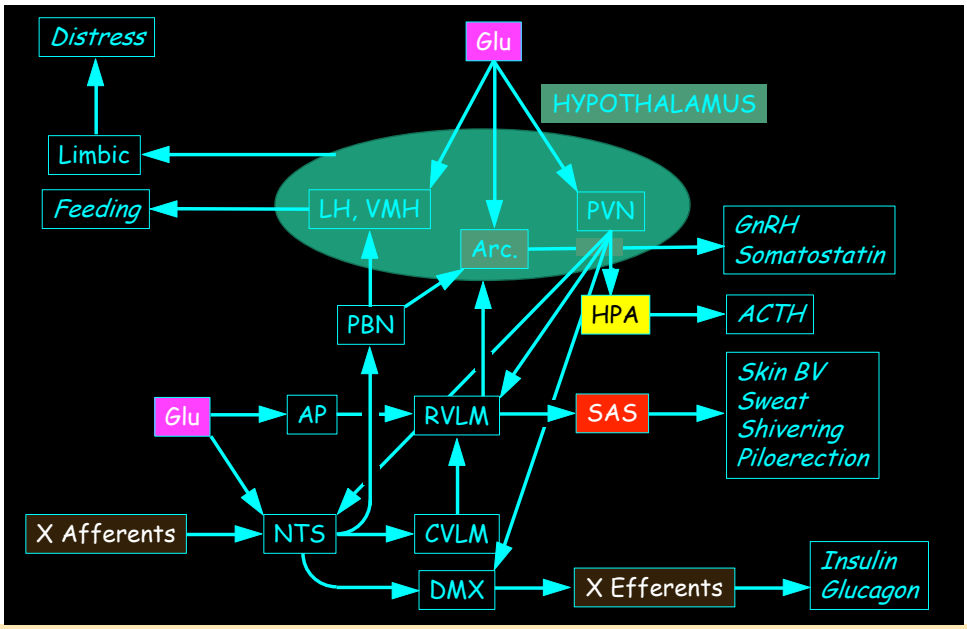


Fig. 172: Glucoregulation centers. *Understanding of brain pathways and centers participating in glucose homeostasis has expanded dramatically since Cannon's time (compare with Fig. 138). The network depicted here is an oversimplification.*

physiological psychology about the James-Lange vs. Cannon-Bard theories of emotion. According to the James-Lange theory, emotion is the product of bodily sensations about physiological arousal reaching the brain, whereas according to the Cannon-Bard theory emotions drive physiological changes. The somatic markers hypothesis incorporates both processes.

In Damasio's recent book, *The Strange Order of Things*, he presents his view that homeostasis is a kind of force ensuring that "life is regulated within a range that is not just compatible with survival but also conducive to flourishing, to a projection of life into the future of an organism or a species."

Damasio seems to be returning here to the teleological positions

of Bernard and Cannon that began this section, with homeostasis being a driving factor and not merely an emergent outcome. About feelings and homeostasis he writes, "…feelings…[are] the subjective experiences of the momentary state of homeostasis within a living body.…"

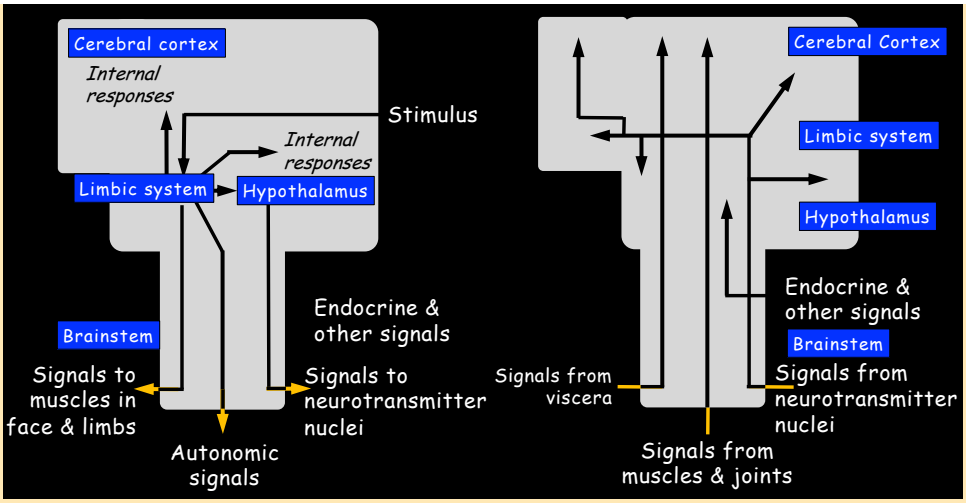


Fig. 173: Damasio's concept of central and peripheral determinants of emotion. *According to the James-Lange theory, emotion is the product of bodily sensations about physiological arousal reaching the brain, whereas according to the Cannon-Bard theory emotions drive physiological changes. Damasio's "somatic markers" hypothesis incorporates both processes.*

STRESS

William Harvey and Autonomic Medicine

William Harvey is regarded as the father of experimental physiology. He was the first to demonstrate the circulation of the blood, in his *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, published in 1628.

Fig. 174: William Harvey (1578-1657). *Harvey's epochal discovery of the circulation of the blood was foundational in physiology and autonomic medicine.*

In the same book Harvey wrote what can be considered the founding statement of autonomic medicine.

> William Harvey wrote, "…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.…"

Selye's "Stress"

Cannon rarely referred to stress. When he did so he always meant an imposed threat to homeostasis.

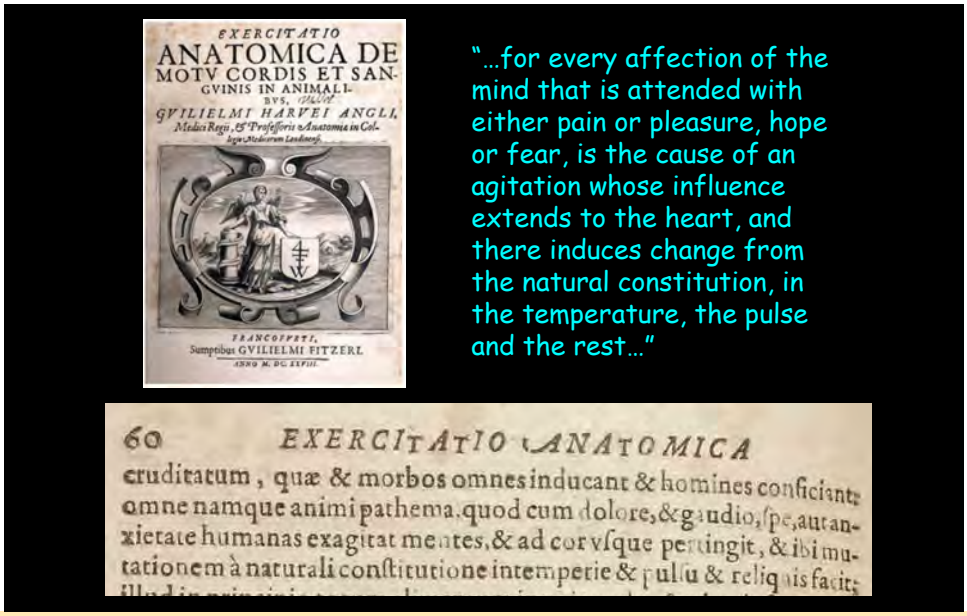


Fig. 175: Harvey, stress, and the heart. *William Harvey's epochal book describing the circulation of the blood also contains a founding statement of autonomic medicine. Translating from the Latin, "…for every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart…."*

Hans Selye popularized stress as a scientific idea.

In a famous letter to *Nature* in 1936 Selye described for the first time what he came to refer to as the "syndrome of just being sick." He injected an extract of ovary tissue in rats for several months and found that the treatment resulted in stomach ulcers, enlargement of the adrenal glands, and shrinkage of the lymph nodes and thymus. To his surprise, control rats that received injections of inactive placebo developed the same pathologic triad. Both the experimental and control rats often avoided injection attempts or wriggled free and had to be chased around the laboratory with a broom.

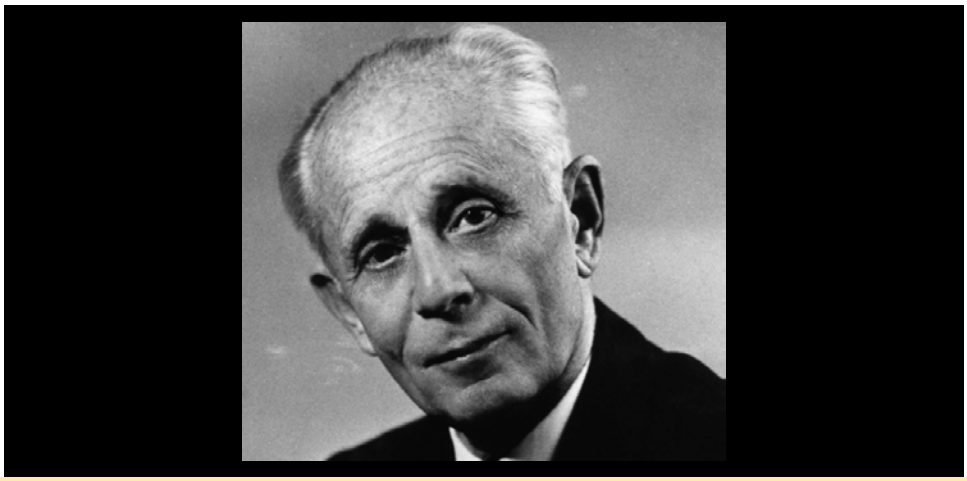


Fig. 176: Hans Selye (1907-1982). *Selye was the father of "the stress response."*

Selye defined stress as the non-specific response of the body to any demand imposed upon it.

Selye proposed that both the experimental and control animals underwent "stress." He defined stress as the non-specific response of the body to any demand imposed upon it.

Selye's theorized that a "General Adaptation Syndrome" occurs in three stages. The first stage, the "alarm reaction," corresponds to Cannon's "fight or flight" reaction and includes release of what Selye referred to as "adrenalines" from the adrenal gland. The second stage is adaptation, and the third is exhaustion.

According to Selye, all challenges to homeostasis are met by both specific and non-specific responses. It is the shared element, the non-specific response, that is stress.

Selye's ambiguity about whether stress is a disturbance that threatens homeostasis, a state produced by the disturbance, or a non-specific response to the state, led to the critical observation, "…stress, in addition to being itself and the result of itself, is also the cause of itself." Subsequently, Selye defined a new word, "stressor," as that which results in a state of stress.

In the remainder of this book, "stressor" is used to denote a disturbance, "stress" a state resulting from the effects of the disturbance, and stress response altered activity of one or more effectors as a result of stress.

It took about 50 years for Selye's doctrine of non-specificity to undergo experimental testing. It was shown mathematically that without simplifying assumptions cannot be disproved, meaning that it has limited scientific value. Given certain assumptions, the doctrine of non-specificity was shown to be testable. Specifically, it predicted equal ratios of responses of plasma corticotropin (ACTH) and adrenaline levels between low- and high-intensity stressors, regardless of the stressor. This was clearly shown not to be the case for all stressors. Given the simplifying assumptions that rendered the doctrine of non-specificity testable, the experimental data were inconsistent with Selye's stress theory and refuted the existence of a unitary stress syndrome. Nevertheless, Selye's notion of a non-specific "stress syndrome" mediated by a central "stress system" persists and remains widely accepted.

An alternative concept views stress responses as having a degree of "primitive specificity" that depends on the particular challenge and on the organism's perceived ability to cope with the stressor. Components of the autonomic nervous system play

important but different roles in stress responses. According to this idea, each stressor has a neurochemical ‘‘signature,’’ with quantitatively if not qualitatively distinct effects on central and peripheral mechanisms and effectors. Fig. 146 conveys what some of these signatures might be. The biochemical changes do not occur in isolation but are orchestrated along with physiological, behavioral, and experiential changes and depend on the history of exposures to the same or different stressors and the organism’s perceived ability to cope with the stressor. In evolutionary terms, by enhancing survival, natural selection would have favored such patterning of stress responses.

A Homeostatic Definition of Stress

If homeostats are teleological, overly simple metaphors that are unnecessary for understanding how homeostasis happens, then what good are they? One benefit of the notion of homeostatic comparators is that it leads rather straightforwardly to definitions for phenomena that otherwise are very difficult to conceptualize scientifically. One of these is stress.

> Stress is a condition in which the brain senses a discrepancy between information about the “inner world” and instructions for responding.

According to the homeostat theory, stress is neither a stimulus (as Cannon presumed) nor a stereotyped response pattern (as Selye often theorized) but a *condition,* a state in which there is a

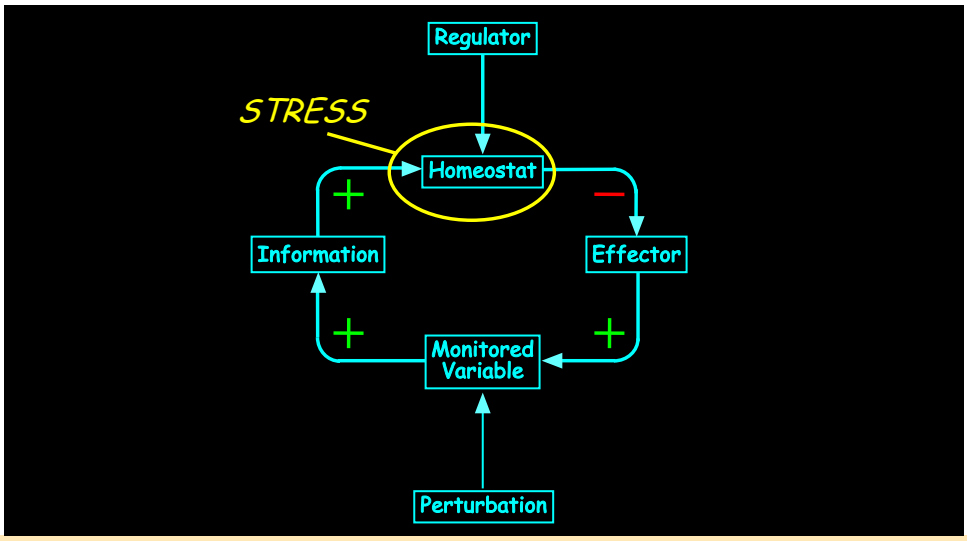


Fig. 177: Homeostatic definition of stress. *According to the homeostat theory stress is a condition in which there is a sensed discrepancy between information about a monitored variable and a set-point for responding. The error signal drives the activities of one or more effectors in a manner that reduces the discrepancy.*

perceived discrepancy between information about the level of a monitored variable and an algorithm for responding, such that the discrepancy leads to alterations in activities of effectors—including components of the autonomic nervous system—closing a negative feedback loop and reducing the discrepancy.

Just like a memory, a motivational state, or an emotional feeling doesn't exist anywhere specifically in the brain, the algorithms for responding to stressors have no anatomic location. They correspond to what Mayr would refer to as "teleonomic" processes.

MULTIPLE EFFECTORS AND COMPENSATORY ACTIVATION

All the key monitored variables of the body are regulated by more than one effector. For instance, blood glucose levels are determined by insulin, glucagon, adrenaline, and cortisol. Such redundancy comes at relatively cost. Meanwhile, having multiple effectors offers clear survival advantages.

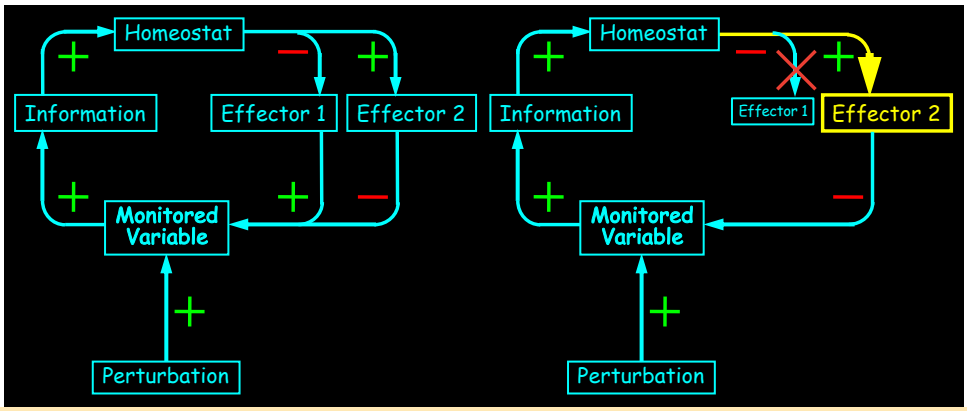


***Fig. 178: Compensatory activation**. Having multiple effectors enables compensatory activation. Here, when Effector 1 is disabled, Effector 2 is more active.*

First, having multiple effectors allows at least some degree of control of the monitored variable if one effector is disabled. This is called "compensatory activation."

Compensatory activation helps explain why, for instance, patients who are hypothyroid have increased sympathetic noradrenergic system (SNS) activity. Both the hypothalamic-thyroid axis and the SNS are effectors that help maintain the homeostasis of core temperature. When the thyroid effector is disabled, compensatory activation of the SNS allows for at least

some thermoregulation.

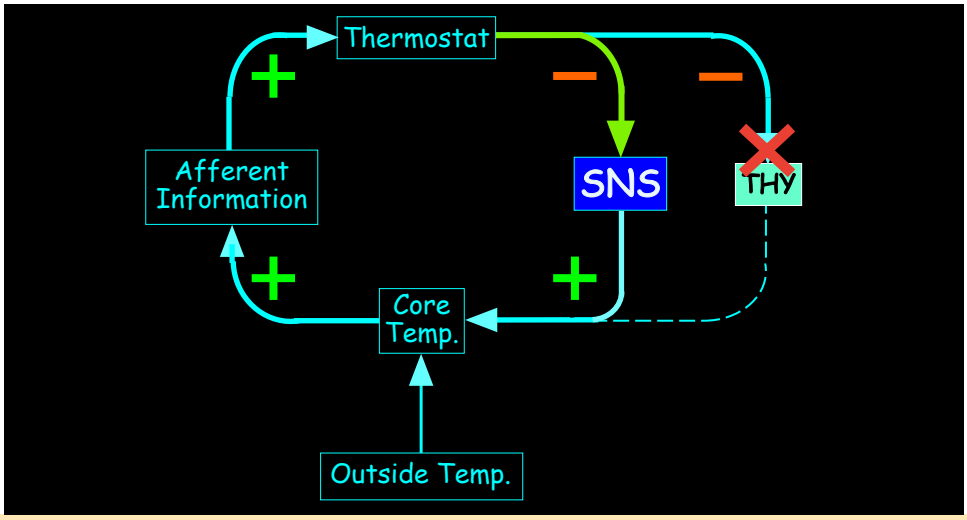


Fig. 179: SNS activation in hypothyroidism. *Compensatory activation of alternative effectors helps explain why hypothyroidism is associated with increased sympathetic noradrenergic system (SNS) outflow.*

Second, having multiple effectors extends the range of control of the monitored variable. Consider how adding an air conditioner to a furnace extends the range of control of the temperature inside your house. There can be different effectors for decreases and for increases in core temperature (as in Fig. 140) just as there can be different effectors for decreases and increases in blood glucose (as in Fig. 139).

Third, having multiple effectors permits the evolution or learning of relatively specific patterns of response that are most adaptive for particular stressors.

MULTIPLE HOMEOSTATS AND EFFECTOR SHARING

Homeostatic systems of the body can share effectors.

For instance, patients who have low blood pressure due to gastrointestinal hemorrhage can have elevated serum glucose levels, because both the "volustat" and "glucostat" use the sympathetic adrenergic system (SAS) as an effector.

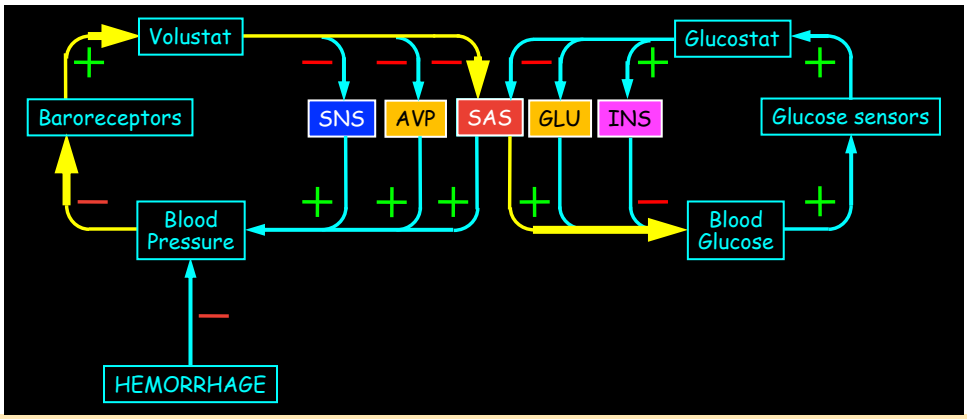


Fig. 180: Effector sharing. *Sharing of the SAS by two homeostats (the volustat and the glucostat) helps explain why cardiovascular shock is associated with high glucose levels.*

One may propose that medical or surgical emergencies in general tend to raise glucose levels because of sharing of the SAS effector. I would guess that "normal" blood glucose levels are high in samples coming from patients in the emergency room.

Analogously, patients with congestive heart failure often have a low serum sodium concentration. Via release from baroreceptor restraint, the sympathetic noradrenergic system (SNS), the

arginine vasopressin (AVP) system, and the renin-angiotensin-aldosterone system (RAS) are activated in heart failure. Norepinephrine, vasopressin, and angiotensin II help maintain systemic blood pressure; however, vasopressin is also the anti-diuretic hormone used by the "osmostat" to force the kidneys to retain free water, and angiotensin II is a potent stimulant of the experience of thirst. The combined effects of vasopressin and angiotensin II help explain the low serum sodium concentration attending heart failure. In this setting the appropriate treatment would not be infusion of hypertonic saline, nor restriction of water intake, but measures to alleviate the heart failure.

Allostasis and Allostatic Load

Allostasis refers to a temporary shift in an input-output curve.

A low-grade fever when you have the flu is an example of allostasis.

Anyone who has had a bad cold with a low-grade fever for a few days knows from personal experience what allostasis is. Your core temperature is higher, your pulse rate is faster, you lose your appetite, you curl up in bed, you sleep more, you withdraw socially, and you become cranky. You are "not yourself." When you have an acute illness like this, the levels of internal variables do not change in a completely uncontrolled way. Your core temperature is regulated but at a different thermostatic setting (whether fever helps fight off viruses has been debated for many years—probably the answer is yes). Once you recover and are back to your "old self," the homeostatic settings return to those before the acute illness,

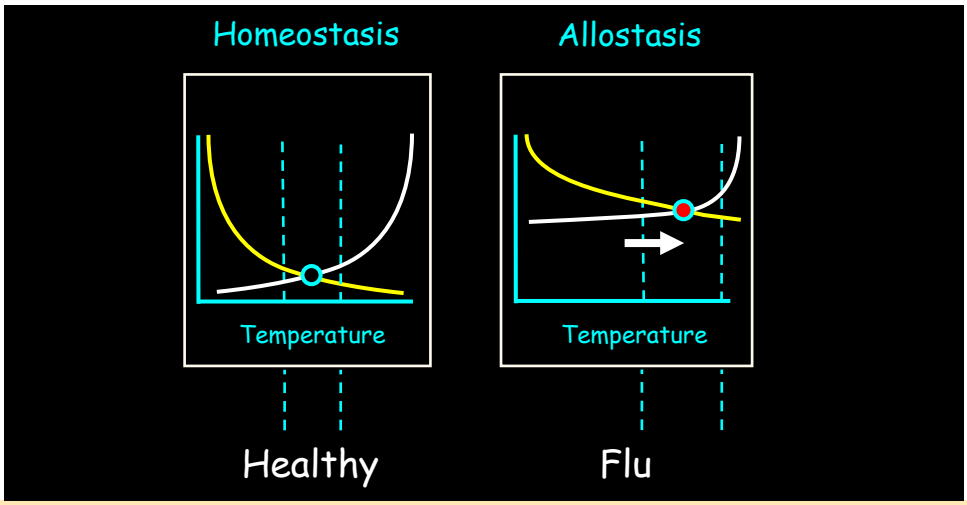


Fig. 181: From homeostasis to allostasis. *In allostasis there is a shift in input-output curves, resulting in regulation of the monitored variable (in this case body temperature) at a different level.*

with no damage done.

Allostatic adjustments use up more energy than do homeostatic adjustments. There is wear and tear on the effector systems—allostatic load. Allostatic load can decrease the efficiencies of the effectors, flattening the input-output curves. The decreased effector efficiencies increase the range of permitted levels of the monitored variable.

Allostatic load corresponds to long-term wear and tear.

Allostatic load is like the wear and tear on your furnace as it cycles on and off during the winter. If you turned the thermostat way up, the furnace would be on more of the time, and there would be more wear and tear on its components.

If you not only turned the thermostat up but also left a large window open for the entire winter, there could be enough wear and tear on the furnace that it would fail completely.

Because of the wear and tear, the efficiency of the furnace declines. When the efficiency declines, then because of the negative feedback loop, the furnace is on more of the time. Because the furnace is on more of the time, there is more wear and tear, and the efficiency declines further.

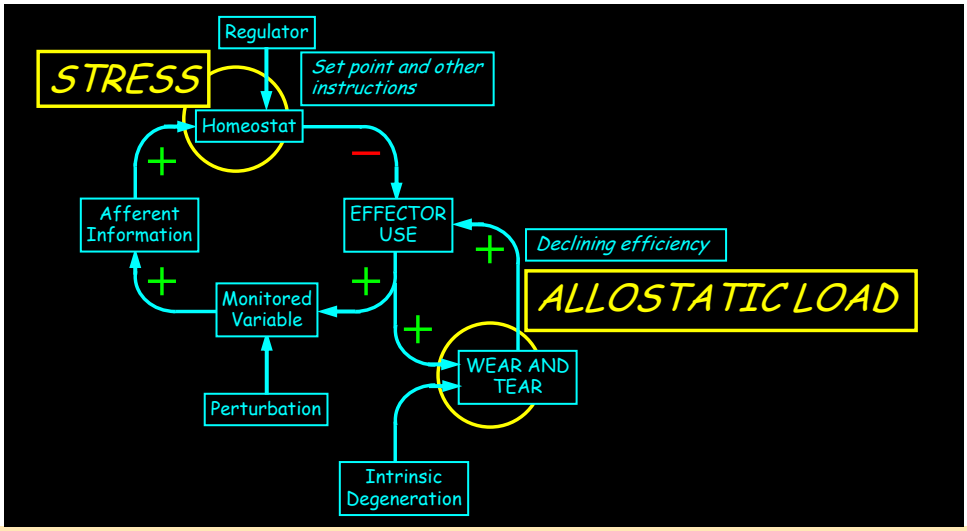


Fig. 182: Stress & allostatic load. *The homeostat theory enables relatively straightforward definitions of stress and allostatic load.*

This is an example of a positive feedback loop. The transition from a negative feedback loop to a positive feedback loop is a transition from a stable to an unstable internal environment and the end of homeostasis.

The concept of allostatic load can link stress with aging-related degenerative diseases. Activation of effectors to counter threats

to homeostasis produces wear and tear on the organs determining the level of the monitored variable and on the effectors themselves.

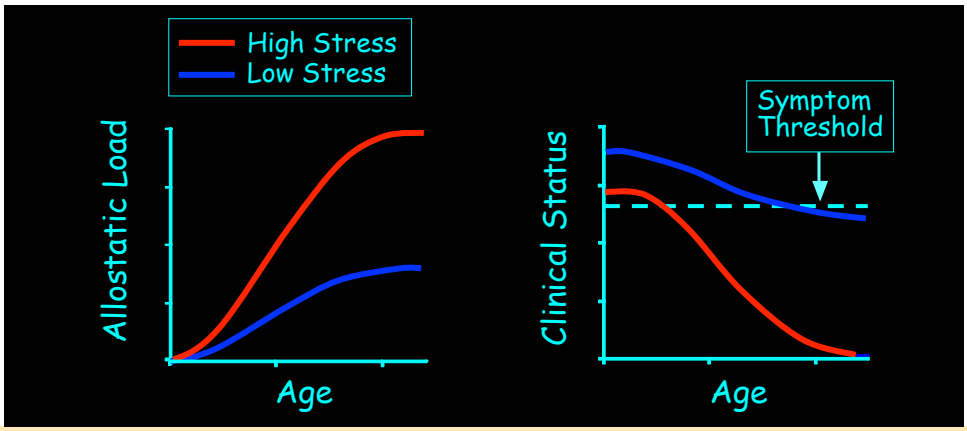


Fig. 183: Stress, allostatic load, and aging-related disease. *Computer-generated curves can relate clinical status to aging-related accumulation of allostatic load.*

Wear and tear, combined with planned obsolescence, decreases effector efficiency. The same perturbation then results in greater wear and tear and further decreases effector efficiency. Eventually, even with the effectors activated maximally, the monitored variable drifts from the allostatic setting. Finally, when the effectors fail, the organism can no longer mount a stress response at all.

The same concept applies to the increased mortality of elderly persons when they are exposed to acute viral illnesses. As people age the efficiencies of their homeostatic systems decline. The ability to keep levels of monitored variables within healthy ranges is reduced. In the setting of this increased susceptibility, exposure to an acute stressor such as a viral illness is more likely to result in multi-organ failure and death.

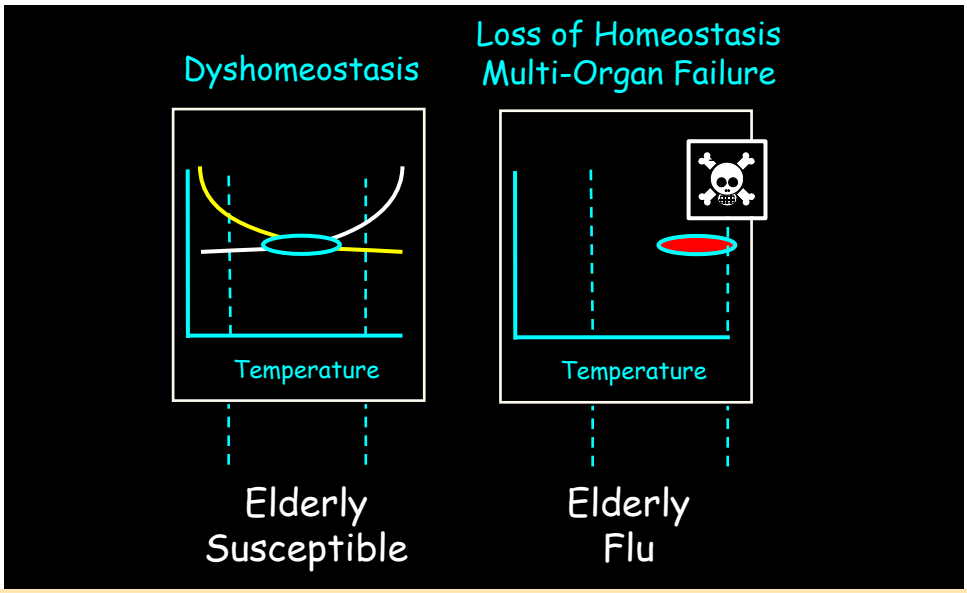


Fig. 184: From dyshomeostasis to death. *Low efficiency of homeostatic systems (dyshomeostasis) in the elderly increases the likelihood of loss of homeostasis, multi-organ failure, and death in the setting of an acute viral illness.*

Differential SNS & SAS Responses to Stressors

Walter B. Cannon conceptualized that the sympathoadrenal system functions as a unitary system maintaining homeostasis in emergencies.

> Walter B. Cannon taught that the body responds to all emergencies in the same way, by evoking increased secretion of adrenaline.

In fact, both the sympathetic noradrenergic system (SNS) and sympathetic adrenergic system (SAS) are active all the time.

Pulse-synchronous bursts of skeletal muscle SNS outflow and plasma levels of norepinephrine (NE) and adrenaline (epinephrine, EPI) are measurable in healthy people even during supine rest.

There is no unitary sympathoadrenal response to all stressors.

Differential plasma EPI and NE responses across different stressors provide some of the strongest evidence that, in contrast with Cannon's view, there is no monolithic sympathoadrenal response to all stressors.

The sympathetic adrenergic system (SAS) is very sensitive to decreases in glucose availability, such as from insulin-induced hypoglycemia, and to emotional distress. (Indeed, increased plasma EPI may be the most sensitive index of distress.)

Meanwhile, the sympathetic noradrenergic system (SNS) is very sensitive to cold exposure, isometric or mild exercise, active avoidance or escape behavior, and orthostasis (upright posture).

Across stressors plasma EPI responses actually are more closely tied to responses of the hypothalamic-pituitary-adrenocortical (HPA) axis, as indicated by corticotropin (ACTH) levels, than to responses of the SNS, as indicated by plasma NE levels. One can conceive of the existence of a unitary adrenal (adrenocortical/adrenomedullary) system just as easily as a unitary sympathoadrenal system.

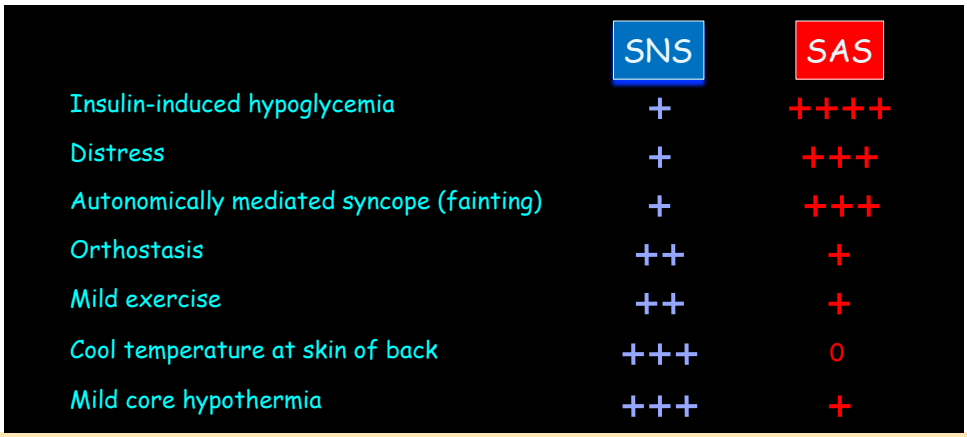


Fig. 185: Differential noradrenergic and adrenergic responses. *Plasma norepinephrine and adrenaline levels can change differentially in different stress situations.*

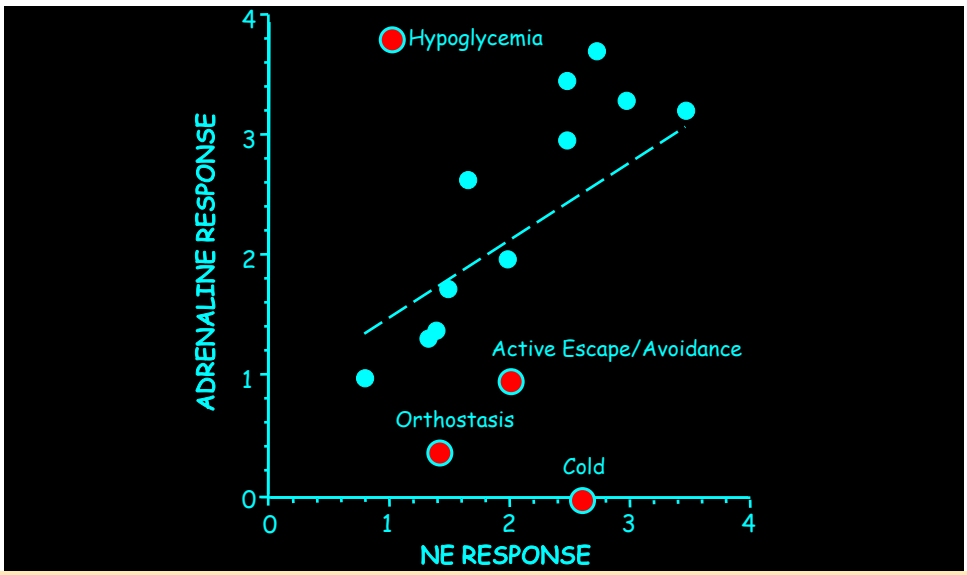


Fig. 186: Plasma adrenaline and norepinephrine responses to stressors. *The responses are different for hypoglycemia and cold exposure.*

Distress

Selye did not view stress as necessarily harmful. Relatively late in his career he coined the term, “eustress,” for stress that is not

harmful and possibly even helpful to the body, in contrast with "distress," which is damaging or unpleasant. Selye did not distinguish between the pathologic and the aversive characteristics in his definition.

Defining distress in terms of pathology is inherently circular and consequently of limited scientific value. This section presents a non-circular definition of distress. Distress is a form of stress with additional characteristics—consciousness, aversiveness, observable signs, adrenal gland activation, and homeostatic resetting.

CONSCIOUSNESS

The experience of distress requires consciousness, because distress involves not only a challenge to homeostasis but also a perception by the organism that adjustments to meet that challenge may not suffice. Such perception implies an ability to interpret afferent information and to simulate future events, which in turn requires cerebral cortical activity.

AVERSIVENESS

Distress is negatively reinforcing and motivates escape and avoidance learning. Distressed organisms avoid situations that are perceived as likely to reproduce the same aversive experience.

The experience of distress enhances vigilance behavior and long-term memory of the distressing event. These adaptive adjustments probably offered substantial survival advantages in

evolution. Bearing such an evolutionary history in mind helps understand potential long-term health consequences of distress such as in post-traumatic stress disorder (PTSD).

Even primitive animals can learn to withdraw or escape from noxious stimuli or habituate after prolonged or repeated exposures. Higher animals can react instinctively not only to a stressor but also to stimuli that resemble the natural threat.

The plasticity afforded by learning decreases the likelihood of inappropriate instinctive responses to symbolic cues. Classical conditioning, or Pavlovian conditioning, is an important refinement on habituation and sensitization, which are forms of "non-associative" learning where the organism learns about single stimuli. In classical conditioning (and operant conditioning, to be discussed shortly) the organism learns based on associations between stimuli.

Instrumental conditioning, or operant conditioning, represents an even more advanced form of learning that probably requires a cerebral cortex. The conditioning is "operant" in that the individual's behavior operates on the environment, determining the occurrence of reinforcement (reward); and the conditioning is "instrumental" in that the learning is a means to an end, since the occurrence of reinforcement depends on the behavior. Operant conditioning differs from Pavlovian or classical conditioning, in which the delivery of the reinforcement occurs independently of the individual's behavior.

If an organism experienced distress consistently in a given situation, subsequent perception of re-exposure to the situation could elicit distress as a classically conditioned response.

Classically conditioned distress could then motivate the acquisition of instrumentally conditioned avoidance behaviors. Situations evoking distress therefore typically involve a complex interplay of classical and operant conditioning, and they evoke coordinated patterns of skeletal muscle and autonomic responses.

INSTINCTIVELY COMMUNICATED SIGNS

A third characteristic of distress is the evocation of signs that others can interpret as indicating the emotional state or intent of the organism. Perceptions of signs of distress by other members of the species automatically elicit involuntary, instinctive emotional and behavioral responses.

The communication value of external signs of distress helps to explain the continued elaboration of observable components of distress responses in modern society, despite the relative rarity of true fight-or-flight reactions in humans. During the course of human evolution, these signs originally may have been by-products of genetically determined, autonomically mediated response patterns. In modern society, they continue to serve important signal functions.

Pale as a ghost

Pallor is an instinctively communicated sign of terror. You turn “white with fright” and look “pale as a ghost.” You seem “ashen,” “wan,” and “pallid,” indicating not only pallor but also sickliness and weakness.

Fig. 187: The white flag of surrender. *This painting by John Trumbull, entitled, "The Surrender of Lord Cornwallis," is on display in the rotunda of the US Capitol in Washington, DC. The painting shows the British surrendering to General George Washington after the battle of Yorktown, Virginia, by waving a white flag.*

One such sign is waving a white flag—perhaps because of an instinctive association of pallor with defeat.
I understand that in Chinese, the calligraphic characters that together mean "fear" literally denote "white face."

In the Old Testament, Moses and Miriam, brother and sister, both turn "white as snow" in separate episodes when confronted directly by God. Miriam's sudden pallor could have indicated an involuntary, automatic, instinctively communicated sign of terror. That sign would result from constriction of blood vessels in the skin, and the constriction would result from the local action of adrenaline.

At the same time and for the same reason that the skin becomes pale during distress, the skin also turns cold. When arterioles in the skin constrict, delivery of blood to the skin's surface decreases. Since the arteries carry blood to the skin at the core temperature, the temperature of the skin falls toward that of the cooler environment. You develop "cold feet."

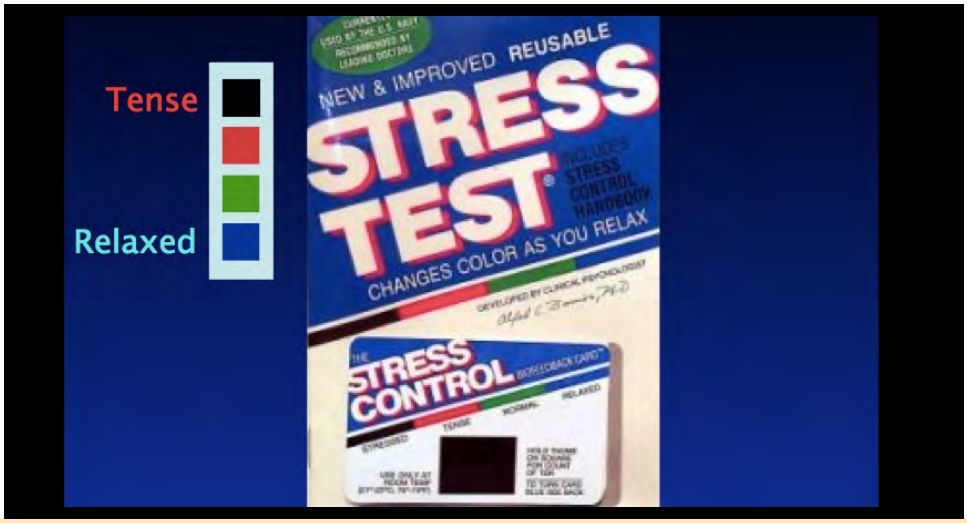


Fig. 188: A stress test card. *The liquid crystal patch is temperature sensitive. Distress decreases skin blood flow and thereby decreases skin temperature.*

StressCards, StressDots, StressRulers, BioDots, StressPens, StressPoints, StressControl cards, and similar items all include a shiny black patch of plastic. You press a fingertip on the patch for a minute or so, and the color changes. Depending on the color, you are "stressed," neutral, or relaxed. You are supposed try to change the color to that corresponding to being relaxed.

These items work by the same principle: the key is the liquid crystal patch or dot, which changes color as the temperature changes. When you learn to control your "stress," you really

learn to increase your skin temperature—a kind of biofeedback.

The "plaintive wail" in the O.J. Simpson trial

Distress-related changes in vocalization can be understood even by members of a different species.

You may remember the highly publicized O.J. Simpson trial, in which the football and movie star stood accused of killing his divorced wife, Nicole Brown Simpson, and a friend of hers, Ron Goldman, in a fit of jealous rage on June 12, 1994.

O.J. had a potential alibi. He was on an 11:45 PM red-eye flight to Chicago. If the murder had occurred late enough in the evening, then too little time would have elapsed for Simpson to have committed the crime and then get to the airport. The case hinged on the timing of the murder. The forensic evidence could not pinpoint the timing accurately enough to reject the alibi. But an instinctively communicated sign of distress may have timed the murder accurately.

A neighbor testified that at around 10 to 15 minutes after 10:00 PM, while he was at home watching the 10 o'clock news, he had heard the "plaintive wail" of a dog. Another neighbor reported loud, persistent barking, which interfered with her sleep, also at around 10:15 PM.

You might ask how, months later, people could remember the exact time at which they heard a dog bark. Dogs bark all the time; no one remembers a bark. But this wasn't a bark. This was a wail, a "plaintive wail." Wailing instinctively conveys the

misery of grief. It is almost as if the individual is sharing the agony that a loved one suffered while dying. This communication is generated instinctively and understood instinctively, even by members of an entirely different species. In both humans and dogs it is a sign of distress. Throughout evolution, communication of the experience of distress has offered important information relevant to survival. The incident, the circumstances, the timing, and one's sensations, emotions, and actions become etched in memory.

The assault, struggle, and death of its master must have occurred before the wail by Nicole Simpson Brown's dog. If so, then there would have been enough time for O.J. Simpson to have committed the crime and ridden to the airport.

Digestive distress

Psalm 23, a triumph of literature, has the core concept of calm confidence, because "The Lord is my shepherd…" Right in the middle of the psalm is the well known verse, "Yea, though I walk through the valley of the shadow of death, I fear no evil: for thou art with me; thy rod and thy staff they comfort me. Thou preparest a table before me in the presence of mine enemies…"

What does setting a table in the presence of one's enemies have to do with the theme of the psalm?

As you learned previously in the biblical story about the trial by ordeal of the woman accused of adultery, distress, via adrenaline, inhibits gut contraction (Fig. 29). If you were able

to eat in the presence of your enemies, you could not be distressed. The passage about setting a table in the presence of enemies therefore fits with the theme of the psalm: Because the "Lord is my shepherd . . . I fear no evil."

Several instances occur in the Old Testament narrative in which a distressed individual cannot eat. Aaron is unable to eat the sacrifice—his priestly duty—after witnessing his sons' suddenly being burnt to death. Hannah cannot eat when tormented by her nemesis Peninah. Jonathan eats no food after Saul obsesses about David. Ahab does not eat because of his hatred of Elijah. Job in his suffering "abhorreth bread, and his soul dainty meat" (Job 33:20).

Blood curdling

You probably have heard the phrase, "running around like a chicken with its head cut off." If you were to chop off a chicken's head, wouldn't the blood spurt out and the animal rapidly lose consciousness and become motionless?

Adrenaline's actions and the hard-wired neural pathway from the motor cortex to the adrenal gland can explain this macabre scene. Chopping off an animal's head instantly evokes drastic release of catecholamines into the bloodstream by the adrenal gland. So much adrenaline pours out so fast that "trunk blood" obtained immediately after decapitation contains about a hundred times the resting concentration of adrenaline. The surge of adrenaline constricts blood vessels and promotes platelet plugging in arteries so efficiently that chickens actually do run around with their heads cut off.

When adrenaline was patented around the turn of the 20th century, the drug's main intended use was to control bleeding. In the setting of a heart attack due to a blood clot in a coronary artery, the associated emotional distress, resulting in adrenaline release, could be lethal by evoking a positive feedback loop. Because anti-anxiety drugs called benzodiazepines inhibit adrenaline release, treatment with a benzodiazepine might be considered for patients with acute myocardial infarction who manifest instinctive signs of emotional distress.

Hair-raising

The association between distress and the hair bristling has been known from antiquity. Job 4.15 states, "Then a spirit passed by my face; the hair of my flesh bristled up." In his *Aeneid* (ii, 774) Virgil sings, *Steteruntque comae, et vox faucibus haesit*, which has been translated as, "I was dumbfounded, my hair stood on end, and my voice stuck in my throat." Charles Darwin mentioned this phenomenon in his *The Expression of the Emotions in Man and Animals.*

Every hair follicle on your body has a small muscle called a pilomotor muscle, or *arrector pili.* When this muscle contracts the hair stands up.

Coursing alongside the smooth muscle fibers are sympathetic noradrenergic nerves. Stimulation of the SNS causes the hair to bristle.

The receptors on the smooth muscle cells are alpha-adrenoceptors. This means that circulating adrenaline, which is

a universal adrenoceptor agonist, can also cause the hair to stand up.

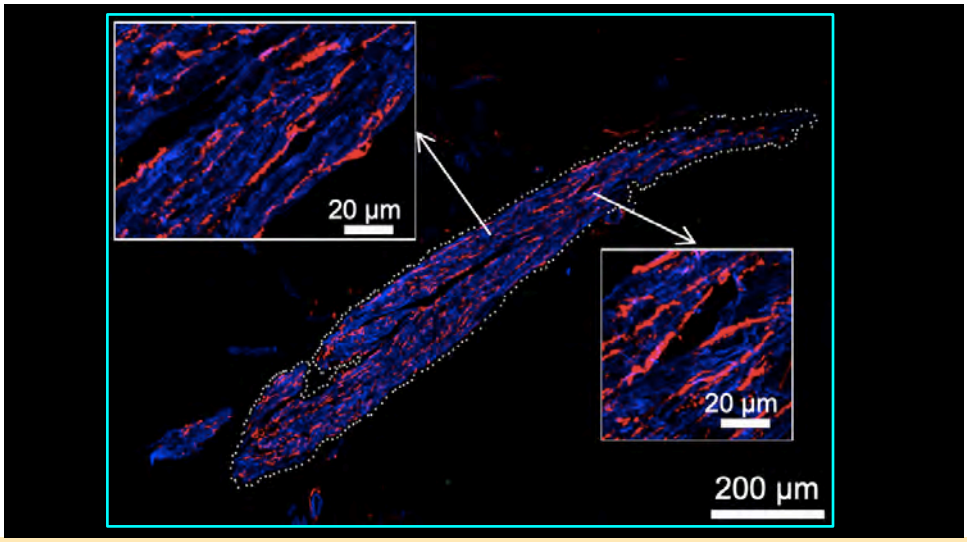


Fig. 189: Arrector pili ***muscle (pilomotor muscle).*** *The blue fibers are smooth muscle fibers. The red fibers are sympathetic noradrenergic nerve fibers. Contraction of* arrector pili *muscles causes the hair to stand up. (Image courtesy of R. Isonaka.)*

Sweating

Not only the sympathetic cholinergic system (SCS) but also the sympathetic noradrenergic system (SNS) and sympathetic adrenergic system (SAS) contribute to emotional sweating.

Several years ago our Nurse Practitioner was going out for the evening and gave instructions to the babysitter. Her daughter had frequent asthma attacks, and so her mother wanted to demonstrate how to use an EpiPen™ in case there was an emergency.

For practice she had a dummy pen, which could be reset by clicking the top—somewhat like clicking the top of a ball point pen. She showed the babysitter how easy it is to use an EpiPen™—just pull off the blue safety release and jab with the orange needle end against the outer thigh and hold it in place for about 10 seconds, to deliver the adrenaline. But when she jabbed herself, to her surprise she felt a sharp needle prick, which was odd for the blunt ended dummy pen; and when she pulled the pen from her thigh, she noticed that she couldn't reset the pen by clicking the top.

That was when she felt a wave of sweat spread over her body. Within several seconds her clothes were drenched. She also noticed she was hyperventilating and jittery and realized that instead of a dummy pen she had used a real EpiPen™ and had injected adrenaline into her leg.

Given that adrenaline constricts cutaneous blood vessels and evokes sweating, one can understand how during distress you brake out in a "cold sweat."

Fear and trembling

Tremulousness is another instinctively communicated sign of fear to the point of panic that has been appreciated by writers since ancient times.

The Old Testament contains several instances of trembling as a sign of emotional upset. Most notably, Isaac trembles as an automatic, immediate response when he realizes that he has been deceived by Jacob into giving his paternal blessing to

Jacob, not Esau.

To “shudder,” “quiver,” “quake,” and “quail” not only mean to tremble but to do so in fear or uncertainty.

Trembling and shivering during distress probably reflect activation of the sympathetic noradrenergic system, since, as Cannon first showed, surgical inactivation of the adrenal glands augments rather than prevents shivering of animals exposed to cold. I have observed that during an infusion of yohimbine, which releases norepinephrine from sympathetic nerves, people can have such severe jaw trembling that their teeth chatter.

Musicians with stage fright or performance anxiety often take a beta-adrenoceptor blocker before concerts. A friend of mine who is a professional cellist once told me that not only did several of his colleagues take a beta-blocker prophylactically before a concert but also that he could tell when they had done so. The performance would be technically accurate but with a subtle emotional restraint and detachment.

An unusual weight-lifting feat

Many years ago, the *Guinness Book of World Records* section on weight lifting contained the following entry, “It was reported that a hysterical 123-lb. woman, Mrs. Maxwell Rogers, lifted one end of a 3,600-lb. car which, after the collapse of a jack, had fallen on top of her son at Tampa, Florida, on April 24, 1960. She cracked some vertebrae” *(Guinness Book of World Records, 1976, 669)*. Apparently, Mrs. Rogers had tapped automatically into what Walter B. Cannon called “reservoirs of power.”

Cannon described a direct augmenting effect of adrenaline on the force of skeletal muscle contraction or an anti-fatigue effect during continual trains of electrical stimulation-induced contraction. Researchers seem to have doubted and certainly subsequently lost interest in the direct effects of adrenaline in augmenting contraction of skeletal muscle and preventing skeletal muscle fatigue. But all would agree that emotionally distressing situations, such as that encountered by Mrs. Maxwell, can temporarily enable people to perform extraordinary feats of strength and speed.

In his *The Expression of the Emotions in Man and Animals*, Charles Darwin noted the self-reinforcing, energizing effect of emotions. He wrote, "The excited brain gives strength to the muscles, and at the same time energy to the will…Anger and joy are from the first exciting emotions, and they naturally lead, more especially the former, to energetic movements, which react on the heart and this again on the brain."
In the early 1960s, the psychologists Stanley Schachter and Jerome Singer, of Columbia University, studied effects of adrenaline on the intensity of emotional experiences. The investigators injected adrenaline into healthy subjects and either informed them correctly or misinformed them about what the side effects of the injected drug might be (this was before the days of institutional review boards). They then exposed the subjects to situations that would provoke annoyance or amusement. The subjects who had been informed correctly about the side effects of the injection did not report feeling more emotional than the subjects who had received an injection of a placebo; however, the subjects who had been misinformed reported feeling more emotional, with more anger or elation

depending on the cognitive circumstances, than did the subjects who been informed correctly about what the injection would do. These findings supported the view that the intensity of the emotional experience, whether negative or positive, is greater when people sense physiological activation and do not have an explanation for that activation besides the emotional experience. That is, both physiological arousal and cognitions consonant with an emotion determine the intensity of an experienced emotion.

It would not be a big leap to propose that the more intense an emotional experience, the greater the amount of involuntary, automatic, unconscious augmentation of the behavioral concomitants of that experience. If adrenaline amplified and prolonged rage, for instance, and rage involuntarily contracted skeletal muscle of the limbs, then adrenaline could augment skeletal muscle contraction and delay the onset of fatigue, even without a direct effect on the skeletal muscle.

A Little Pain Can't Hurt

We all know that emotion-related feats of strength and speed are associated with remarkable loss of the sensation of pain. This is called “stress-induced analgesia.” Pain causes adrenaline release from the adrenal gland, as Walter B. Cannon showed about a century ago. A difficult question—which remains incompletely answered—is what if anything does adrenaline or any other member of its chemical family have to do with the perception of pain?

Adrenaline or norepinephrine may alter the experience of pain

by occupying alpha-2 adrenoceptors in the spinal cord. These receptors appear to contribute to a “gate” for transmitting pain impulses up to the brain. The source of the chemical transmitter that would occupy these alpha-2 adrenoceptors may not be circulating adrenaline, or even norepinephrine released as a neurotransmitter from sympathetic nerves, but norepinephrine released from nerves that project from the brainstem to the spinal cord. The locus ceruleus, a small cluster of cells in the back of the pons, is the main source of norepinephrine in the brain. Locus ceruleus neurons send widely branching fibers throughout the brain, probably contributing to psycho-emotional phenomena such as vigilance and the memory of distressing events. It is unclear whether locus ceruleus neurons are the source of the norepinephrine that modulates the transmission of pain impulses in the spinal cord.

The main known modulators of pain sensation are endogenous opioids. Behaviors such as exercise increase occupation of opioid receptors in the brain, explaining the sense of elation some people feel after a workout. In response to painful stimuli, the brain releases opioids that apparently limit the severity of experienced pain, because blockade of opioid receptors augments the amount of pain for a given amount of stimulation. Blockade of opioid receptors also augments the release of adrenaline. Finally, stimulation of the adrenal gland releases not only adrenaline but also endogenous painkiller opiates called enkephalins.

ADRENAL ACTIVATION

A fourth characteristic of distress is adrenal gland activation.

This involves enhanced release of catecholamines from the adrenal medulla and of glucocorticoids from the adrenal cortex.

As noted previously, Cannon viewed the neural and hormonal components of the "sympathico-adrenal" system as functioning as a unit to preserve homeostasis in emergencies. A more modern view holds that it is specifically the adrenomedullary hormonal component that characterizes distress, while sympathetic noradrenergic system outflows may increase, decrease, or stay the same. This might depend partly on whether there is a locomotor response (e.g., escape behavior), which entails increased skeletal muscle sympathetic noradrenergic outflows as part of "central command."
Plasma levels of adrenaline constitute an extraordinarily rapid and sensitive chemical index of this activation and therefore of experienced distress. When an animal is killed by decapitation, arterial adrenaline levels are increased by many-fold, while concurrently obtained glucocorticoid levels are unchanged.

HOMEOSTATIC RESETTING

A fifth characteristic of distress is that it is associated with shifts in input-output curves determining autonomic outflows. These in essence are allostatic changes. An example is the shift in arterial baroreflex function curves during distress.

It seems that the baroreflex is being reset here temporarily to enable behaviors, emotional experiences, and physiological changes that are appropriate for the particular situation—but this is the teleologic viewpoint of an integrative physiologist.

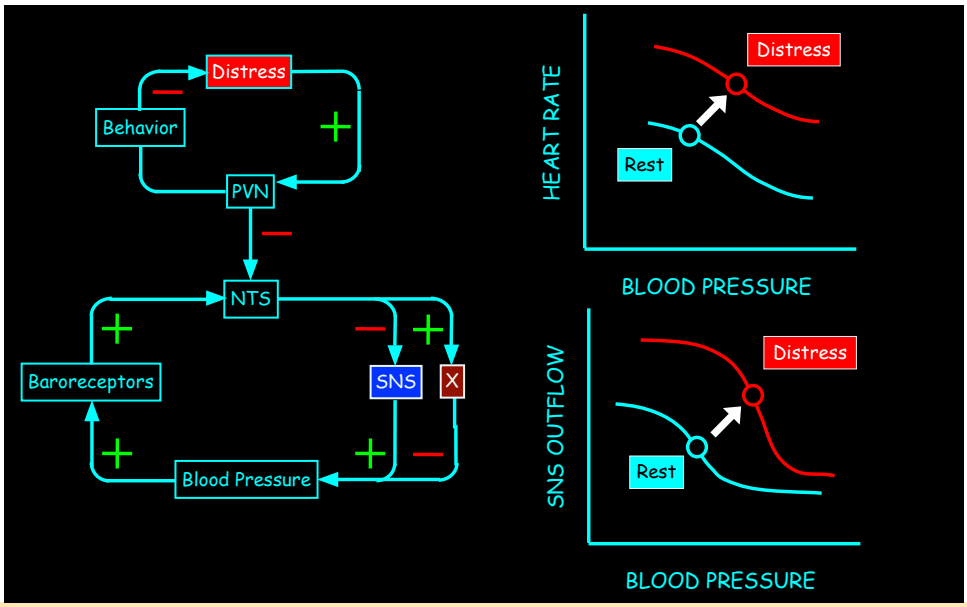


Fig. 190: Baroreflex inhibition by distress. *In this model, distress augments inhibition by the hypothalamic paraventricular nucleus (PVN) of the nucleus of the solitary tract (NTS).*

The homeostatic diagram in Fig. 190 is an over-simplification. First, it presumes that the SNS and vagus are regulated equivalently. The input-output curves on the right argue against such equivalence. In both curves the setpoint is shifted upward and to the right, but the slope of the relationship between heart rate and blood pressure (baroreflex-cardiovagal gain) is unaffected, whereas the slope of the relationship between SNS outflow and blood pressure (baroreflex-sympathoneural gain) is accentuated. Second, the model presumes that there is the same response to a decrease as to an increase in blood pressure, whereas there may be differential responses during distress such that a decrease in blood pressure results in a larger increase in SNS outflow.

A Central Stress System?

In the early 1990s George Chrousos and Phil Gold at the NIH proposed the existence of a central stress system, activation of which would elicit a "stress syndrome," in line with Selye's conceptualization.

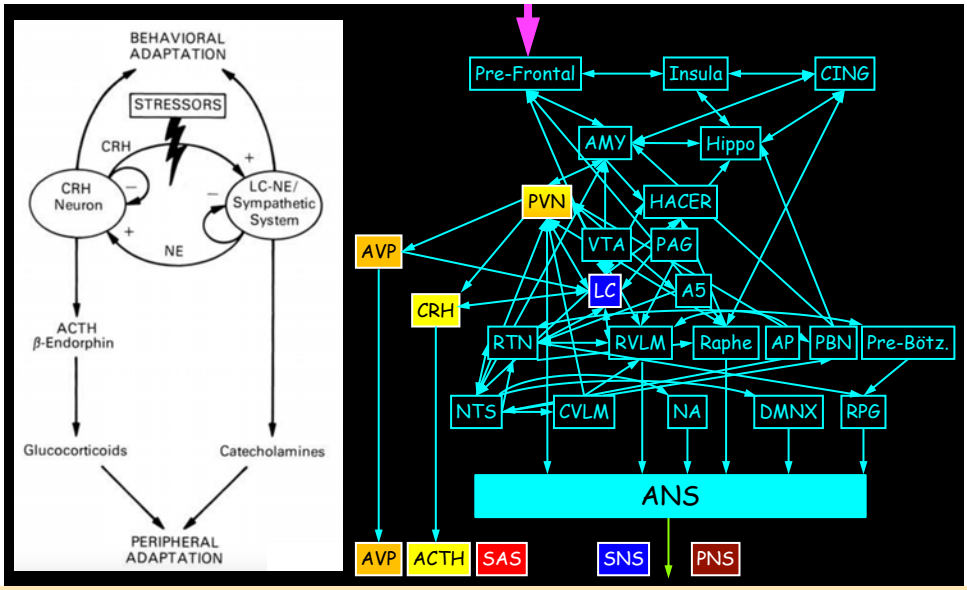


Fig. 191: Central stress systems. *The concept diagram on the left shows Chrousos and Gold's model of "the central stress system." The concept diagram on the right relates the central stress system to the central autonomic network.*

The two key components of the central stress system are the paraventricular nucleus (PVN) of the hypothalamus, which is the source of corticotropin-releasing hormone (CRH), and the locus ceruleus (LC) of the pons, which is the main source of norepinephrine in the brain. According to the Chrousos/Gold model, the LC is also the source of drive to the "sympathetic system" and peripheral catecholamines.

As depicted in the right panel in Fig. 191, the components of the central stress system are embedded within the central autonomic network. From the complex and multiple interrelationships in the network, it would be reasonable to conceptualize that there is no "stress syndrome" and instead that there are primitively specific patterns of responses. One of these patterns may correspond to distress as defined above.

HPA responses are especially pronounced in distressing situations that are novel. With repeated exposure to a stressor, the magnitude of the response decreases. Habituation is a characteristic of even primitive animals. The term, "dishabituation," is used to refer to a return to the initial magnitude of response after habituation has taken place. A related phenomenon is exaggerated responsiveness of adapted organisms to a novel ("heterotypic") stressor. The occurrence of "stressor switch hyper-responsiveness" argues against Selye's doctrine of non-specificity.

"EUSTRESS" REVISITED: ADAPTATION AND RESILIENCE

Higher organisms have capabilities to habituate, anticipate, heal, regenerate, and in general increase resilience. These processes may operate at multiple sites within homeostatic loops to increase the useful life of the effectors for the same amount of chronic exposure to a stressor.

One can conceive of a non-circular definition of eustress that is a kind of mirror image of the non-circular definition of distress. Just as distress is consciously experienced, negatively

reinforcing, motivates escape and avoidance behavior, and enhances vigilance, eustress is consciously experienced, positively reinforcing, motivates approach and appetitive behavior, and enhances attention to oneself. Both distress and eustress have offered survival advantages in evolution, but either can be pathogenic in the setting of modern humanity. That is, neither may be only good or only bad for health. Just as modern-day pathologic consequences of distress are thought to include panic/anxiety, melancholic depression, or post-traumatic stress disorder, pathologic consequences of eustress might include drug and alcohol abuse, sex offenses, gambling and other risk-taking behaviors, and overeating.

Organisms can protect and repair themselves after stress and even learn to anticipate and proactively make “feed-forward” adjustments that mitigate damage from future stress exposures. The concept is emerging that certain aspects of lifestyle, such as exercise training and some psychological interventions, enhance resilience. There is evidence that repeated exposures may increase resilience to heterotypic stressors.

WHAT ARE DYSAUTONOMIAS?

IN DYSAUTONOMIAS WHAT GOES WRONG?

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

Probably the most common type of dysautonomia involves compensatory, otherwise normal autonomic nervous system responses that worsen an independent disease process, rather

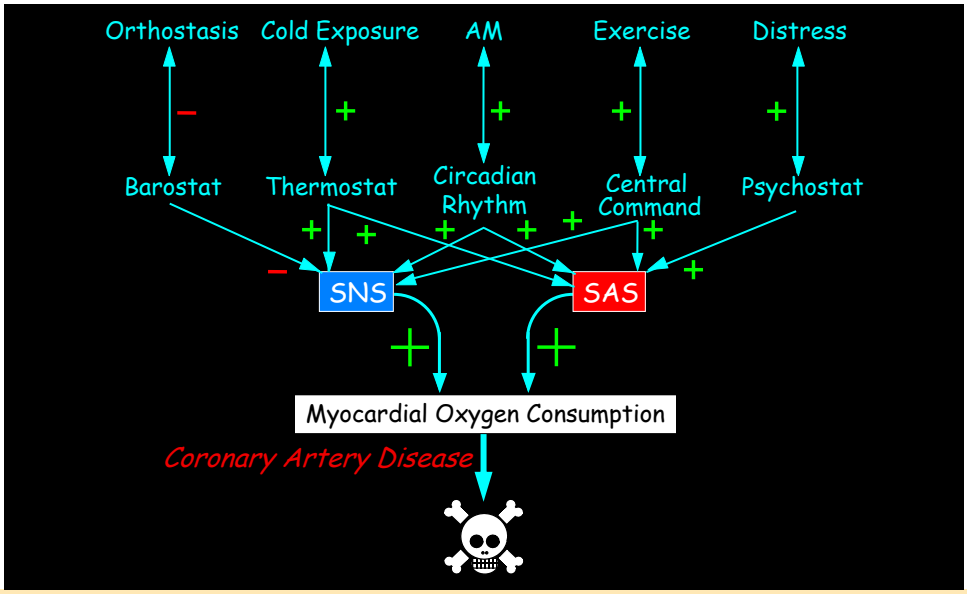


Fig. 192: Sudden cardiac death while shoveling snow. *In coronary artery disease, what otherwise would be appropriate changes in autonomic functions can be lethal. This is an example of a dysautonomia from worsening of an independent pathological state. Several factors combine to increase sympathetic noradrenergic and adrenergic outflows, resulting in myocardial oxygen consumption exceeding the supply.*

than involving an abnormality of the autonomic nervous system itself.

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

A classic example is sudden death in an old man shoveling snow. In a person with ischemic coronary artery disease, normal sympathetic noradrenergic and adrenergic system activation can incite a lethal positive feedback loop when myocardial oxygen consumption exceeds the supply.

Changes in activities of components of the autonomic nervous system can also be harmful when the changes compensate for abnormal functioning of an innervated target organ. For instance, in heart failure, the heart fails to deliver an appropriate amount of blood to body organs. Among several compensatory adjustments, one is increased sympathetic noradrenergic system (SNS) outflow to heart. This improves the pumping function of the heart; however, compensatory SNS activation also promotes growth of heart muscle, which can stiffen the heart walls and worsen the heart failure.

The Ironic Case of Dr. John Hunter

One of the earliest, best-documented, and most ironic illustrations of this principle was the case of Dr. John Hunter, the academic surgeon considered to be the father of

experimental pathology in England.

His colleague, William Heberden, provided the first clear description of angina pectoris as a symptom of coronary artery disease. In March, 1775, Hunter performed an autopsy on one of Heberden's patients who had died suddenly during a spell of anger.

Hunter himself was notoriously prone to defensive argument, obstinance, impatience, and irrational outbursts. In 1785 he began to experience the same symptoms as had occurred in the patient he had autopsied.

Fig. 193: John Hunter (1728-1793) from a portrait by Sir Joshua Reynolds. *The story of Hunter's death is one of the most ironic and instructive in the history of autonomic medicine.*

Hunter's brother-in-law, Everard Home, wrote:

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

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

Home described eloquently the prolonged episodes of severe chest pain from which Hunter suffered. These episodes were accompanied by pallor followed by swooning: "I was with him during the whole of this attack, and never saw anything equal to the agonies he suffered; and when he fainted away, I thought him dead…" Heberden diagnosed his friend with angina pectoris. Hunter claimed, "My life is in the hands of any rascal who chooses to annoy or tease me."

This proved to be one of the most ironic statements in the history of medicine. In Home's words, "On October 16, 1793, when in his usual state of health, he went to St. George's Hospital, and meeting with some things which irritated his mind, and not being perfectly master of the circumstances, he withheld his sentiments, in which state of restraint he went into the next room, and turning around to Dr. Robertson, one of the physicians of the hospital, he gave a deep groan and dropt down dead."

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

Bony tubes, but not tubes clogged with clot. Hunter did not die of a coronary thrombosis. He also did not die of congestive heart failure, which produces cardiac enlargement, since according to Home, "The heart itself was very small, appearing too little for the cavity in which it lay, and did not give the idea of its being the effect of an unusual degree of contraction, but more of its having shrunk in its size."

Given Hunter's previous episodes of emotion-provoked severe chest pain accompanied by pallor and followed by faintness and collapse, one may speculate that adrenaline release induced an acute increase in myocardial oxygen consumption that was not balanced by an increase in oxygen supply because of the rigidified coronary arteries. Ischemic anoxia evokes non-exocytotic release of norepinephrine, so that catecholaminergic bombardment of myocardial adrenoceptors may have precipitated a lethal ventricular arrhythmia.

The Dysautonomias Universe

The dysautonomias encountered in autonomic medicine usually arise from abnormal functioning within the autonomic nervous system itself. This is the form of dysautonomia emphasized for much of the rest of this book.

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

Rather there being one condition, "dysautonomias," there are numerous distinctive entities in an ever-expanding "universe." One way of conceptualizing the dysautonomias universe is to

divide them up in terms of patient age group—pediatric, adult, and geriatric.

There is no single entity, "dysautonomia." There is a universe of dysautonomias. Different types of dysautonomia occur in the different stages of life.

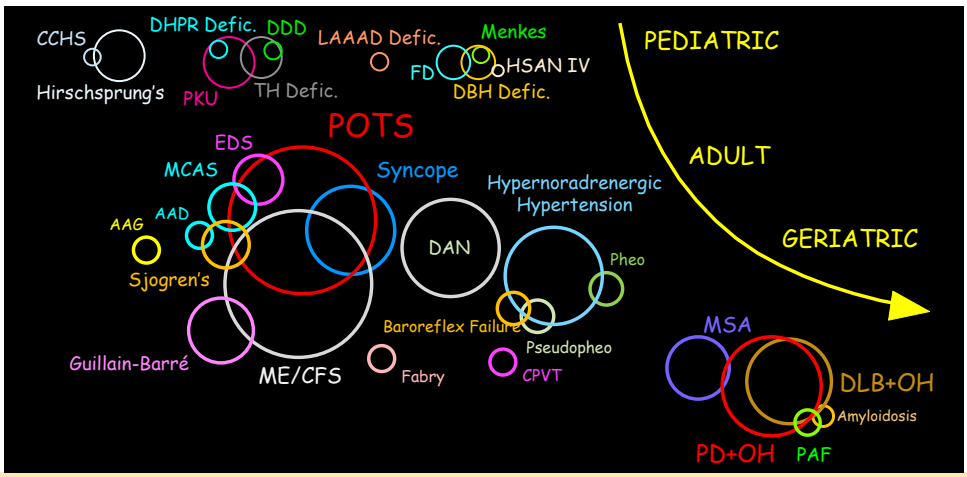


Fig. 194: The Dysautonomias "Universe." *There are many forms of dysautonomia. Dysautonomias occur in all the stages of life. The different syndromes overlap substantially.*

Fig. 195: Some pediatric dysautonomias. *Dysautonomias in infants and young children often reflect genetic or developmental disorders of the autonomic nervous system.*

Dysautonomias in youth often reflect problems in autonomic nervous system development.

Frequently, but by no means always, the cause is a genetic abnormality such as a mutation.

A mutation is like a “typo” in the genetic encyclopedia.

A mutation found in people of Ashkenazic extraction causes familial dysautonomia (FD). Another mutation produces dysautonomias in children because of a type of phenylketonuria (PKU). Another causes “kinky hair disease” (Menkes disease). There are also genetic diseases of proteins required for synthesizing or storing catecholamines.

In general, dysautonomias from genetic mutations are rare. In Hirschsprung’s disease, there is a lack of development of nerve cells of the enteric nervous system in the colon, usually without an identified mutation.

In adolescents or adults, dysautonomias frequently involve inappropriate regulation of an intact autonomic nervous system. Examples are neurocardiogenic syncope (also called vaso-vagal syncope or autonomically mediated syncope), in which the person suffers from frequent episodes of fainting or near fainting; postural tachycardia syndrome (POTS), in which the person cannot tolerate being upright up for long periods and has a rapid pulse rate during standing; and hypernoradrenergic hypertension, in which overactivity of the sympathetic noradrenergic system causes a form of high blood pressure.

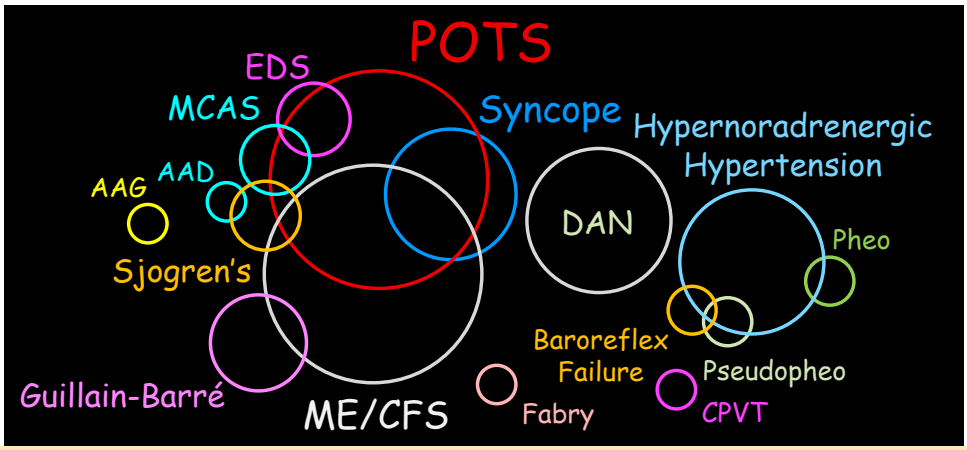


Fig. 196: Adolescent/adult dysautonomias. *Dysautonomias in this age group often reflect functional changes in a generally intact autonomic nervous system. There is increasing recognition of autoimmune aspects of the functional changes (e.g., autoimmune autonomic ganglionopathy (AAG), autoimmunity-associated autonomic failure with sympathetic denervation (AAD), Guillain-Barré syndrome, Sjogren's syndrome, myalgic encephalitis/chronic fatigue syndrome (ME/CFS), mast cell activation syndrome (MCAS), Ehlers-Danlos syndrome (EDS), and postural tachycardia syndrome (POTS)).*

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

Dysautonomias in adults often are associated with—and may be secondary to—another disease process or a drug. Common secondary causes include medications, diabetes (diabetic autonomic neuropathy, or DAN), chemotherapy for cancer, irradiation of the neck, and alcoholism. Activities of components of the autonomic nervous system can change in an

attempt to compensate for dehydration or low blood volume. A viral infection may impact the autonomic nervous system, or autonomic nerves may be subject to autoimmune attack, as in autoimmune autonomic ganglionopathy, or AAG.

There is increasing recognition of autoimmune contributions to the functional autonomic changes that occur in adolescent/adult dysautonomias. Examples are autoimmune autonomic ganglionopathy (AAG), autoimmunity-associated autonomic failure with sympathetic denervation (AAD), Guillain-Barré syndrome, Sjogren's syndrome, myalgic encephalitis/chronic fatigue syndrome (ME/CFS), mast cell activation syndrome (MCAS), Ehlers-Danlos syndrome (EDS), and postural tachycardia syndrome (POTS). This currently is an area of active research.

Rarely, dysautonomias in adults can reflect genetic mutations. There is a rare form of POTS that is associated with a mutation that decreases the ability to inactivate norepinephrine, the chemical messenger of the sympathetic noradrenergic system. Sympathetic noradrenergic failure can also result from a mutation of the gene that encodes dopamine-beta-hydroxylase (DBH), which is required to synthesize norepinephrine.

In the elderly, dysautonomias typically reflect neurodegeneration. The degeneration may take the form of lesions in the central nervous system, as in multiple system atrophy (MSA), loss of autonomic post-ganglionic nerves, as in pure autonomic failure (PAF), or both, as in Parkinson's disease with orthostatic hypotension (PD+OH). PAF and PD+OH are Lewy body diseases. So is dementia with Lewy bodies (DLB). PAF can evolve into PD+OH, DLB+OH, or both.

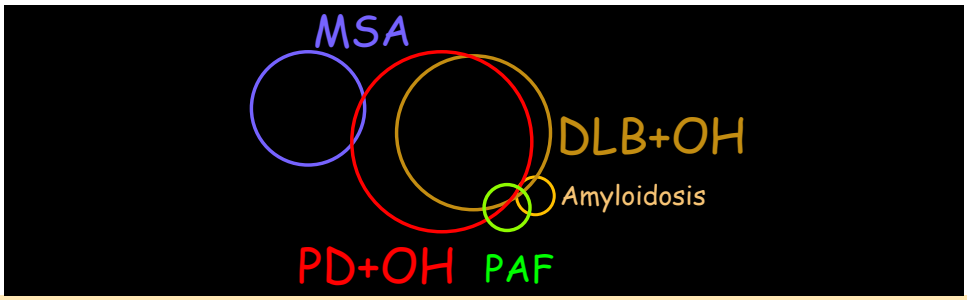


Fig. 197: Some geriatric dysautonomias. *In the elderly, dysautonomias often result from neurodegeneration involving dysfunctions or loss of nerve cells in the central autonomic network or in the autonomic nervous system itself.*

HOW ARE DYSAUTONOMIAS CLASSIFIED?

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

Doctors can disagree about how to classify dysautonomias.

As you read about dysautonomias, keep in mind that the particular diagnostic labels given for many of these conditions are often best guesses. Such labels can refer to essentially sets of symptoms and signs without regard to causal mechanisms. Even with the same label, different people can have very different symptoms. Actual mechanisms for many of these conditions are not well understood. Hopefully, further research will lead to discoveries about pathogenetic mechanisms and to more informative names.

In many cases of dysautonomia, a specific diagnosis cannot be made.

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

Conditions Associated with Autonomic Inhibition or Failure

The autonomic nervous system has component sub-systems, which can be affected differentially in different forms of dysautonomia. It is quite rare for the entire autonomic nervous system to fail as part of a disease process. It is also unusual for there to be a completely isolated abnormality of one ANS component.

Underactivity of the entire autonomic nervous system (ANS) as part of a disease is rare. So is an isolated abnormality of one ANS component.

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

Several drugs inhibit functions of the sympathetic noradrenergic system (SNS). These include adrenoceptor blockers, tricyclic antidepressants, clonidine, and prednisone.

Among diseases, diabetes probably is the most common cause of SNS underactivity, but this depends importantly on the

patient age group. SNS failure may occur in the setting of a cancer or as a side effect of chemotherapy. Primary causes of SNS failure such as familial dysautonomia (FD) and autoimmune autonomic ganglionopathy (AAG) are rare.

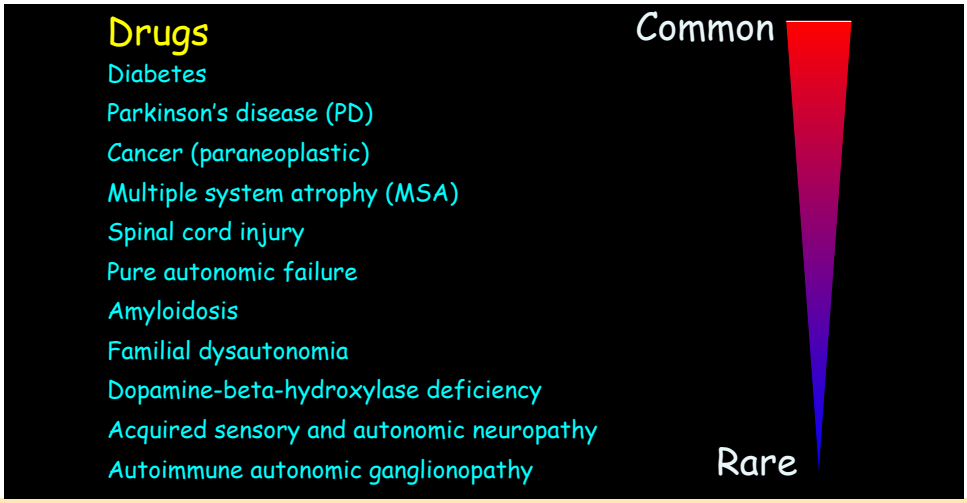


Fig. 198: Some causes of SNS underactivity or failure. *Probably the most commons cause of underactivity or failure of the sympathetic noradrenergic system (SNS) is drugs. Further classification would depend on the patient age group.*

Probably the most common cause of under- or over-activity of the sympathetic noradrenergic system (SNS) is drugs.

The parasympathetic nervous system (PNS) is underactive in some common conditions, including heart failure, diabetes, and Parkinson's disease. PNS underactivity in these conditions probably reflects decreased neuronal outflow from the brainstem rather than loss of parasympathetic nerves. These conditions can also feature SNS underactivity (diabetes is an example) or SNS overactivity (heart failure is an example).

PNS functions tend to decrease also with normal aging.

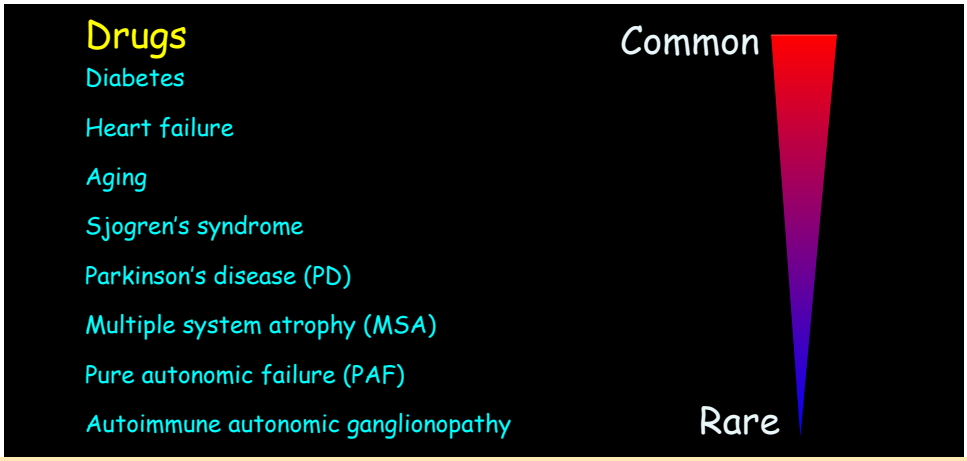


Fig. 199: Some causes of parasympathetic nervous system (PNS) underactivity or failure. *As for SNS underactivity, the most common cause of PNS underactivity is drugs.*

Unlike the parasympathetic nervous system (PNS) and the sympathetic noradrenergic system (SNS), which play important roles in everyday activities such as digesting and standing up, the sympathetic adrenergic system (SAS) is associated with responses to global metabolic challenges or threats to survival.

When you are at rest, your adrenal glands release very little adrenaline into the bloodstream, and plasma adrenaline levels are so low that until relatively recently they were below the limit of detection of available assay methods. It is unclear if under resting conditions there are any symptoms from SAS failure.

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

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

Conditions Associated with Autonomic Stimulation

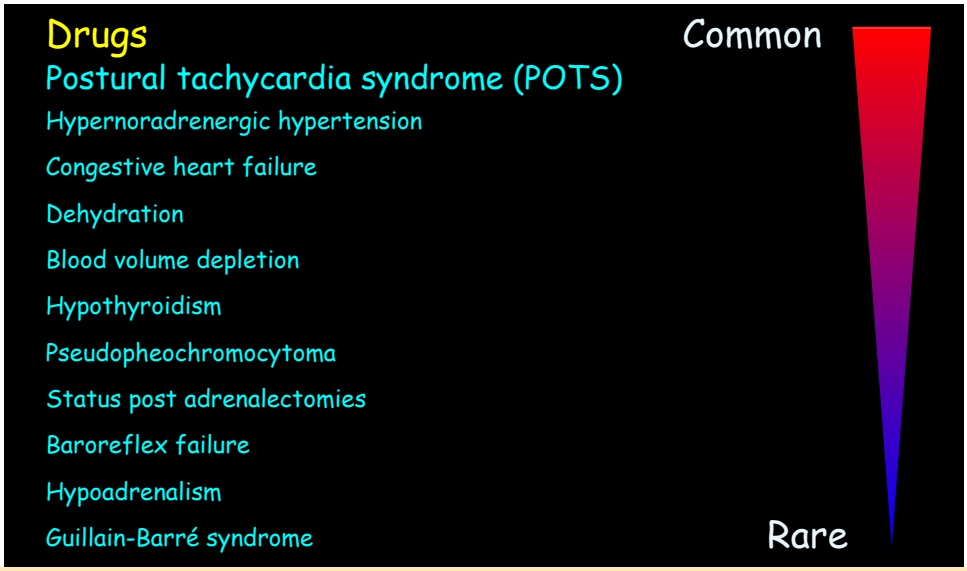


Fig. 200: Some causes of sympathetic noradrenergic system (SNS) overactivity or stimulation. *The frequencies of these conditions depend on the patient age group.*

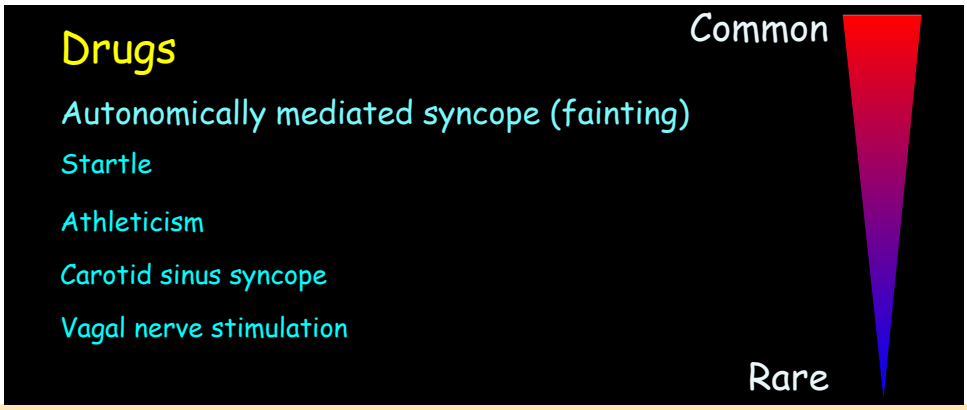


Fig. 201: Some causes of parasympathetic nervous system (PNS) overactivity or stimulation.

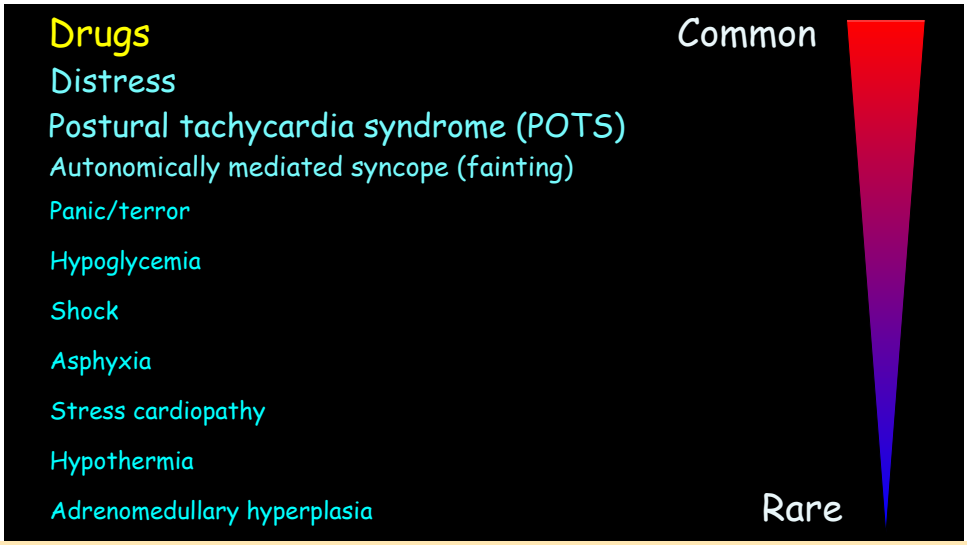


Fig. 202: Some causes of sympathetic adrenergic system (SAS) stimulation. *Virtually any threat to overall well-being activates the SAS.*

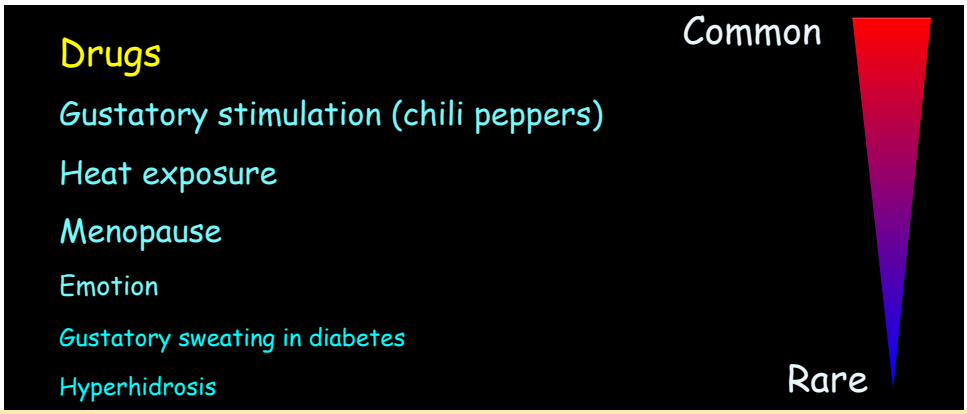


Fig. 203: Some causes of sympathetic cholinergic system (SCS) stimulation. *SCS activation is manifested by sweating.*

THE SYNDROMIC NATURE OF DYSAUTONOMIAS

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

The concepts of “autonomic failure” and “autonomic hyperactivity” have limited usefulness, because some dysautonomias involve abnormal functions of specific components of the autonomic nervous system.

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

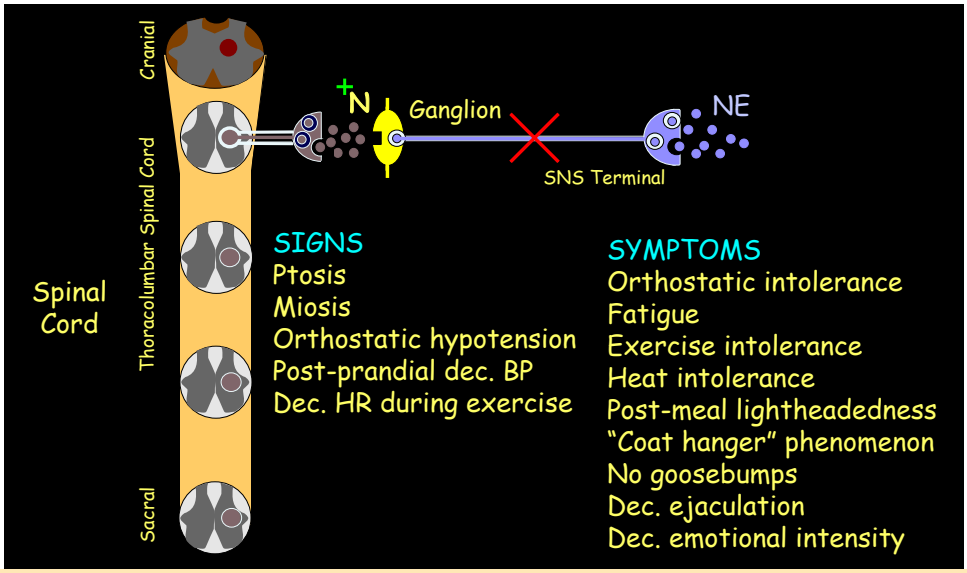


Fig. 204: Signs and symptoms of sympathetic noradrenergic system (SNS) underactivity or failure. *Orthostatic hypotension is a cardinal sign of SNS failure. (Dec.=decreased)*

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

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

About 1/3 of patients with Parkinson's disease have orthostatic

hypotension, and all such patients have a loss of sympathetic noradrenergic nerves in the heart. By definition, pure autonomic failure (PAF) patients have SNS failure.

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

Norepinephrine released from sympathetic nerves in the skin also causes the hair to stand up and produces goosebumps. Stimulation of the sympathetic nerves in the salivary glands increases the flow of thick saliva.

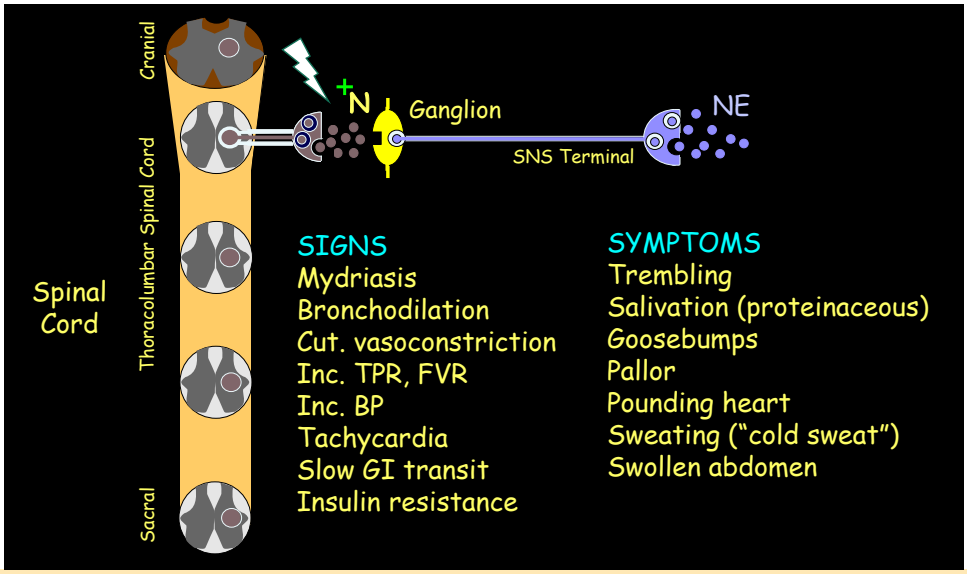


Fig. 205: Signs and symptoms sympathetic noradrenergic system (SNS) overactivity or stimulation. *(Inc.=increased; TPR=total peripheral resistance to blood flow; FVR=forearm vascular resistance)*

nmOther manifestations of increased SNS outflows include increased blood pressure or heart rate, pallor, and trembling.

Increased activity of the parasympathetic nervous system (PNS) produces effects via release of acetylcholine in several organs of the body. The patient notes increased gut motions, nausea, urinary urgency or frequency, increased production of watery saliva, increased tear production, and decreased visual adaptation in the dark. Signs of increased PNS activity include slowed heart rate, increased bowel sounds, increased salivation and tear production, and constricted pupils.

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

When the PNS is underactive, the person has a dry mouth (associated with a raspy voice), constipation, a tendency to retain urine in the bladder, a relatively fast pulse rate, dry eyes, and, in men, erectile failure. Several drugs can cause these symptoms, such as medications to treat urinary incontinence or diarrhea. Signs of PNS failure include decreased bowel sounds, increased heart rate, and enlargement of the urinary bladder due to urinary retention.

Increased activity of the sympathetic cholinergic system (SCS) produces effects via release of acetylcholine in sweat glands.

The patient reports increased sweating—during heat exposure, exercise, after eating (gustatory sweating), during emotional

distress, or at rest. The symptoms and signs of SCS failure are from decreased sweating.

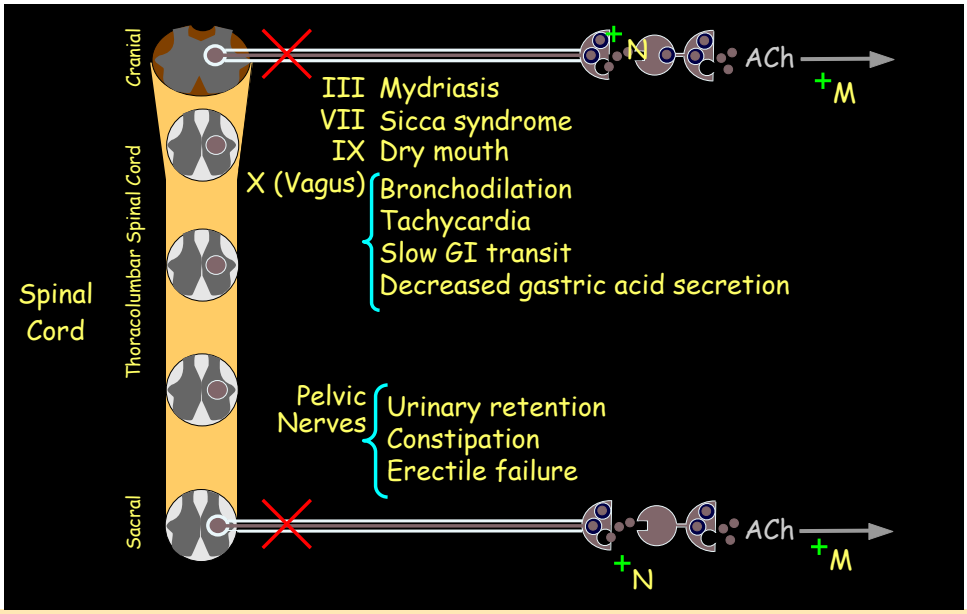


Fig. 206: Signs and symptoms of parasympathetic nervous system (PNS) underactivity or failure. *Probably the most prominent manifestations are dry mouth and constipation.*

Since acetylcholine is the main chemical messenger used by the sympathetic nervous system for sweating, while norepinephrine is the main chemical messenger used by the sympathetic nervous system to tighten blood vessels and maintain blood pressure during standing, a patient with a specific problem in the production, release, or receptors for norepinephrine may have orthostatic hypotension and yet sweat normally.

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

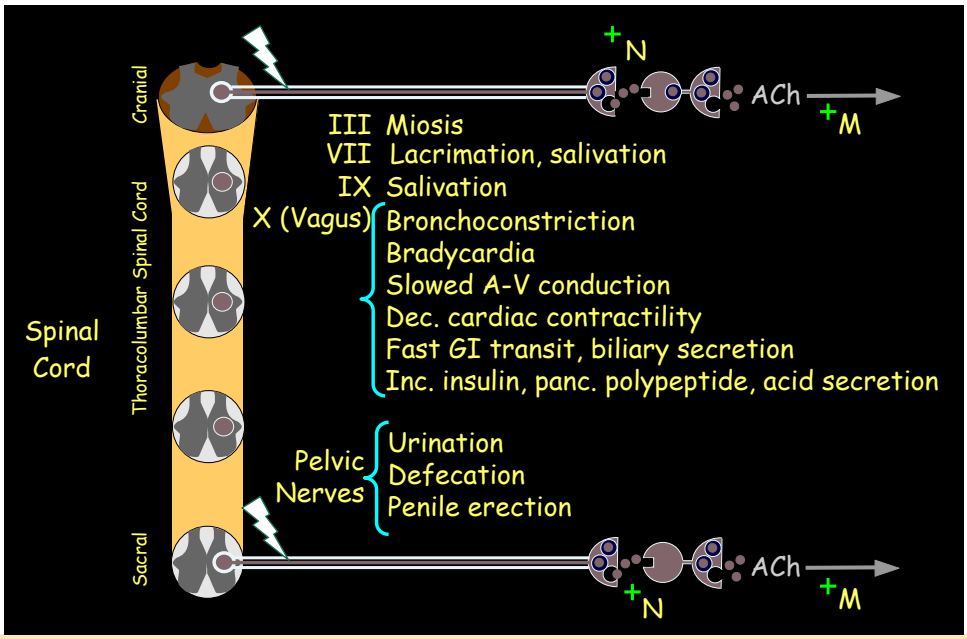


Fig. 207: Signs and symptoms of parasympathetic nervous system (PNS) overactivity or stimulation.

Increased activity of the sympathetic adrenergic system (SAS) produces effects via release of adrenaline from the adrenal glands.

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

Whether SAS failure produces symptoms or signs is unclear. Perhaps there is a tendency to hypoglycemia.

It is difficult to distinguish alterations in enteric nervous system

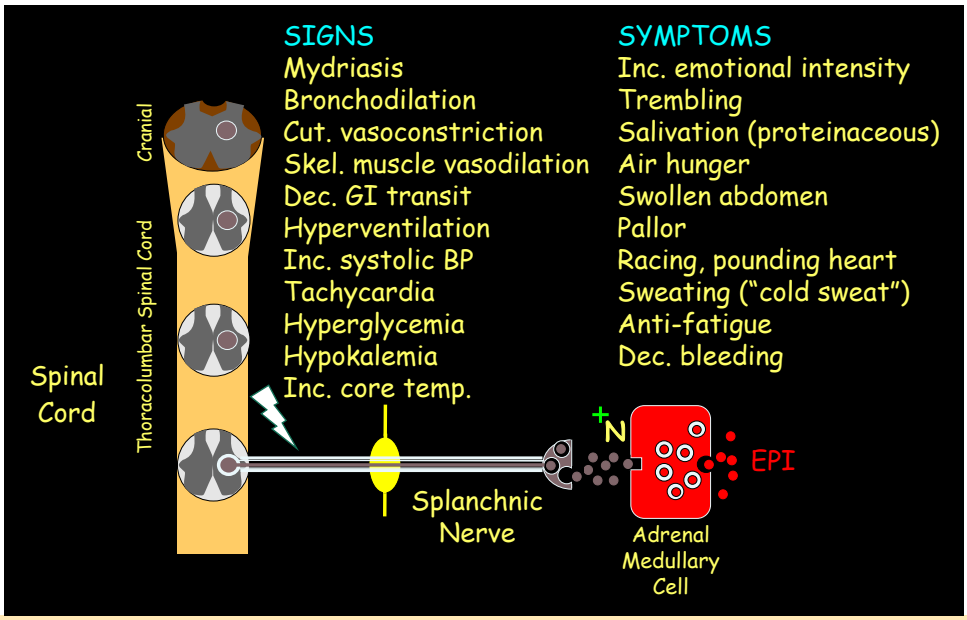


Fig. 208: Signs and symptoms of sympathetic adrenergic system (SAS) overactivity or stimulation. *(Cut.=cutaneous; Dec.=decreased; Inc.=increased)*

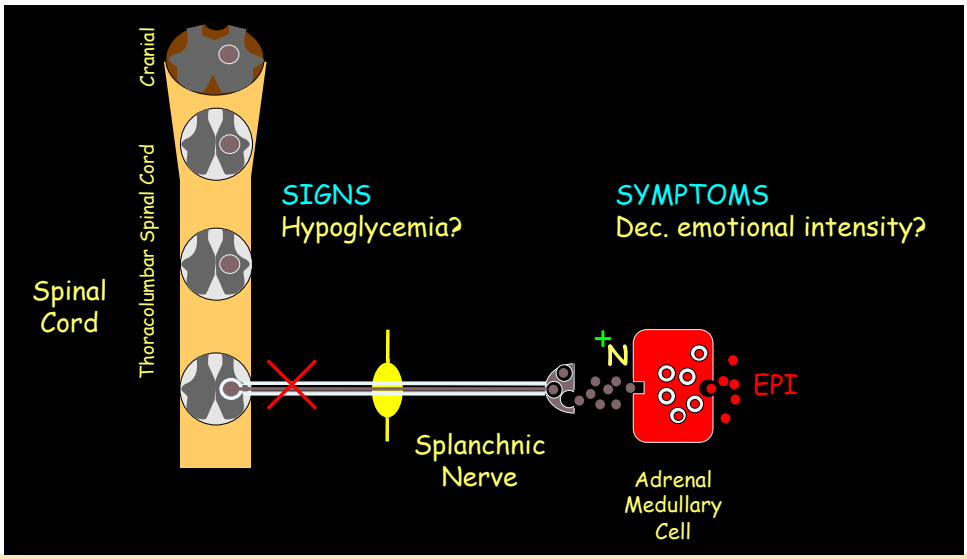


Fig. 209: Signs and symptoms of sympathetic adrenergic system (SAS) underactivity or failure. *There seem to be few clinical manifestations of decreased SAS activity.*

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

WHAT IS ORTHOSTATIC HYPOTENSION?

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

Orthostatic hypotension (OH) is a sign, something a doctor can observe or measure that provides objective evidence of a disease. By consensus, experts define OH in terms of a fall in the systolic blood pressure by at least 20 mmHg or a fall in diastolic blood pressure by at least 10 mmHg between lying down and upright posture for at least 3 minutes. Doctors sometimes use different definitions, but the 20 mmHg fall in systolic blood pressure seems to be a common theme in research reports. If the blood pressure while lying down is very high, then more than a 20 mmHg fall in systolic pressure may be required for the doctor to diagnose OH.

Orthostatic hypotension (OH) refers to a persistent, consistent problem, not to episodes. If the systolic blood pressure persistently and consistently falls by more than 20 millimeters of mercury (mmHg) between lying on the back (supine) and standing up, this is OH.

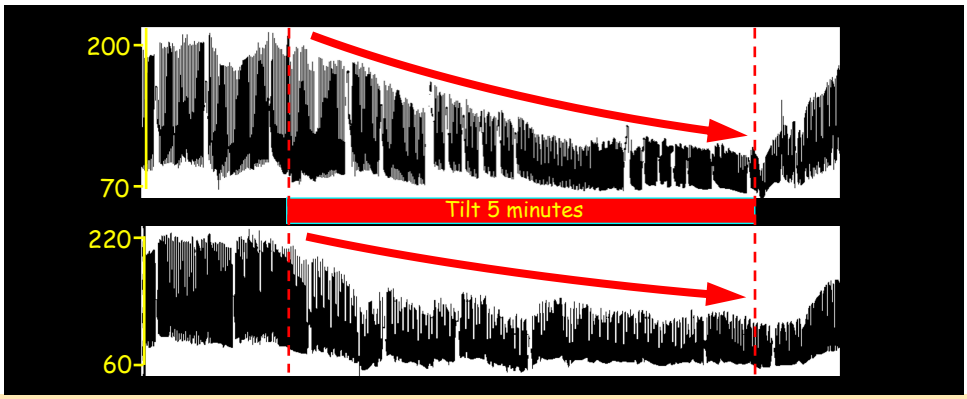


Fig. 210: Orthostatic hypotension. *In OH there is a progressive fall in systolic blood pressure that exceeds 20 mmHg by a few minutes with the patient upright. Both patients in these recordings have OH. Tilt-induced OH often is asymptomatic.*

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

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

Many factors besides failure of the sympathetic noradrenergic system (SNS), however, can cause orthostatic hypotension (OH). OH can result from conditions that cause depletion of blood volume, such as heavy menstrual periods or gastrointestinal hemorrhage from a bleeding ulcer. Any of several drugs can do this, including tricyclic anti-depressants, monoamine oxidase inhibitors, and ganglion blockers.

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

Doctors may have different opinions about the amount of OH that is clinically significant. Normally the systolic blood pressure falls slightly during standing up, because the heart is ejecting less blood, and normally the diastolic pressure does not fall at all, because of the constriction of blood vessels in the body as a whole by way of the baroreflex and activation of the sympathetic noradrenergic system.

Some people have a fall in blood pressure accompanied by lightheadedness as soon as they get up, but then the blood pressure comes up to normal. Most experts do not consider this to be OH, because the fall in blood pressure is not sustained.

Any of several diseases can produce orthostatic hypotension from sympathetic neurocirculatory failure. These include diabetes, amyloidosis, pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson's disease (PD), and dementia with Lewy bodies (DLB).

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

WHAT IS CHRONIC ORTHOSTATIC INTOLERANCE?

A major way dysautonomias cause problems in adolescents and adults is by producing chronic orthostatic intolerance (COI), an inability to tolerate prolonged standing.

Patients with orthostatic intolerance can't tolerate prolonged standing. In chronic orthostatic intolerance (COI) this problem can goes on for months or years.

COI is a symptom, a complaint about something abnormal a person notices that provides subjective evidence of a disease. Orthostatic intolerance is not a sign, because it isn't something an observer can measure objectively. And it isn't a disease, although there are many diseases that produce COI.

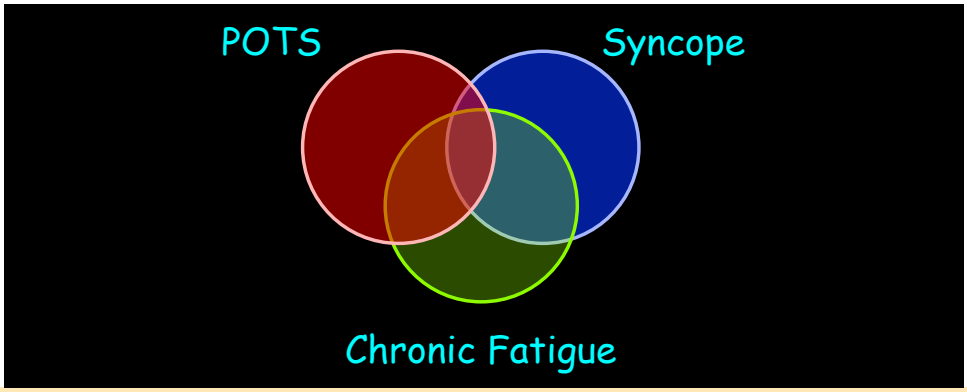


Fig. 211: POTS, syncope, & chronic fatigue. *Chronic orthostatic intolerance (COI) occurs in several conditions. A large proportion of patients with chronic fatigue syndrome have COI.*

Neither chronic orthostatic intolerance nor orthostatic

hypotension is a diagnosis. (A diagnosis is a decision about the cause of a specific case of disease.)

It is thought that about 60% of patients with chronic fatigue syndrome have COI, with postural tachycardia syndrome (POTS), neurocardiogenic syncope (fainting), or both. Much less commonly, COI can be a manifestation of arterial baroreflex failure.

The fact that there are many possible causes of COI poses a challenge to doctors trying to come up with a diagnosis to explain orthostatic intolerance in a particular patient. A starting point in identifying a cause of COI is to determine whether the patient has failure of the sympathetic noradrenergic system (SNS) to regulate the heart and blood vessels correctly. In dysautonomias that produce chronic SNS failure, the patient always has a fall in blood pressure during standing (orthostatic hypotension).

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

Orthostatic hypotension may or may not produce chronic orthostatic intolerance. Chronic orthostatic intolerance usually occurs without orthostatic hypotension.

In the evaluation of a patient with chronic orthostatic intolerance in which the patient does not have persistent, consistent orthostatic hypotension, doctors often prescribe a tilt table test. A section later about autonomic function testing discusses the tilt table test.

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

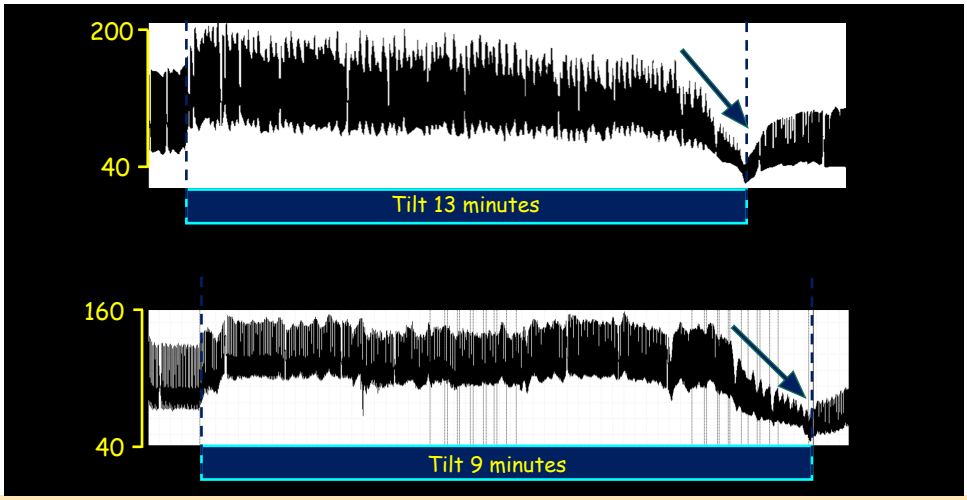


Fig. 212: Neurally mediated hypotension. *In patients with chronic orthostatic intolerance, head-up tilt table testing can evoke a rapid fall in blood pressure—neurally mediated hypotension (NMH). NMH is often associated with acute symptoms such as lightheadedness and nausea and signs such as sweating, pallor of the lips, and retching.*

In patients with COI, head-up tilt table testing can evoke an acute, symptomatic fall in blood pressure. This is called neurally mediated hypotension (NMH). An alternative designation is tilt-evoked hypotension (TEH), which doesn't presume a pathophysiologic mechanism.

It is usually relatively easy to distinguish OH from NMH by reviewing the blood pressure trends and associated symptoms and signs (compare the tracings in Fig. 210 with those in Fig. 212). In NMH, the fall in blood pressure is sudden.

Uncommonly, COI reflects baroreflex failure. In this situation the sympathetic noradrenergic system is not activated appropriately in response to a decrease in blood pressure or to a decrease in venous return to the heart. Baroreflex failure does not consistently cause orthostatic hypotension, but it always causes large swings in blood pressure, both high and low, because of the inability to keep the blood pressure within limits. Baroreflex failure occurs in some people years after irradiation of the neck, such as for treating a cancer. The radioactivity exposure accelerates aging-related stiffness of the carotid arteries in the neck—arteriosclerosis. Since the baroreceptors are distortion receptors, the stiffening interferes with the ability of the baroreceptors to sense changes in blood pressure.

Baroreflex failure is also a known complication of tumors and surgery for tumors in the lower brainstem, the location of the "barostat" for blood pressure regulation.

TESTS FOR DYSAUTONOMIAS

OVERVIEW OF AUTONOMIC FUNCTION TESTS

There are many tests that can be used to evaluate patients with known or suspected dysautonomias. No single test assesses all the components of the autonomic nervous system simultaneously.

It can be difficult to distinguish a functional problem of the nerves themselves from a central nervous system problem that alters reflexes mediated by those nerves.

Most centers that carry out autonomic function testing use more than one type of test. No center uses all the tests described in this section.

Tests for dysautonomias can be divided into physiological, neuropharmacological, neurochemical, neuroimaging (macroscopic and microscopic), and genetic.

Physiological tests

Physiological tests involve measurements of a body function in response to a manipulation such as standing, tilt table-testing, or a change in room temperature.

There are always several steps between the brain's directing changes in nerve traffic in the autonomic nervous system and the physiological measures that are chosen to track the

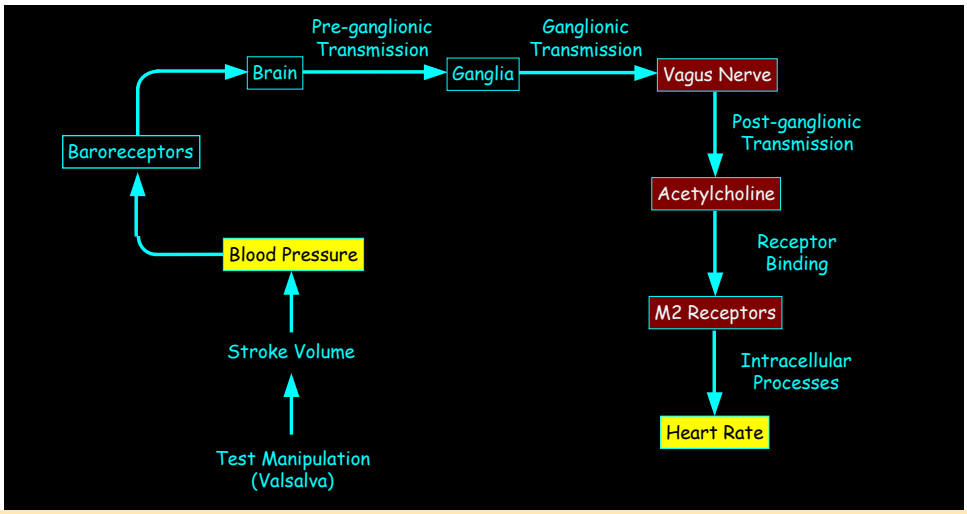


Fig. 213: A physiological test (the Valsalva maneuver). *Physiological tests involve manipulation of a body function such as blood pressure and measurement of a different body function such as pulse rate.*

autonomic changes. Because of this indirectness, results of physiological tests can be difficult to interpret or may not identify a problem accurately.

Electromyographic measurements assess conduction of traffic in large, myelinated, rapidly conducting nerve fibers and cannot assess autonomic fibers, which because they are non-myelinated conduct nerve impulses slowly. Bursts of pulse-synchronous sympathetic outflow in skeletal muscle can be measured by microneurography.

Neuropharmacological tests

Pharmacological tests involve giving a drug and measuring its effects. Neuropharmacological tests of the autonomic nervous system (ANS) involve giving a drug and measuring its effects

on physiological measures of ANS functions or on levels of a biochemical such as norepinephrine.

There always is at least some risk of side effects of test drugs. In addition, test drugs can interact with medications the patient is on to treat the disease or with other conditions the patient has.

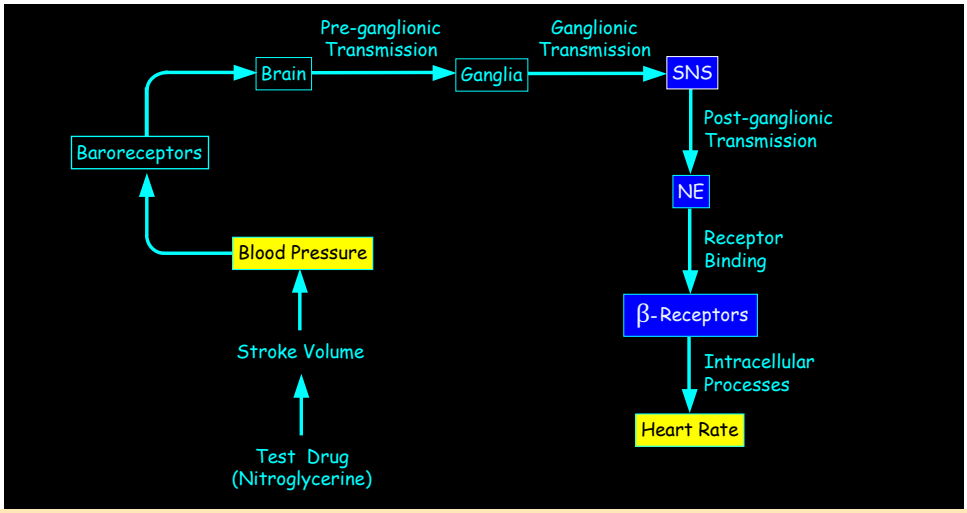


Fig. 214: A neuropharmacological test (injection of nitroglycerine). *Neuropharmacological tests involve drugs that directly or indirectly affect the autonomic nervous system. Here, nitroglycerine injection drops blood pressure, and the extent of increase in heart rate is measured as an index of reflexive stimulation of the sympathetic noradrenergic system (SNS).*

Sometimes results of neuropharmacological tests can be as difficult to interpret as those of physiologic tests. For instance, a neuropharmacological test of the role of the sympathetic noradrenergic system (SNS) in a person's high blood pressure might include measuring the effects of a drug that blocks sympathetic nerve traffic on blood pressure, because a large fall

in blood pressure would suggest an important role of the SNS in keeping the blood pressure high. But if blocking the sympathetic nerve traffic compensatorily activated another system that also increased blood pressure, then the sympathetic blocking drug would not decrease the pressure, and the doctor might mistakenly think that the SNS wasn't involved with the patient's high blood pressure.

Neurochemical tests

Neurochemical tests involve measuring levels of body chemicals, such as the catecholamines norepinephrine and adrenaline, either under resting conditions, in response to physiological manipulations such as exercise and head-up tilt, or in response to a neuropharmacological manipulation.

Neurochemical tests themselves are safe, but the type of body fluid sampling, such as arterial blood sampling or cerebrospinal fluid sampling after a lumbar puncture, can involve some risk. The results can be affected importantly by diet, posture, drugs or dietary supplements the patient is taking, and the environmental conditions at the time of sampling. Moreover, relatively few centers have a clinical neurochemistry laboratory to carry out the relevant assays.

There is no neurochemical test of parasympathetic nervous system (PNS) activity. This is because acetylcholine, the chemical messenger of the PBS, is broken down by an enzyme almost as soon as acetylcholine enters body fluids such as the plasma. There are indirect measures, such as pancreatic polypeptide levels.

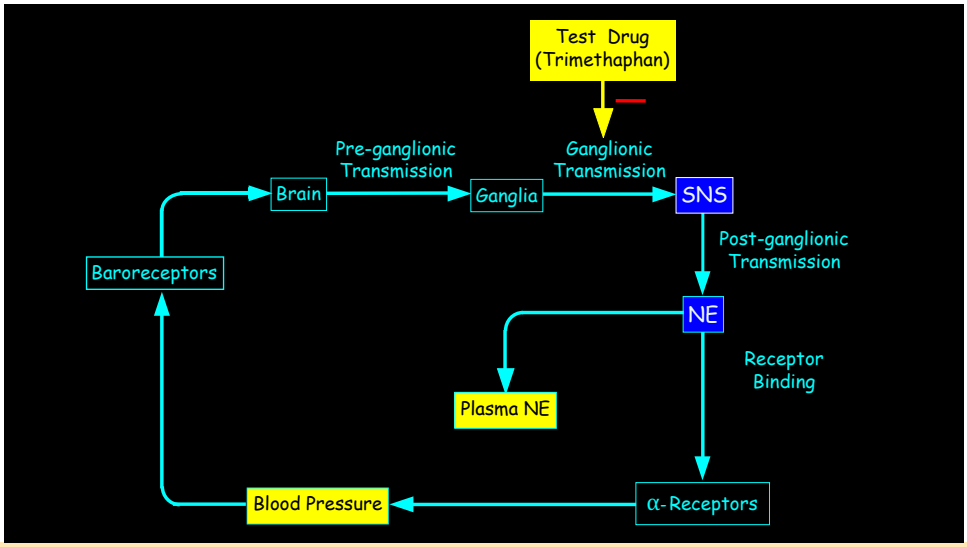


Fig. 215: A combined physiological/neurochemical test (ganglion blockade by trimethaphan infusion). *Neurochemical tests involve measuring chemicals such as norepinephrine (NE) in plasma that indicate particular autonomic functions. Physiological and neurochemical measures can be assessed simultaneously.*

Some blood tests involve measuring levels not of neurochemicals but of factors in the circulation that affect the functioning of one or more components of the autonomic nervous system. For instance, there are uncommon forms of dysautonomia in which there are high titers of antibodies to the nicotinic cholinergic receptor that is required for relaying signals in the autonomic ganglia.

Neuroimaging tests

Neuroimaging tests involve visualizing the autonomic nerve supply in body organs, either macroscopically or microscopically.

MACROSCOPIC NEUROIMAGING

Cardiac sympathetic noradrenergic neuroimaging is done commonly in Japan and Europe but rarely in the United States, even though this type of testing can produce informative images of the sympathetic innervation of the heart. Usually sympathetic neuroimaging provides only anatomic information about whether sympathetic nerves are present in the heart. It is more difficult to determine whether the nerves that are present are functioning normally or not.

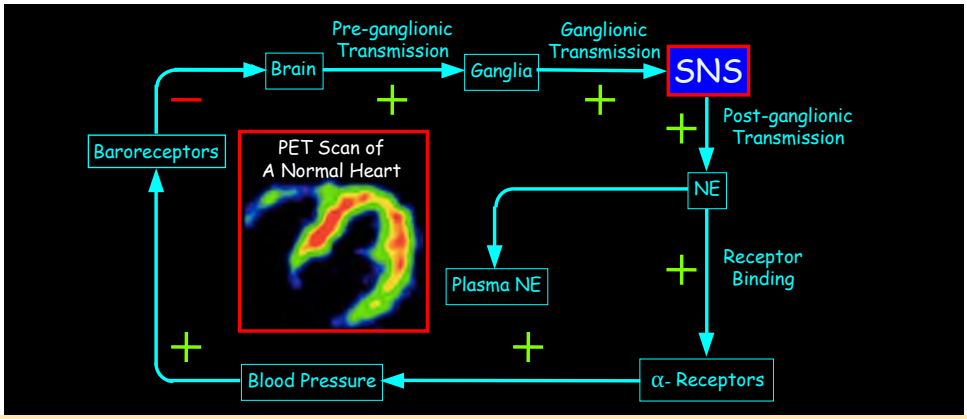


Fig. 216: A macroscopic neuroimaging test (cardiac ^{18}F-dopamine positron emission tomographic (PET) scanning). *Cardiac neuroimaging depicts sympathetic noradrenergic innervation of the left ventricular myocardium.*

Central nervous system neuroimaging can identify brain diseases associated with dysautonomias. For instance, different types of scans can identify the loss of nerve terminals that contain dopamine in the brain in Parkinson's disease or identify abnormalities of brain structures in the central autonomic network.

MICROSCOPIC NEUROIMAGING

Examining nerves in skin biopsy specimens under a microscope can be considered to be another form of autonomic neuroimaging. Microscopic examination of small nerve fibers in the epidermis provides a way to identify small fiber neuropathy. This usually is done by staining for the non-specific axonal marker, protein gene product 9.5, or PGP 9.5. PGP 9.5 staining cannot easily distinguish sensory from autonomic fibers.

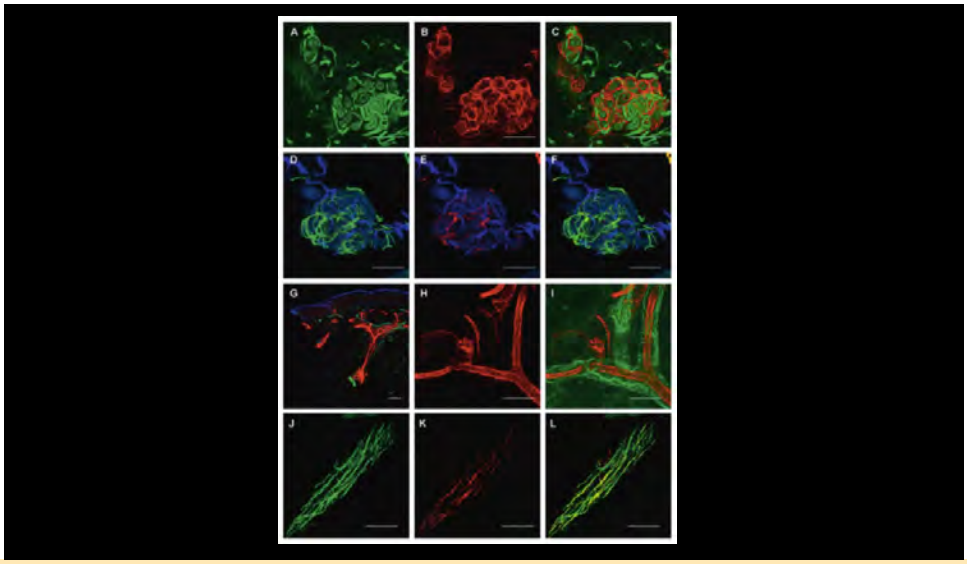


Fig. 217: Microscopic autonomic neuroimaging. *Analyses of skin biopsy specimens can delineate autonomic nerves supplying sweat glands, blood vessels, and pilomotor muscles (images courtesy of C. Gibbons).*

Three types of skin constituents in the dermis receive autonomic post-ganglionic innervation—sweat glands, blood vessels, and *arrector pili* (pilomotor) muscles. The autonomic fibers can be visualized by immunofluorescence confocal

microscopy.

Sweat glands have sympathetic cholinergic fibers, which can be identified specifically by staining for immunoreactive vasoactive intestinal peptide (VIP) or choline acetyltransferase (ChAT). Sweat glands also have sympathetic noradrenergic fibers, which can be identified by specifically by staining for immunoreactive dopamine-beta-hydroxylase (DBH) or tyrosine hydroxylase (TH). Since blood vessels and arrector pili muscles receive sympathetic noradrenergic innervation exclusively, PGP 9.5 staining of these structures can be used to assess the status of local sympathetic noradrenergic innervation.

Genetic Tests

The area of genetic testing in autonomic medicine is rapidly expanding.

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 genetic 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 50% that they will donate the chromosome carrying the mutation, and the chances are 25% that their offspring will carry the mutation on both chromosomes and have the disease.

An X-linked recessive disease involves a mutation on the X chromosome. The disease is expressed in males but not in females, because in females 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).

Genetic tests involve analyses of genetic material (DNA) for abnormalities of specific genes that produce or predispose to the development of particular diseases.

In general, the more common the genetic alteration in the population, the lower the risk associated with that alteration.

TH	HSAN III *(IKBKAP)*
DDD *(GCH1)*	HSAN IV *(NTRK1)*
PKU *(PAH)*	CCHS *(PHOX2B)*
LAAAD *(DDC)*	Hirschsprung's, MEN2 *(RET)*
VMAT2 *(SLC18A2)*	EDS *(COL…)*
DBH	Fabry *(GLA)*
Menkes *(ATP7A)*	Erythromelalgia *(SCN9A)*
Vitamin C *(CYB561)*	*ASIC…*
MAOA	Amyloidosis *(hATTR)*
NET *(SLC6A2)*	Alpha-Synuclein *(SNCA)*
ALDH…	Gaucher disease *(GBA)*
COMT	*COQ2*

Fig. 218: Genes in autonomic medicine. *There is a rapidly expanding roster of gene mutations that cause or predispose to dysautonomias. Gene names are in italics.*

Genetic tests involve several ethical issues. For instance, it is difficult to ensure confidentiality of the data when patient pedigrees are published or available from data repositories. An individual may not wish to be informed of the test result if there is no way to prevent the disease. Researchers may be reluctant to provide results of genetic tests if the laboratory is not certified to do diagnostic testing.

The following text highlights some dysautonomias or catecholamine-related disorders involving genetic mutations.

FAMILIAL DYSAUTONOMIA

The most well known inherited dysautonomia is familial dysautonomia (FD), or Riley-Day syndrome. FD runs in families of Ashkenazi extraction. The cause is a mutation of the

gene, IKBKAP. Genetic screening for FD is now available.

DBH DEFICIENCY

A very rare cause of orthostatic hypotension is deficiency of the enzyme, dopamine-beta-hydroxylase (DBH). This enzyme is required to produce norepinephrine. Genetic testing may be indicated in patients with orthostatic hypotension who have biochemical test results that are consistent with DBH deficiency.

NET DEFICIENCY

Postural tachycardia syndrome (POTS) can result from mutation of the gene that encodes the cell membrane norepinephrine transporter (NET). Although POTS is common, POTS from this genetic cause is very rare. Genetic screening for NET deficiency might be indicated in POTS patients who have biochemical or neuroimaging test results that are consistent with NET deficiency.

MENKES DISEASE

Menkes disease is a rare disease of copper metabolism. Because dopamine-beta-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine, is a copper enzyme, Menkes disease involves a form of dysautonomia due to decreased norepinephrine production.

The Menkes disease is on the X chromosome. This means that Menkes disease is transmitted as an X-linked recessive trait.

The patients are virtually always boys, since males have only 1 X chromosome. The mother is a carrier. If a woman has given birth to a baby with Menkes disease, then chances are 50:50 that if she has another son the baby will be affected. Genetic testing for the mutated gene can be done in the fetus, but as discussed later the most efficient test to diagnose Menkes disease in at-risk newborns is measuring plasma levels of catechols.

PARKINSON'S DISEASE

The first identified genetic cause of PD was mutation of the gene encoding the protein, alpha-synuclein, in 1997. The discovery was in a Greek-Italian-American kindred in which PD was transmitted as an autosomal dominant trait. In other words, half the family members had PD. Subsequently it was found in another family that PD can result from replication of a normal alpha-synuclein gene. People who carry the mutation that produces Gaucher disease are at increased risk of developing PD. Ashkenazim and North African Arabs with familial PD often carry a mutation of the gene encoding a protein called LRRK2. In the United States the frequencies of all these genetic abnormalities are low.

WHICH TESTS ARE DONE WHERE?

Few hospitals in the United States carry out comprehensive autonomic function testing.

Physiological tests such as measurements of heart rate

responses to the Valsalva maneuver are readily available, beat-to-beat blood pressure responses to the maneuver and the QSART and skin biopsies are done in several specialized autonomic function testing centers, neurochemical tests such as plasma norepinephrine and adrenaline levels are done in fewer centers, and as of this writing neuroimaging tests are hardly available at all in the United States, because third party payers don't cover them. At this point there are only a few genetic tests for particular forms of dysautonomia, such as familial dysautonomia.

At a minimum the autonomic function testing at a given medical center should be able to identify abnormalities of regulation of the circulation by the sympathetic noradrenergic system (SNS), sweating by the sympathetic cholinergic system (SCS), and heart rate by the parasympathetic nervous system (PNS).

Other types of indicated autonomic testing depend on the particular problem the patient is facing. In my opinion, for complete assessment of dysautonomia in a patient with evidence of a neurodegenerative disease such as Parkinson's disease, neuroimaging should be available to examine dopamine centers in the brain and the supply of sympathetic nerves in the heart. To evaluate a patient with postural tachycardia syndrome, obtaining a panel of serum autoimmune markers, measuring blood volume and orthostatic shifts in blood volume, examining the efficiencies of tubular reabsorption of sodium and water, and assessing the renin-angiotensin-aldosterone system during controlled sodium intake may be informative. Because of the likelihood of sympathoadrenal imbalance as a proximate cause of tilt-evoked

hypotension, I think that provocative tilt table testing to evaluate frequent fainting should include serial blood sampling for plasma catecholamines.

There is now a certification program in autonomic disorders, under the United Council of Neurological Subspecialties (UCNS). Physicians who are certified under the program are knowledgeable about autonomic function testing.

THE MOST IMPORTANT TEST OF ALL

The most important autonomic function test is the medical history.

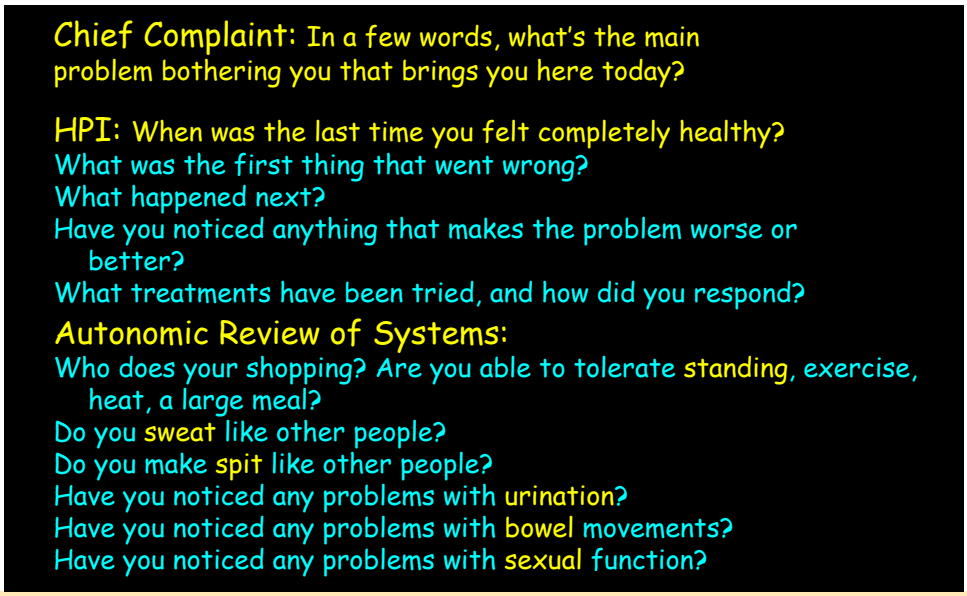


Fig. 219: Screening autonomic history. *Elements of the screening autonomic history are the Chief Complaint, the History of the Present Illness (HPI), and the autonomic Review of Systems.*

In the United States, payment by third party payers for diagnostic testing of patients with dysautonomias is based mainly on procedures, even though it is the autonomic history that is most important. Autonomic history-taking can't be done well in a brief clinic visit. This is a growing problem for community based physicians.

Symptoms are feelings that the patient reports to the medical professional as part of the medical history. Signs are medical findings that a medical professional detects during a physical examination.

The medical history consists of several parts. These include the Chief Complaint, the History of the Present Illness (HPI), the Past History, the Family History, the Personal and Social History, and the Review of Systems (ROS). Each of these parts is important for diagnosing and managing dysautonomias, but of these the key components are the Chief Complaint and the HPI.

The Chief Complaint

The Chief Complaint is a single phrase or sentence that describes in the patient's own words what has been bothering the patient that has led the patient to come in for evaluation.

Perhaps surprisingly, the Chief Complaint can be remarkably informative. I once evaluated a local elderly woman who was referred for pure autonomic failure, because she had persistent, consistent orthostatic hypotension. I asked her, "We'll be going into detail about your medical history, but for now, in a single

phrase or sentence, can you tell me what it is that's been bothering you that's brought you here today?" I was expecting she would report dizziness or lightheadedness when she was upright, or perhaps fainting episodes while standing on line at a checkout counter. Instead, her Chief Complaint was that she couldn't make spit and she was constipated.

Dry mouth and constipation are symptoms of parasympathetic nervous system (PNS) failure, not sympathetic noradrenergic system (SNS) failure. I asked if she sweated like other people, and she said no, because she couldn't sweat at all. Sweating is a sympathetic cholinergic system (SCS) function. In other words, she had symptoms of a pandysautonomia that involved failure of all the components of the autonomic nervous system. Eventually she was found not to have pure autonomic failure but a previously undescribed condition, autoimmune autonomic ganglionopathy from a circulating antibody to the neuronal nicotinic receptor. The initial clue to the diagnosis was her unexpected Chief Complaint.

The History of the Present Illness (HPI)

The History of the Present Illness (HPI) is a narrative history of the condition. It is best to obtain the HPI from the patient directly. Of course there are records to review of hospitalizations, test results, and previous accounts of the medical history and physical examination; however, these are subject to mistakes and often are uninformative. On the other hand, the patient's own story of the chronology of his or her symptoms, especially with the help of family or significant others, is likely to be both correct and informative.

Unfortunately, this key aspect of the medical encounter is not reimbursed adequately considering its importance and the time and effort involved.

I take what the patient says as gospel. The patient knows best how he or she feels. In my experience patients always tell the truth.

Obtaining the medical history, especially the HPI, is a skill that must be honed by learning and experience, ideally under the supervision of a mentor.

MEDICATIONS

A complete listing of all prescribed and over-the-counter medications, herbal remedies, and dietary supplements is a key part of the medical history, not only because these agents can affect autonomic functions and complicate or confound test results but also because they can interact with each other or with the condition to produce unanticipated problems and serious adverse events.

Even herbal remedies must be considered carefully. Years ago I had a patient with multiple system atrophy (MSA) who first came to medical attention because of paroxysmal high blood pressure after taking *ma huang* tea. He had thought this would alleviate his sense of fatigue and lack of energy. The active ingredient in *ma huang* is ephedrine, an amphetamine. The drug increased delivery of norepinephrine to its receptors, which caused the blood pressure to increase, and because of baroreflex failure, which is part of the clinical laboratory picture in MSA,

the increase in blood pressure was not buffered by the baroreflex. The patient developed a severe headache and went to the emergency room. Because of his headache and paroxysmal hypertension the physicians thought at first that he was having a stroke from subarachnoid hemorrhage.

Ma huang is no longer sold as a dietary supplement in the US, but yohimbe bark is. Yohimbine, a drug derived from yohimbe bark, increases norepinephrine release. In a patient with baroreflex failure, taking this dietary supplement could result in severe hypertension, just as in the MSA patient.

TIMING IS EVERYTHING

In obtaining the history of the present illness (HPI) one of the most important skills a clinician can acquire is the ability to get the sequence straight.

I usually start by asking the patient, "When was the last time you felt completely well?" The answer can range from "I've always been sick," to "I was fine until…" a particular date, to "It was such a gradual thing, I don't know."

Some dysautonomias develop in a rather stereotyped sequence. An example is the cerebellar form of multiple system atrophy (MSA-C) in a man. Men with MSA-C typically relate that the first thing to go wrong, in retrospect, was erectile failure. In my opinion, in a man with central neurodegeneration and orthostatic hypotension, the absence of erectile failure as an early finding rules out MSA-C. The erectile failure is followed by urinary problems—especially urinary retention, eventually

to the point of requiring self-catheterization. Then come slurred speech, a wide-based, unsteady gait “like a drunken sailor,” and lightheadedness when standing.

In obtaining the details about symptoms of dysautonomias, it is also important to determine which situations make things worse and which make them better. For instance, patients with neurogenic orthostatic hypotension often relate that their symptoms are worst in the morning, upon heat exposure, after eating a large meal, or after exercise.

Because of associations of autonomic failure with non-motor aspects of Parkinson’s disease and other Lewy body diseases, it is important to ask about whether the patient is able to smell things like other people do, whether the patient sees things like other people do, and whether the patient has any problems with sleep. The clinician is looking for evidence of olfactory dysfunction, visual hallucinations (a feature suggestive of dementia with Lewy bodies), and dream enactment behavior.

In patients with possible postural tachycardia syndrome (POTS) it is valuable to ask about whether the patient has “double-jointedness” or stretchy skin, since these can be clues to the occurrence of Ehlers-Danlos syndrome. Later on you will learn about the “coat hanger sign” and the “water bottle sign” in dysautonomias like POTS. Again, the sequence of events can be very informative. Subacute development of orthostatic intolerance after a viral illness suggests an autoimmune pathophysiology, whereas a history since childhood of frequent fainting or “seizures” points suggests a congenital, genetic component. In the evaluation of a patient with POTS, which occurs mainly in relatively young women, it is important to ask,

in a private setting, about emotional, physical, or sexual abuse in childhood. These can have long-term consequences in terms of chronic fatigue, altered memory or concentration, post-traumatic stress disorder, and panic or anxiety.

In a patient with labile blood pressure and orthostatic intolerance, a remote history of irradiation of the neck brings up the possibility of arterial baroreflex failure due to accelerated arteriosclerosis in the carotid sinus area.

SYMPTOMS & SIGNS OF DYSAUTONOMIAS: ANOTHER LOOK

Altered functions of each of the components of the autonomic nervous system result in particular symptoms and signs.

Failure of the sympathetic noradrenergic system (SNS) manifests as orthostatic hypotension, meaning a persistent, consistent fall in blood pressure each time the patient stands up.

Orthostatic hypotension can produce symptoms such as lightheadedness, dizziness, faintness, “brain fog,” visual changes, “coat hanger phenomenon,” and muscle weakness.

Orthostatic hypotension is a cardinal sign of SNS failure.

Orthostatic hypotension can also occur without any symptoms.

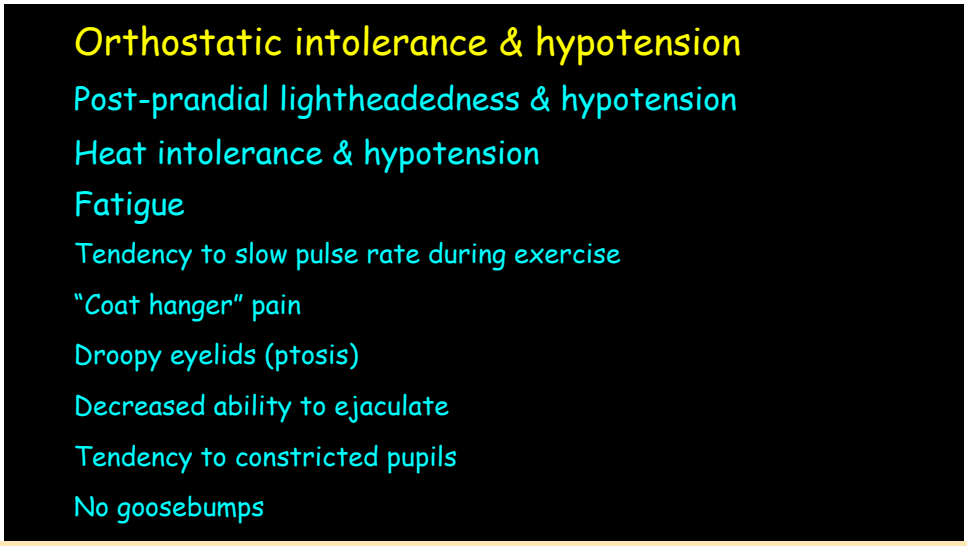


Fig. 220: Sympathetic noradrenergic system (SNS) failure. *SNS failure is characterized by orthostatic intolerance due to orthostatic hypotension. There are several other symptoms.*

Florida Chinese restaurant syndrome

Orthostatic hypotension often is accompanied by post-prandial lightheadedness and hypotension. "Post-prandial" means after eating a meal. In patients with SNS failure, heat exposure also can decrease the blood pressure.

I refer to this combination as "Florida Chinese restaurant syndrome." Picture a stereotypical elderly male retiree in Florida who happens to have SNS failure. He visits an all-you-can-eat Chinese buffet restaurant, which is air conditioned and chilly if not downright cold inside. Over the course of about a half hour he stuffs himself with food, and then he leaves. Meanwhile, his car has been baking in the sun in the parking

Fig. 221: Florida Chinese restaurant syndrome. *Post-prandial hypotension, heat exposure, and orthostatic hypotension can be a morbid combination in patients with SNS failure.*

lot, and it is blistering hot when he gets in. A few minutes later he enters the local lanes on the way to I-95, sitting upright at the wheel and almost motionless. Soon after accelerating to get into the express lanes of I-95 at high speed, he begins to feel lightheaded; his limbs don't work, and he can't think straight. He loses control of the car and is injured or killed in an accident. The take-home point is that in patients with failure of the sympathetic noradrenergic system (SNS), post-prandial hypotension, cutaneous vasodilation from intense heat exposure, orthostatic hypotension, and absence of muscle pumping constitute a highly morbid and potentially lethal combination.

SNS hyperactivity produces pallor due to constriction of blood vessels in the skin. Blood pressure and heart rate tend to increase. The heart may pound (palpitation). The hair may

bristle, due to activation of noradrenergic nerves supplying *arrector pili* (pilomotor) muscles in the skin. The pupils may be dilated, and there may be increased salivation.

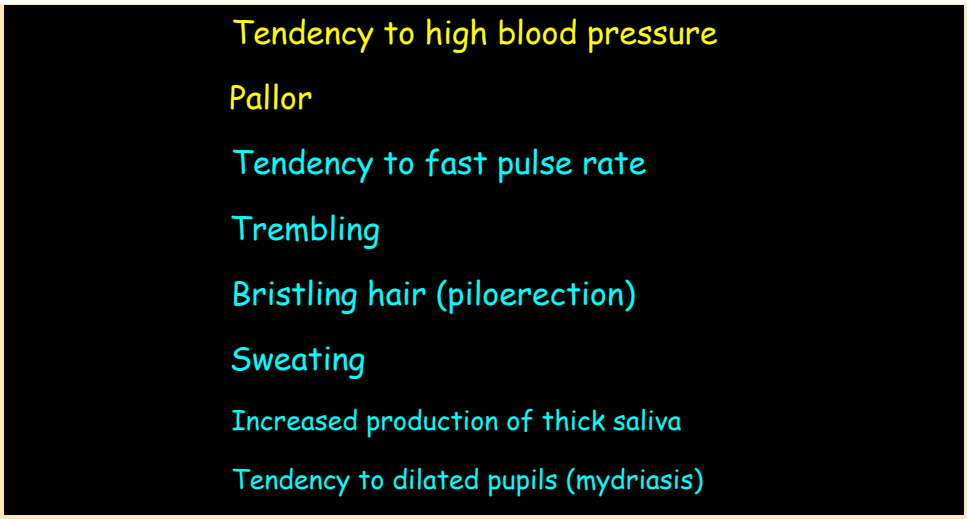


Fig. 222: Sympathetic noradrenergic system (SNS) hyperactivity.

Parasympathetic nervous system (PNS) failure produces a variety of symptoms. Probably the most prominent are dry mouth and constipation. Other manifestations include a tendency to urinary retention, slowed gastrointestinal transit, and erectile failure in men.

The sympathetic cholinergic system (SCS) is the main part of the autonomic nervous system mediating sweating. SCS failure manifests as decreased sweating and SCS hyperactivity as increased sweating.

Conversely, PNS hyperactivity can produce gastrointestinal upset, nausea, retching, vomiting, increased salivation, a tendency to slow pulse rate, and urinary frequency or urgency.

There can also be poor dark adaptation because of pupillary constriction (miosis).

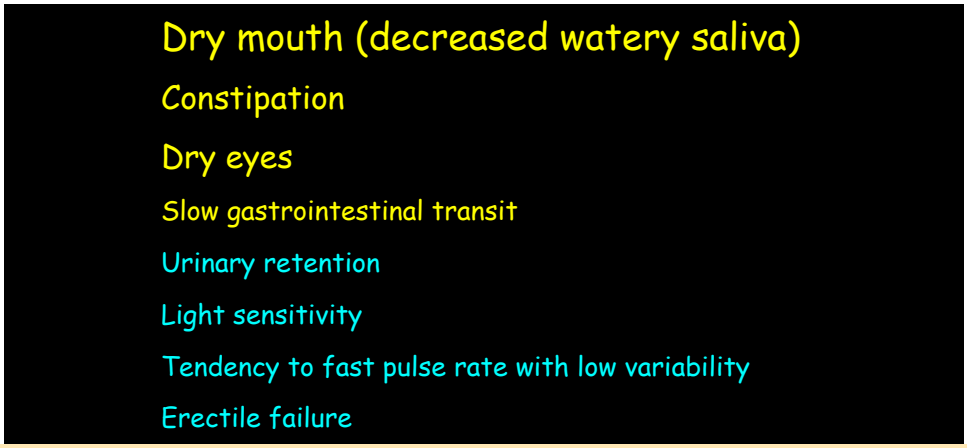


Fig. 223: Parasympathetic nervous system (PNS) failure. *Dry mouth and constipation are prominent symptoms of PNS failure.*

The main symptoms of parasympathetic nervous system (PNS) failure are dry mouth and constipation.

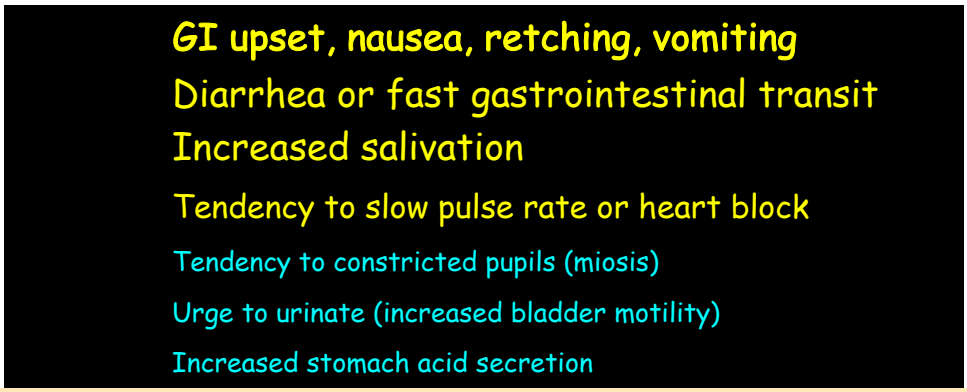


Fig. 224: Parasympathetic nervous system (PNS) hyperactivity. *Major symptoms are from increased gastrointestinal motility.*

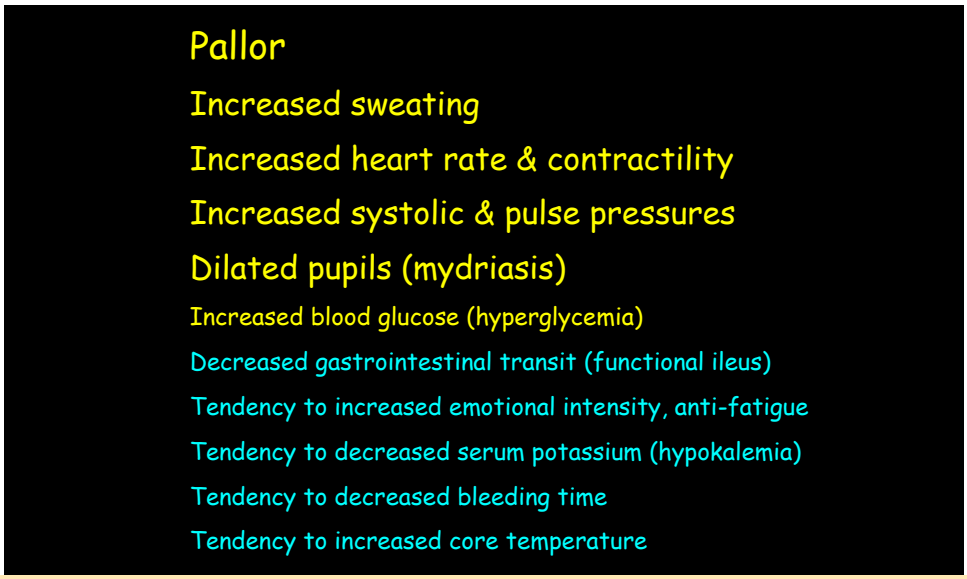


Fig. 225: Sympathetic adrenergic system (SAS) hyperactivity. *High circulating adrenaline (epinephrine, EPI) levels produce many manifestations found in distress.*

SAS hyperactivity produces many symptoms and signs, such as pale skin, increased sweating, a forceful heartbeat, and dilated pupils. These are manifestations of distress.

Adrenaline, the main chemical messenger of the sympathetic adrenergic system (SAS), is a hormone; adrenaline is distributed by the bloodstream to all the organs (with the exception of most of the central nervous system). Adrenaline injection produces characteristic symptoms, including pallor, increased sweating, cardiovascular stimulation, dilated pupils, and increased blood glucose levels. Adrenaline exerts well-known anti-fatigue effects and tends to increase the intensity of emotional experiences. SAS failure, on the other hand, produces relatively few symptoms or signs—perhaps a

tendency to fatigue or to hypoglycemia.

Composite Autonomic Symptom Score (COMPASS)

Over the years, progressively more refined "composite" autonomic symptom scores (COMPASS) have been introduced. The "COMPASS 31" scale contains a total of 31 questions in 6 domains, yielding an overall autonomic symptom score from 0 to 100. The domains are orthostatic intolerance (4 questions), vasomotor (3 questions), secretomotor (4 questions), pupillomotor (5 questions), bladder (3 questions), and gastrointestinal (including diarrhea, constipation, and gastroparesis, 12 questions). Erectile dysfunction is not included, since this is sex-specific. For each question there is a numeric rating based on factors such as site, consistency, severity, frequency, or trends.

Here are the topics and simplified questions of the COMPASS 31:

1. Orthostatic intolerance: In the past year, have you ever felt faint, dizzy, "goofy", or had difficulty thinking soon after standing up from a sitting or lying position? If so, how frequently? How severe are these feelings or symptoms? Have they changed?

2. Vasomotor: In the past year, have you ever noticed color changes in your skin, such as red, white, or purple? If so, which body parts are affected? Have these symptoms changed?

3. Secretomotor: In the past 5 years, what changes, if any, have occurred in your general body sweating? Do your eyes feel excessively dry? Does your mouth feel excessively dry? For the symptom of dry eyes or dry mouth that you have had for the longest period of time, has this symptom changed over time?

4. Gastrointestinal: In the past year, have you noticed any changes in how quickly you get full when eating a meal? Have you felt excessively full or persistently full (bloated feeling) after a meal? Vomited after a meal? Had cramping or colicky abdominal pain? Bouts of diarrhea? If so, how frequently? How severe are the episodes? Have they changed? In the past year, have you been constipated? If so, how frequently? How severe are the episodes? Have they changed?

5. Bladder: In the past year, have you ever lost control of your bladder function? If so, how frequently? Have you had trouble completely emptying your bladder? If so, how frequently?

6. Pupillomotor: In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes? If so, how frequently? How severe is this sensitivity to bright light? Have you had trouble focusing your eyes? How frequent is the problem? How severe is the problem? Is the problem with light sensitivity or focusing changing?

While internally consistent statistically and useful for research purposes, composite scoring of autonomic symptoms is inadequate from the point of view of the diagnostic interview as applied to dysautonomias. For instance, within the “orthostatic intolerance” domain, time of day, relationships with meals, exercise, and heat exposure, associated symptoms such as the

coat hanger phenomenon, chronic fatigue, chronic pain, and "brain" fog all should be considered. Within the "bladder" domain, a report of urinary retention and the need for self-catheterization is important for differentiating the parkinsonian form of multiple system atrophy (MSA-P) from Parkinson's disease with orthostatic hypotension (PD+OH). Urinary retention strongly favors MSA-P over PD+OH. The lack of inclusion of erectile dysfunction in men is rather glaring.

The COMPASS approach does not take into account the syndromic nature of particular forms of dysautonomia. For instance, in an elderly patient with parkinsonism, it is highly relevant to ask about olfactory dysfunction, since anosmia (lack of sense of smell) is common in Parkinson's disease with orthostatic hypotension (PD+OH) but not in multiple system atrophy (MSA); about cognitive function, since dementia is more commonly associated with PD+OH than with the parkinsonian form of MSA (MSA-P); about speech, since slurred speech favors the cerebellar form of MSA (MSA-C) over PD+OH; and about breathing, since stridor favors MSA-P over PD+OH. In a young women with orthostatic intolerance, asking about double-jointedness and stretchy skin may reveal Ehlers-Danlos syndrome. In a patient with labile hypertension, the past history may disclose a remote history of neck irradiation, raising the possibility of arterial baroreflex failure from acceleration of carotid arteriosclerosis by radiation.

Perhaps most importantly, the COMPASS approach does not take into account the sequence of symptoms, the chronology that is the essence of the history of the present illness (HPI). For instance, in a man with central neurodegeneration, the lack of early erectile function casts doubt on the diagnosis of MSA.

The checklist concerns only events within the past year (except for 5 years for secretomotor). In contrast, the non-directed approach to the HPI starts with a question like, “What was the first thing you noticed that went wrong?”

My screening questions generally query each of the components of the autonomic nervous system. The questions are designed not to be leading. For instance, about sympathetic cholinergic function, I ask, “Do you sweat like other people?” About sympathetic noradrenergic function, I ask, “Do you have any issues standing still?” About parasympathetic cholinergic function, I ask, “Are you able to make spit and tears like other people?” Have you noticed anything different about how your GI system is working? Have you noticed anything different about your urination? In a man I ask, “Are you able to have an erection and ejaculate?”

A pain in the neck

In patients with orthostatic intolerance or orthostatic hypotension, standing upright can result in an annoying pain in the back of the neck and along the shoulders.

Because of the distribution of the discomfort, this is sometimes referred to as the coat hanger sign or coat hanger phenomenon.

The mechanism of the coat hanger phenomenon is not well understood. I think of it as a kind of cramp, when the anti-gravity muscles holding up the head receive too little blood flow. These muscles are active all the time, which means that they are continuously using up the oxygen that is delivered to

them via the arterial blood. If the blood flow falls to below a certain rate, then metabolic waste products can build up that produce pain.

Fig. 226: Coat hanger phenomenon. *The "coat hanger phenomenon" refers to pain in the back of the neck during standing.*

Who Does Your Shopping?

Most patients with orthostatic intolerance are women. At the risk of seeming chauvinistic, a screening question I ask to a woman referred for orthostatic intolerance is, "Who does your shopping?" If the answer is, "I do. I love to shop," then that is the end of the line of questioning. A positive answer is something like, "Well not me." When I ask, "Why not?" the answer I'm looking for is, "Because I can't tolerate standing still in line. I start to feel faint or lightheaded or weak, or I have to sit down, or I have to twist my legs like a pretzel."

Pretzel Legs and the Water Bottle Sign

I remember well the first patient I ever saw with pure autonomic failure (PAF). PAF is a rare disease in which orthostatic hypotension dominates the clinical picture. She was sitting in a chair in the examining room with her legs twisted around each other like a pretzel.

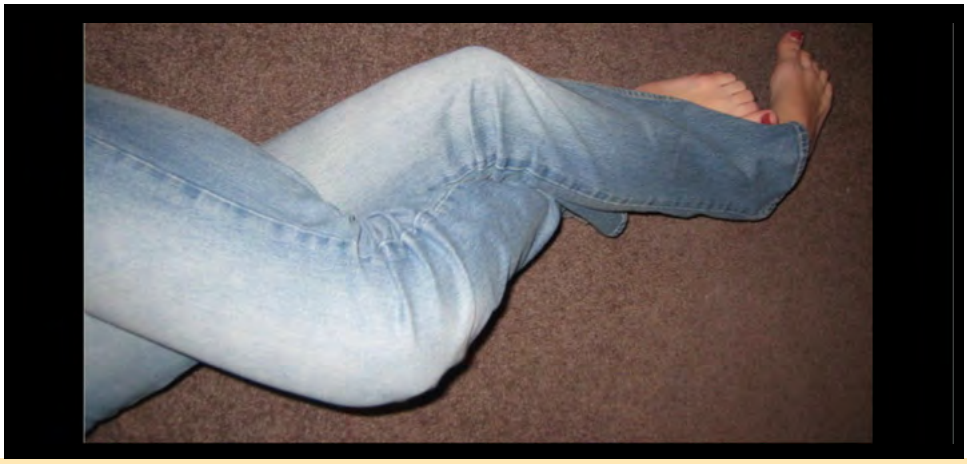


Fig. 227: Pretzel legs. *Twisting the legs around each other like a pretzel is a sign of orthostatic intolerance.*

She had learned from experience that doing this when she was sitting up delayed the onset of lightheadedness. By working the muscles of the legs against each other and tightening her buttocks she was squeezing blood upward in her body toward the heart.

When there is deficient reflexive sympathetically-mediated vasoconstriction during orthostasis, “pretzel legs” help maintain venous return to the heart. Adopting this posture can be an effective countermeasure in patients with autonomically mediated presyncope.

It is common for a patient with orthostatic intolerance to bring a bottle of water to the clinical encounter and sip from it periodically as the history is taken. I call this the "water bottle sign." The patients often report that although drinking water doesn't eliminate the symptoms, not drinking water rapidly makes them worse.

To me this could be a clue as to the pathophysiology of chronic orthostatic intolerance. Perhaps the kidneys are less efficient in reabsorbing filtered water, and the water bottle sign is part of a behavioral compensation. The kidneys filter about 100 mL of plasma per minute, or about 144 liters per day. Since normal urine output is about 1.5 liters per day, the kidneys are roughly 99% efficient in reabsorbing water. One might expect that even the slightest decrease in the efficiency of water reabsorption would result in a tendency to dehydration.

Kidney cells possess water channels called aquaporins. A medical school classmate of mine, Peter Agre, discovered aquaporins; for this he received a Nobel Prize in Chemistry in 2003. It might be worth looking into whether there is a problem with aquaporins in patients with chronic orthostatic intolerance who have the water bottle sign.

A Bit of a Stretch

Joint hypermobility ("double jointedness") occurs rather frequently among patients with postural tachycardia syndrome (POTS). When obtaining the medical history in a patient with chronic orthostatic intolerance, it is worthwhile to ask whether

the patient is double jointed and if so to ask what sorts of "tricks" the patient can perform with his/her body that other people can't.

Ehlers-Danlos syndrome (EDS) is an inherited connective tissue disease in which the patients have joint hypermobility, lax skin, a tendency to joint dislocation or subluxation, musculoskeletal pain, and easy bruising. EDS patients often have a "Marfanoid" appearance, in that they are tall, thin, have long arms and legs, and have long thin fingers (arachnodactyly, or "spider fingers"), as in the Marfan syndrome (described by the French pediatrician Antonin Marfan in 1942).

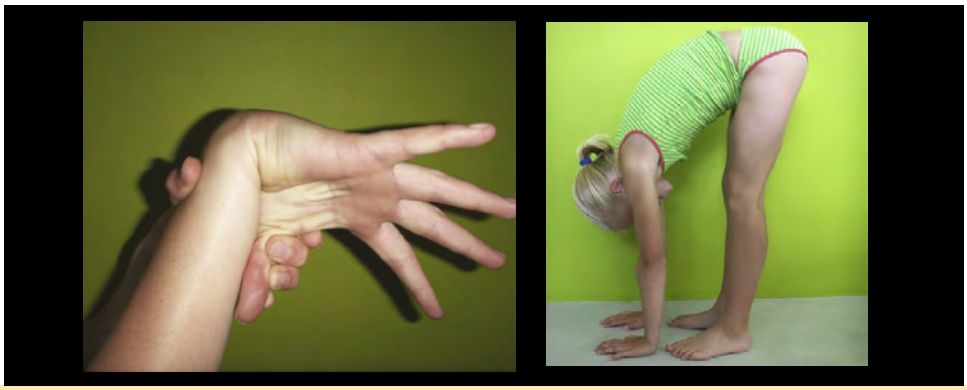


Fig. 228: Beighton scoring. *Shown here are two components of the 9-point Beighton score*

POTS occurs frequently in EDS, for reasons that remain poorly understood. A possible explanation for the association is that a problem with collagen in blood vessel walls makes them more stretchy or compliant, so that blood tends to pool in the abdomen or pelvis during standing.

Beighton scoring is used to gauge the severity of joint hypermobility, based on 5 tests. The Beighton score is

calculated as follows:

1. One point for each little finger that you can bend backwards by more than 90 degrees.
2. One point for each thumb that you can touch to your forearm when bent backwards.
3. One point for each elbow that you can bend backwards.
4. One point for each knee that you can bend backwards.
5. One point if while standing you can bend forward and place your palms on the ground with your legs straight.

PHYSIOLOGICAL TESTS

Orthostatic vital signs

Measuring the blood pressure during supine rest and then after being upright is required to identify orthostatic hypotension (OH), which in turn is a key manifestation of failure of the sympathetic noradrenergic system.

At first glance it would seem that detecting orthostatic hypotension is a simple matter. But there are issues.

According to a consensus of autonomics experts, orthostatic hypotension (OH) is "a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 min of standing or head-up tilt to at least 60º on a tilt table."

The consensus definition seems straightforward. There are some aspects, however, that bear comment. Briefly, the consensus definition involves compromises due to different practices among autonomics centers.

(1) What is a "sustained reduction…within 3 minutes"? How can a decrease in pressure be "sustained" if the duration of observation is less than 3 minutes?

What the experts have in mind by "sustained reduction…within 3 minutes" is that in many apparently healthy people blood pressure falls rapidly but transiently as soon as they stand up

from lying down. On the other hand, patients with neurogenic OH can have such a rapid, severe fall in blood pressure that it is unsafe to keep the patient upright for a long period of time. The consensus definition is a compromise that leaves open the possibility that a rapid fall in blood pressure may be a positive finding if the pressure doesn't return toward normal within 3 minutes.

I avoid trying to detect OH by brachial automated cuff measurements, because they take too long. I don't want to put patients who have rapid, severe OH at increased risk from low blood flow to the brain if I can avoid doing so. To detect OH efficiently and safely, I use continuous (beat-to-beat) blood pressure recording via a finger cuff device.

(2) The definition doesn't mention the posture before the person stands up or is tilted, nor the time the person should be at that posture before the person stands up or is tilted.

This also is a compromise, because autonomics centers differ in their methods of obtaining orthostatic vital signs. It seems intuitively obvious that in patients with failure of the sympathetic noradrenergic system the extent of fall in blood pressure between lying down and standing is greater than the fall between being sitting and standing.

In my opinion, before the baseline blood pressure is measured, the patient should be supine (with head on pillow) for at least 10 minutes. During this time, the observer can list all the medications and dietary supplements that the patient has taken within the past 24 hours and when they were taken. The location of the measurement, the time of day, and when and

what the patient last ate should be noted (the latter because of the possibility of post-prandial hypotension).

(3) The use of "or" in "reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg" seems ambiguous. Must there be both findings, or is one sufficient?

This is another compromise. In a healthy person, diastolic pressure typically increases during orthostasis and doesn't fall at all. Several research reports have relied only on the orthostatic fall in systolic pressure. The "or" in "reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg" allows OH to be identified even if the fall in diastolic pressure is less than 10 mmHg.

(4) How can "standing or head-up tilt to at least 60º" yield comparable results? In a patient with OH, wouldn't head-up tilt to 90º evoke a greater fall in blood pressure than tilt to 60º? And is standing equivalent to being tilted on a tilt table?

This is yet another compromise. Many practitioners don't have access to a tilt table. Among those who do, some tilt the patient to a full head-up position—i.e., the patient is standing upright—and others tilt the patient to 60º or another angle less than 90º. Tilting to 60º or 70º makes sense for provocative tilt table testing, since interfering with muscle pumping might increase the likelihood of a positive result (excessive orthostatic tachycardia, neurally mediated hypotension, or syncope). I don't understand the rationale of tilting to less than 90º in the evaluation of possible OH.

In order to avoid gravitational effects when the brachial cuff is below heart level, the patient's arm should be supported at heart level when the patient is upright. The patient should not have the arm extended without support, because this introduces the possibility of effects of isometric exercise on the measurement.

If you don't have access to a device for measuring blood pressure continuously and check orthostatic vital signs with an automated brachial cuff device, here's a checklist you may want to use.

Name of Test: Orthostatic Vital Signs
Patient ID: Age/Gender:
Date: Location of Test:
Recording Personnel:
Medications and When Last Taken:
Dietary Supplements and When Last Taken:
Content of Most Recent Meal and When Eaten:
Patient supine at least 10 minutes?
Supine BP (in mmHg) and Time of Day:
Concurrent Supine HR (in bpm):

Time of Day When Posture Changed to Standing Up:
Arm supported passively with brachial cuff at heart level?

Upright BP at 1 minute:
Upright BP (in mmHg) and Time of Day:
Concurrent Upright HR (in bpm)

Upright BP at 2 minutes:
Upright BP (in mmHg) and Time of Day:
Concurrent Upright HR (in bpm)

Upright BP at 3 minutes:
Upright BP (in mmHg) and Time of Day:
Concurrent Upright HR (in bpm)

Upright BP at 4 minutes:
Upright BP (in mmHg) and Time of Day:
Concurrent Upright HR (in bpm)

Upright BP at 5 minutes:
Upright BP (in mmHg) and Time of Day:
Concurrent Upright HR (in bpm)

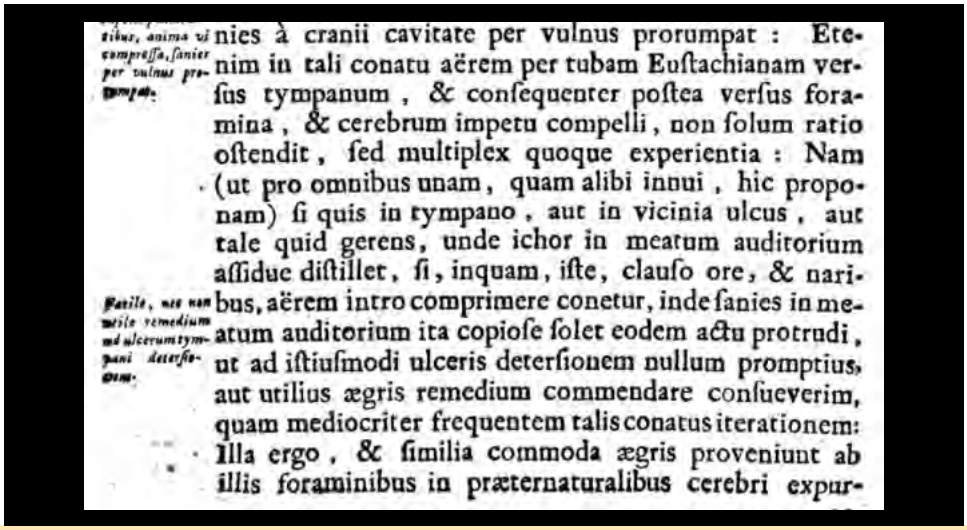
If a patient with suspected OH doesn't meet the criterion fall in systolic blood pressure by 5 minutes, then in my book the patient doesn't have OH.

Heart rate usually is measured simultaneously with blood pressure. Patients with baroreflex-cardiovagal failure have a small orthostatic increment in heart rate for a given fall in blood pressure; however, such patients still have some increase in heart rate. The occurrence of an increase in heart rate during standing should not be taken as evidence against neurogenic OH.

The Valsalva maneuver

Despite its apparent simplicity, the Valsalva maneuver test is one of the most important clinical physiological tests for autonomic failure. The test is done using a method to measure blood pressure continuously (beat-to-beat).

In the Valsalva maneuver, the patient blows against a resistance for several seconds and then relaxes.



nies à cranii cavitate per vulnus prorumpat : Etenim in tali conatu aërem per tubam Euſtachianam verſus tympanum , & conſequenter poſtea verſus foramina , & cerebrum impetu compelli , non ſolum ratio oſtendit , ſed multiplex quoque experientia : Nam (ut pro omnibus unam , quam alibi innui , hic proponam) ſi quis in tympano , aut in vicinia ulcus , aut tale quid gerens, unde ichor in meatum auditorium aſſidue diſtillet , ſi , inquam , iſte , clauſo ore , & naribus, aërem intro comprimere conetur, inde ſanies in meatum auditorium ita copioſe ſolet eodem actu protrudi , ut ad iſtiuſmodi ulceris deterſionem nullum promptius, aut utilius ægris remedium commendare conſueverim, quam mediocriter frequentem talis conatus iterationem: Illa ergo , & ſimilia commoda ægris proveniunt ab illis foraminibus in præternaturalibus cerebri expur-

Fig. 229: Antonio Valsalva's 1704 description of the maneuver that bears his name. *Valsalva devised the maneuver not as a means to track reflexive blood pressure responses to decreased cardiac filling but as a means to clear material from the middle ear.*

The maneuver consists of blowing against a resistance for several seconds and then relaxing. Often the patient is asked to blow into a tube connected to a blood pressure gauge, moving the gauge's needle to a particular pressure (30-40 mmHg) and keeping the needle there for 10-15 seconds.

In Phase I, just after starting to squeeze, the blood is forced out of the chest, and the blood pressure increases briefly. This is mechanical and has nothing to do with reflexes.

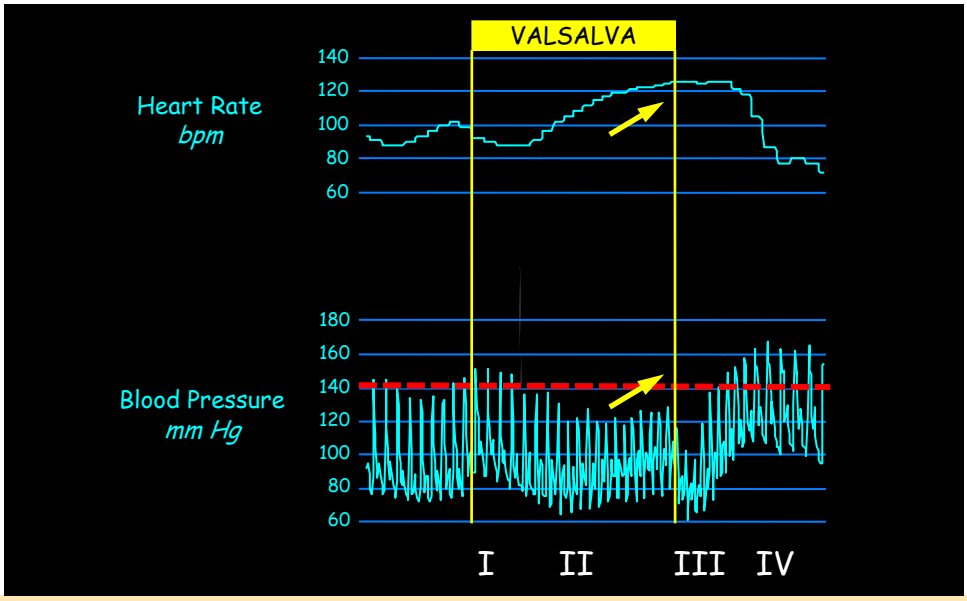


Fig. 230: Normal responses to the Valsalva maneuver: *This continuous recording of blood pressure and heart rate shows normal responses during the 4 phases of the Valsalva maneuver.*

As you continue to strain, the high pressure in the chest and abdomen results in less blood reaching the heart, and the heart pumps less blood, so normally in Phase II the blood pressure falls.

The brain picks up on this immediately and directs a reflex to occur in which outflows in the sympathetic noradrenergic system (SNS) increase, norepinephrine, the chemical messenger of the SNS, is released, the norepinephrine binds to its receptors in the heart and blood vessel walls, and the blood vessels constrict. As a result, at the end of Phase II blood pressure increases, even though the heart is still pumping out less blood.

To understand this reflex better, think of the water pressure in a

garden hose.

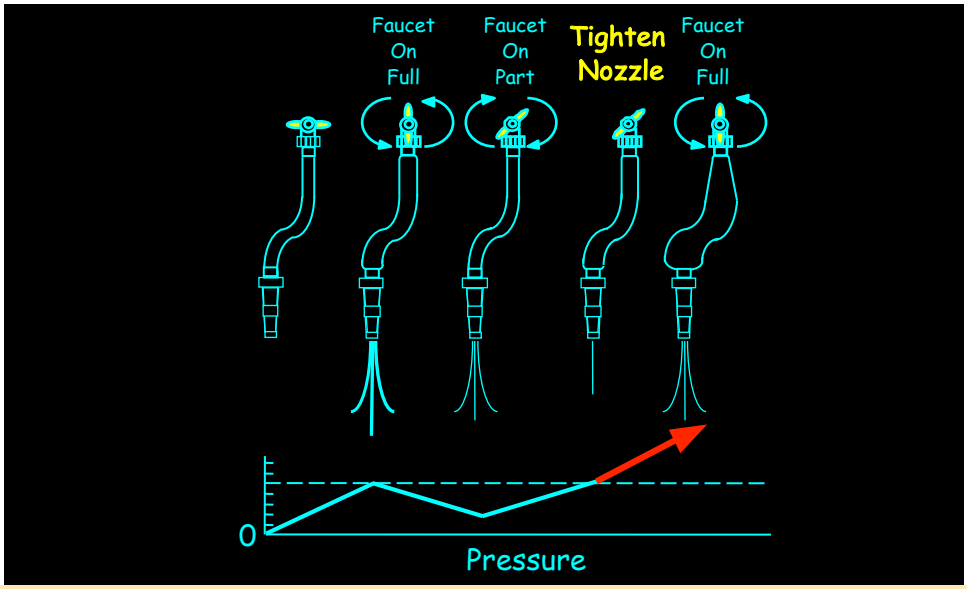


Fig. 231: The garden hose analogy. *The garden hose analogy helps understand reflexive regulation of blood pressure associated with the Valsalva maneuver—especially the pressure overshoot in Phase IV.*

Turning down the faucet decreases the pressure in the hose, but you can bring the pressure back up by tightening the nozzle. The brain uses the sympathetic noradrenergic system to tighten the vascular nozzle, and so the blood pressure increases at the end of Phase II.

Also during Phase II the heart rate normally goes up, due to withdrawal of parasympathetic nervous system outflow to the heart via the vagus nerve.

Then the patient relaxes. The blood pressure immediately falls (Phase III)—a kind of mirror image of the increase in Phase I. The decrease in pressure in Phase III has nothing to do with

reflexes.

Finally, in Phase IV the patient is relaxed, and now there is no impediment in blood returning to the heart. The heart pumps the blood, but it pumps the blood into the reflexively constricted vasculature, and so the blood pressure rapidly increases and overshoots the baseline value. It's as if you turned the faucet back to where it was originally, but you forgot to loosen the nozzle.

Because of the overshoot in pressure, in Phase IV the heart rate rapidly reflexively falls back to baseline.

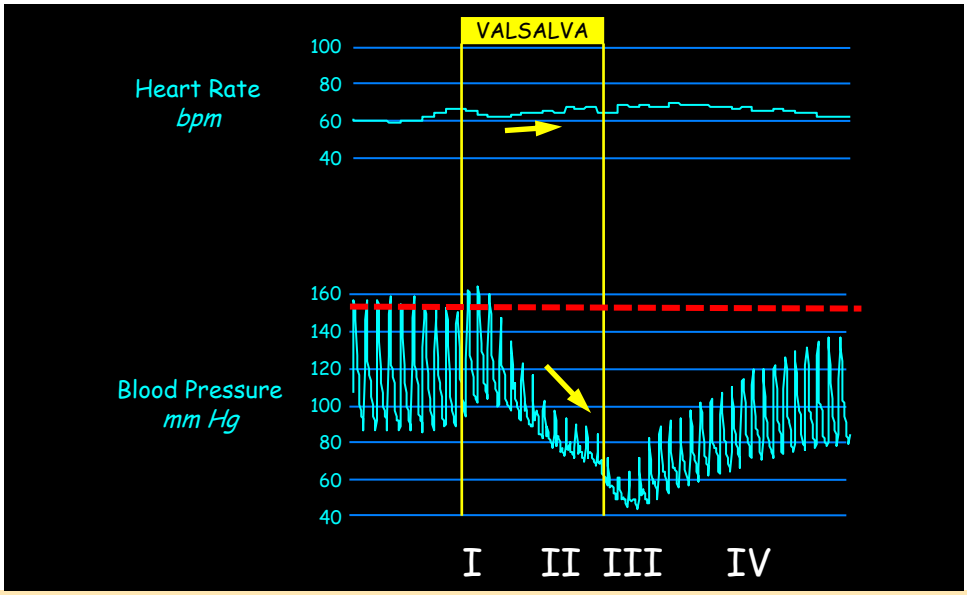


Fig. 232: Abnormal responses to the Valsalva maneuver. *The blood pressure (BP) decreases progressively in Phase II, and in Phase IV the BP slowly returns to baseline, but there is no overshoot above the baseline value. Heart rate increases by relatively little considering the large fall in BP.*

In a patient with failure of this reflex—whether because of a decrease in afferent information from the baroreceptors to the

brain, or because the brain doesn't act on the information due a brain disease, or because the sympathetic nerves are gone, or because norepinephrine isn't released, or because the adrenoceptors receptors are blocked—there is the same abnormal pattern of blood pressure (BP) during and after the Valsalva maneuver. In Phase II the BP goes down progressively, because the patient can't tighten the vascular nozzle, and in Phase IV the BP returns slowly to the baseline value but doesn't overshoot the baseline value, for the same reason. These are signs of baroreflex-sympathoneural failure.

In most (but not all) forms of chronic autonomic failure manifesting with orthostatic hypotension, the heart rate doesn't change as much as it should given the magnitude of the fall in blood pressure. The extent of increase in heart rate (or more formally the extent of decrease in the cardiac interbeat interval) per mmHg decrease in systolic blood pressure during Phase II of the Valsalva maneuver is a measure of baroreflex-cardiovagal gain.

Note that one must monitor the blood pressure (BP) changes beat-to-beat in order to identify baroreflex-sympathoneural failure based on the BP responses to the Valsalva maneuver. Until recently such continuous monitoring required insertion of a catheter into an artery. Since physicians rarely feel comfortable doing this, they usually settle for recording only the peak and trough pulse rates during and after performance of the maneuver. This cannot diagnose baroreflex-sympathoneural failure.

Nowadays there are several non-invasive devices available to track blood pressure beat-to-beat and detect baroreflex-

sympathoneural failure.

The finding of abnormal blood pressure responses to the Valsalva maneuver is valuable for diagnosing sympathetic neurocirculatory failure (orthostatic hypotension associated with baroreflex-sympathoneural failure) but is of no value in the differential diagnosis of autonomic failure syndromes.

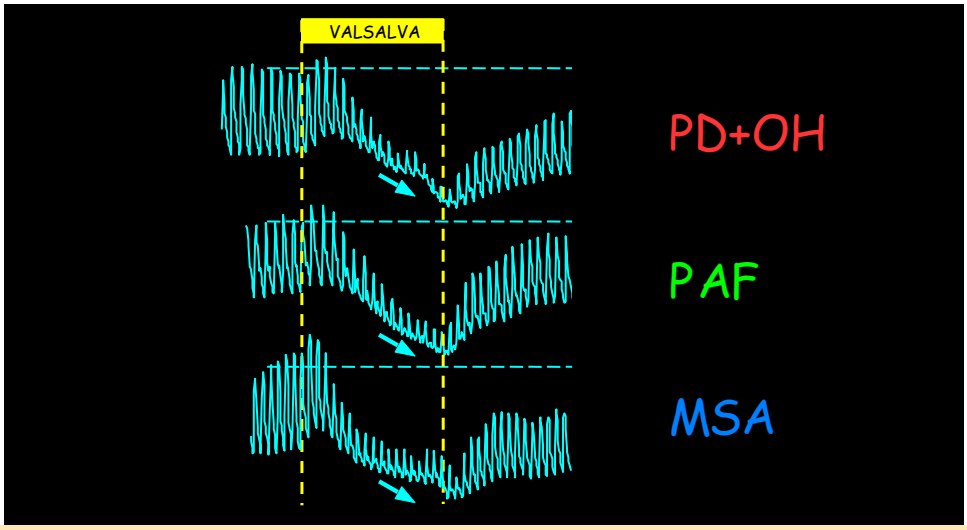


Fig. 233: Blood pressure (BP) responses to the Valsalva maneuver in different forms of neurogenic orthostatic hypotension. *The same abnormal pattern of beat-to-beat BP occurs in Parkinson's disease with orthostatic hypotension (PD+OH), pure autonomic failure (PAF), and multiple system atrophy (MSA).*

The same abnormal pattern occurs in Parkinson's disease with orthostatic hypotension (PD+OH), pure autonomic failure (PAF), and multiple system atrophy (MSA).

THE SQUARE WAVE PHENOMENON

In some people, instead of the blood pressure decreasing to below baseline during Phase II of the Valsalva maneuver, the pressure fails to decrease or even increases. The Phase III fall in pressure is still present, but because blood pressure does not fall to below baseline during Phase II—the stimulus for reflexive activation of sympathetic noradrenergic outflow—there is no Phase IV overshoot of pressure. This has been called the "square wave response" or the "flat top response," because the pattern of the pressure during and after the maneuver resembles a mathematical square wave sign.

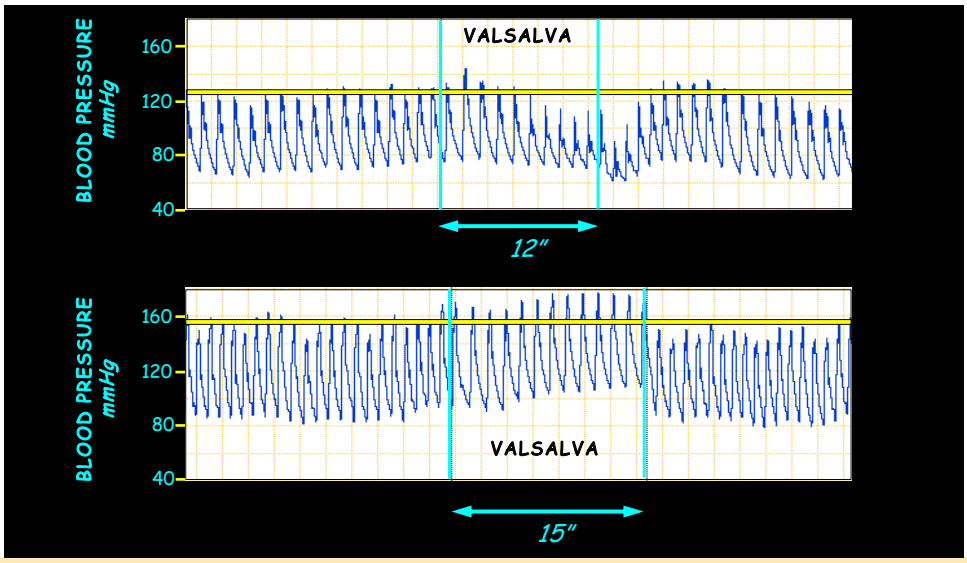


Fig. 234: The "square wave" or "flat top" phenomenon. *These blood pressure recordings were obtained in a healthy volunteer before and after central intravenous infusion of 2 liters of ice-cold saline over about 20 minutes. This increased the central venous pressure and evoked marked sympathetic noradrenergic stimulation.*

The square wave response occurs in situations where there is increased cardiac filling coupled with increased sympathetic noradrenergic outflow. This combination is well-known to occur in congestive heart failure. In healthy people, infusion of norepinephrine increases cardiac filling and changes the shape of the blood pressure pattern to the square wave phenomenon. We noted this also in a healthy volunteer who performed the Valsalva maneuver after having undergone rapid infusion of 2 liters of ice-cold saline via a centralized IV catheter. The infusion increased central venous pressure, evoked profound, generalized sympathetic noradrenergic activation, and produced the square wave phenomenon (Fig. 234). Perhaps surprisingly, the subject merely felt cool, without anxiety or shivering.

Tilt Table Testing

Tilt table testing is done to see if standing up (orthostasis) provokes a progressive fall in blood pressure (orthostatic hypotension), an excessive increase in heart rate (as in postural tachycardia syndrome (POTS)), a sudden fall in blood pressure (neurally mediated hypotension), a prolonged period with no electrocardiographic signal (asystole), or presyncope (near fainting).

The testing is quite safe when done by experienced personnel, in a setting where emergency backup is available.

Tilt table testing is used to evaluate patients with a complaint of frequent fainting or of inability to tolerate prolonged standing.

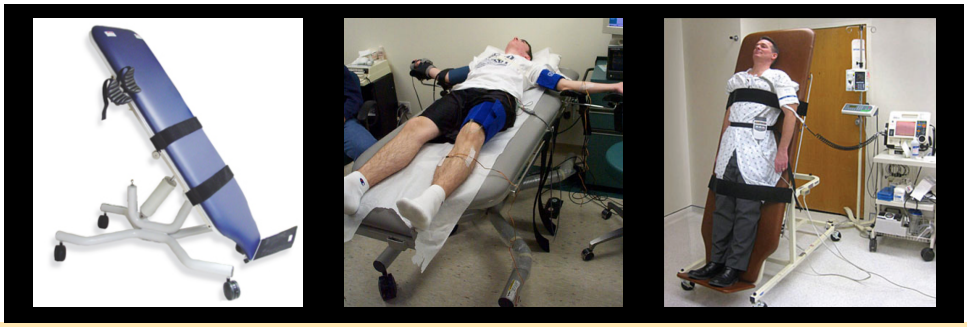


Fig. 235: Tilt table testing. Tilt table testing usually is done with a motorized tilt table.

The testing itself is relatively simple. The patient lies on a stretcher-like table, security straps are attached around the upper abdomen and legs, and the patient is tilted upright at an angle.

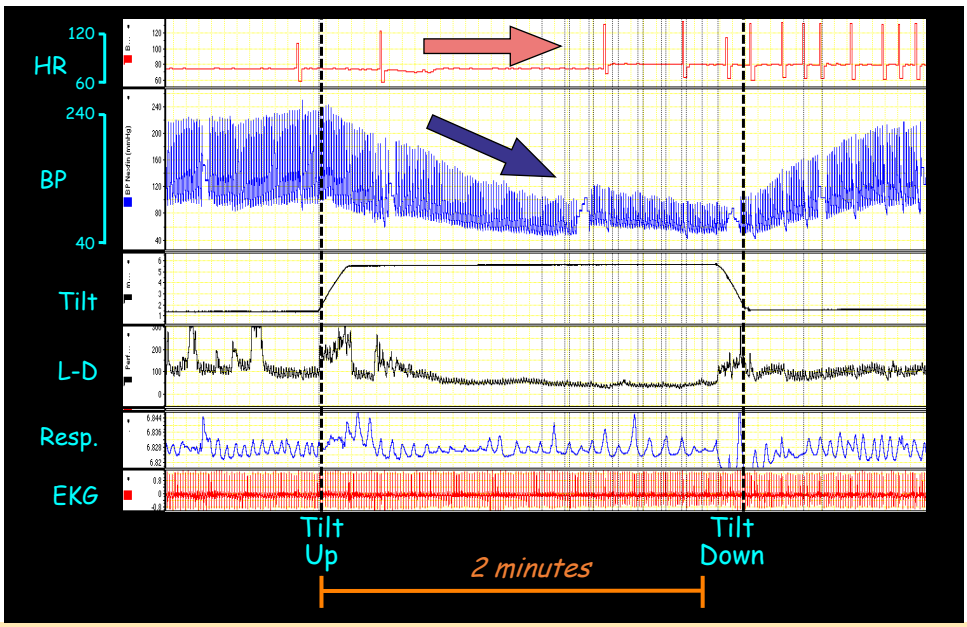


Fig. 236: Neurogenic orthostatic hypotension (nOH) identified by tilt table testing. *There is a substantial fall in blood pressure, but the heart rate increases by relatively little*

The exact angle used varies from center to center and may be from 60º to 90º. The tilting goes on for up to about 40 minutes (this again varies from center to center).

For evaluating possible neurogenic orthostatic hypotension (nOH), 5 minutes of tilting should suffice (Fig. 235). If there were a relatively small increase in heart rate while the blood pressure was falling, this would confirm nOH.

For evaluating possible POTS or autonomically mediated syncope in a patient with chronic orthostatic intolerance, a relatively long period of tilting is used. The tilting is a form of provocative test. The doctors are hoping to reproduce the patient's problem in a controlled laboratory situation.

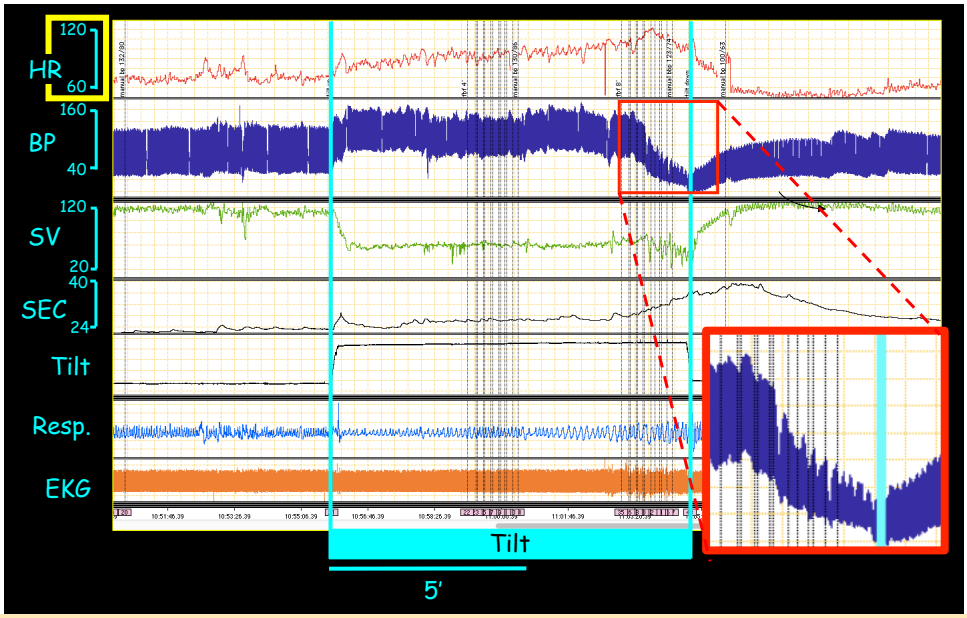


Fig. 237: POTS and NMH. *Excessive orthostatic tachycardia during head-up tilt table testing, as in postural tachycardia syndrome (POTS), can be followed by a sudden drop in blood pressure—neurally mediated hypotension (NMH).*

If the patient had an excessive increase in heart rate during the tilting, this would be consistent with the postural tachycardia syndrome (POTS). If the patient had a sudden decrease in the level of consciousness (presyncope) or actually lost consciousness (syncope), this would be consistent with neurocardiogenic syncope (also called vaso-vagal syncope, autonomically mediated syncope, or fainting). Autonomically mediated syncope is virtually always associated with a fall in blood pressure (neurally mediated hypotension, NMH).

A tilt table test can also yield results consistent with both POTS and neurocardiogenic syncope, such as when the patient has a large increase in pulse rate followed by a sudden fall in pulse rate back to normal but with NMH (Fig. 237).

As soon as the test becomes positive, such as by a sudden fall in blood pressure (this has been called tilt-evoked hypotension), the patient is put back down to the supine position. Sometimes fluid is given by vein. Consciousness, if lost, rapidly returns; however, symptoms such as clouded thinking, a vague sense of imbalance or disorientation, or headache can persist for hours or even days later.

There are some disadvantages to tilt table testing. One is false-positive test results. In a false-positive test, the results of the test are positive, but some healthy people can have a positive test result, so that a positive test result might not actually mean that anything really is “wrong.” A positive result could lead the doctor to conclude incorrectly that the condition is merely fainting, a relatively benign situation, whereas the patient may actually have a serious medical problem. This is what happened in the case of the basketball star Reggie Lewis, discussed

below. Tilt table testing might also not reproduce the patient's problem—a false-negative test result.

Another disadvantage is that most tilt table testing does not provide information about disease mechanisms. This means that, beyond verifying the patient's complaints, the testing does little to suggest pathophysiologically rational treatments that might be effective. "Augmented" tilt table testing involves measurements of physiological functions such as forearm vascular resistance and blood sampling for assays of levels of norepinephrine and adrenaline. Augmented testing can provide information about mechanisms; however, few centers offer this form of tilt table testing.

THE REGGIE LEWIS CASE

Reggie Lewis was a star basketball player for the Boston Celtics. On April 29, 1993, in game 1 of the Eastern Conference First Round of the NBA Playoffs, he collapsed on the basketball court. He came back later and finished with 17 points. Soon afterward he was evaluated by a 12-member cardiology "dream team" that included Dr. Thomas Graboys at the New England Baptist Hospital. They thought Lewis had a form of cardiomyopathy and recommended that he cease playing.

Needless to say, millions of dollars were at stake. Lewis went for a second opinion, which was provided by Dr. Gilbert Mudge of the Peter Bent Brigham Hospital. Mudge concluded that Lewis had "athlete's heart" and neurocardiogenic syncope—benign conditions—and could resume playing.

Mudge's assessment became one of the most widely publicized and second-guessed opinions in the history of sports medicine. According to a New York Times article, a key procedure that led to Mudge's opinion was a tilt table test. During head-up tilting at 60º from horizontal, Lewis reported the same lightheadedness that he had experienced before collapsing on the Celtics' NBA court. He was freed to resume playing.

Before Lewis ever appeared in another NBA game, while shooting hoops at Brandeis University on July 27, 1993 he collapsed suddenly again—and died. He was autopsied and found to have an abnormal, enlarged, extensively scarred heart, but the exact cause of death was never made public. His death was attributed variously to hypertrophic cardiomyopathy, a viral myocarditis, or even cocaine cardiotoxicity.

A lawsuit filed by the widow against Mudge resulted in a mistrial.

The take-home lesson is that Reggie Lewis had a false-positive tilt table test.

The story of the Reggie Lewis case leads ironically to the story of one of his cardiologists, Dr. Thomas Graboys. The Graboys case is discussed in the section on dementia with Lewy bodies.

Sweat Tests

Sweating plays an important role in the regulation of body temperature when a person is exposed to environmental heat.

The brain increases sweating by directing an increase in sympathetic cholinergic system (SCS) traffic to sweat glands in the skin. The chemical messenger, acetylcholine, is released, the acetylcholine occupies muscarinic receptors on the sweat glands, and the glands secrete sweat. This promotes evaporative heat loss.

One can examine SCS function from the sweating response to external heat—the thermoregulatory sweat test, or TST.

Sweat tests evaluate a particular part of the "automatic" nervous system.

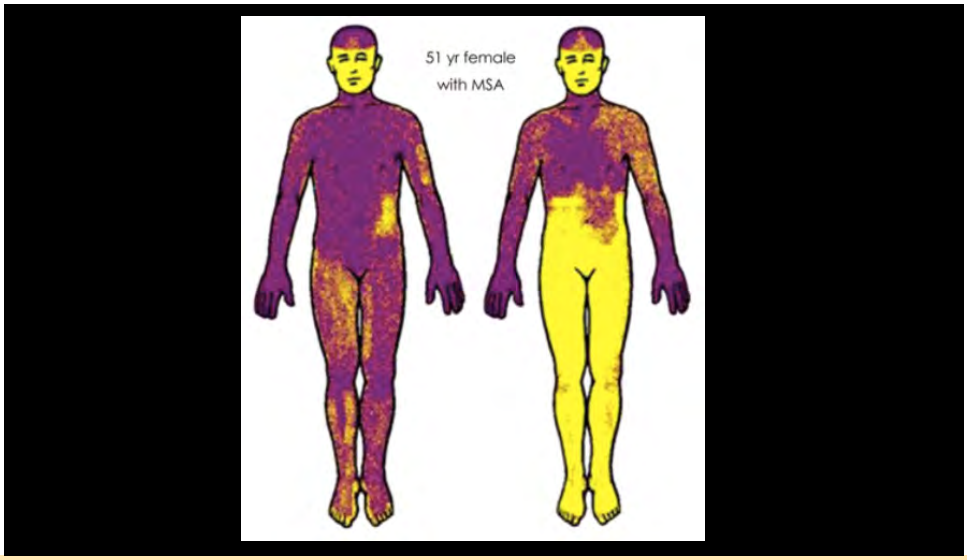


Fig. 238: The thermoregulatory sweat test. *Sweating is measured using an indicator powder and a heat chamber. The patient on the right has extensive lack of sweating (anhidrosis) in the skin of the abdomen and lower extremities. (Images courtesy of P. Low).*

Sweat production can be visualized by sprinkling starch with iodine or other indicator powder (e.g., alizarin red) all over the body and testing the patient in a heat chamber. When the powder is wetted because of perspiration the powder turns color. One can then photograph the body and see which parts sweated. This sort of sweat testing can be informative in detecting small fiber neuropathy, sympathetic cholinergic denervation in the feet or hands, or denervation in large areas of the trunk.

Sweating increases local humidity, and one can monitor the humidity in a chamber strapped to a limb and applied to the skin. One can also take pictures of sweat droplets or obtain a latex impression of the droplets to quantify the amount of sweating.

When the skin becomes sweaty, the ability to conduct electricity increases because of the salt and water in the sweat, and one can monitor the electrical conductivity. The galvanic skin response (GSR), or skin sympathetic test (SST), is part of polygraphic “lie detector” testing. When a person is startled or a small electric shock is delivered, increased sweating is detected by the increase in skin electrical conductance (SEC).

These sweat tests are generally safe, simple, and quick. A disadvantage is that they mainly or only measure physiological changes as a result of release of acetylcholine from sympathetic nerves. That is, they assess only one component of the autonomic nervous system.

The TST cannot distinguish sympathetic cholinergic denervation from a lesion in central neural pathways involved

in thermoregulation. Carrying out the TST requires a specialized heat chamber that is not available at many centers. Commonly used drugs for urinary incontinence block acetylcholine receptors and can interfere with the results of the TST.

THE QSART

"QSART" stands for "Quantitative Sudomotor Axon Reflex Test."

This test is a special form of sweat test. The QSART is a test of the ability of sympathetic nerves in the skin to release endogenous acetylcholine and increase sweat production.

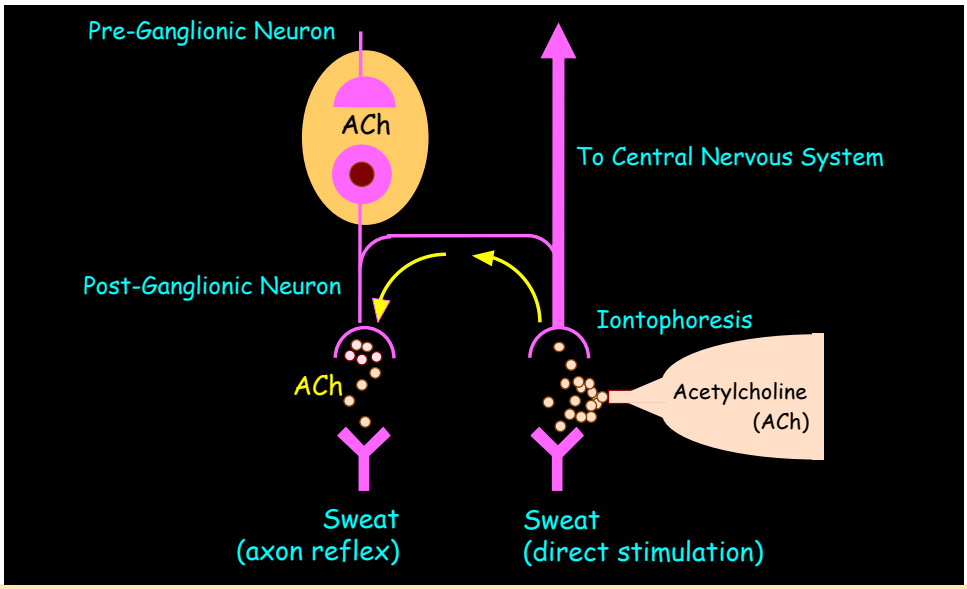


Fig. 239: The quantitative sudomotor axon reflex test (QSART). *The QSART is a special type of sweat test that assesses the sympathetic cholinergic system.*

In the QSART, dried air is pumped through a small plastic capsule placed on the skin. When the person sweats, the humidity in the chamber increases. This provides a measure of sweat production.

For QSART testing, acetylcholine is applied to the skin by a special procedure called iontophoresis, in which a small amount of electricity enables the acetylcholine to penetrate the skin. The locally applied acetylcholine evokes sweating at the site where it is given, but in addition, by way of a type of reflex called an axon reflex, sympathetic nerves under the plastic capsule release the body's own (endogenous) acetylcholine. This results in sweat production measured by increased humidity in the capsule.

If a person had a loss of sympathetic cholinergic nerves in the region being tested, then applying acetylcholine to the skin around the test capsule would not lead to increased sweating or increased humidity in the test capsule. If the person had a brain disease that prevented increases in sympathetic cholinergic nerve traffic during exposure to increased environmental temperature, then the person would not be able to increase the humidity in the capsule in response to an increase in the room temperature, yet the person would have a normal QSART response. This combination of findings occurs in some patients with multiple system atrophy.

By this sort of combined neuropharmacological/physiological test doctors can distinguish sympathetic cholinergic system failure due to loss of sympathetic cholinergic nerves from failure due to abnormal regulation of nerve traffic in intact

nerves.

Advantages of the QSART are that it is generally safe, quick, quantitative, and easy to perform; however, the equipment is expensive. As in other tests where the dependent measure is physiological (in this case, sweat production), the results are indirect. If the patient had a decreased ability to synthesize or store acetylcholine in sympathetic cholinergic nerve terminals, decreased numbers of acetylcholine receptors on the sweat-secreting cells, or decreased numbers of sweat glands, the patient would have the same abnormal QSART responses as if the sympathetic cholinergic nerves were lost. QSART results may not identify problems with other components of the autonomic nervous system. In other words, the QSART results might not be representative.

QSART testing is a useful way to detect loss of autonomic nerve fibers in the feet, as occurs in small fiber neuropathies and "neuropathic" POTS.

Forearm Blood Flow

Blood flow in the forearm can be measured non-invasively using an automated blood pressure cuff and a bracelet-like device.

Measuring forearm blood flow is useful to test whether the patient tightens blood vessels reflexively, as normally happens during assumption of upright posture.

To measure forearm blood flow one can use a technique called impedance plethysmography. A blood pressure cuff is wrapped around the upper arm, and a bracelet-like device called a strain gauge is attached around the upper forearm. The strain gauge measures stretch very sensitively. For a measurement of forearm blood flow, the blood pressure cuff is inflated rapidly using a compressor to just above the venous pressure and below the diastolic blood pressure (typically 40 mmHg). This is like tightening a tourniquet around the upper arm to obtain a blood sample. Because the cuff pressure is above the venous pressure, blood in the forearm and hand can't get past the cuff, and because the cuff pressure is below the arterial pressure, blood

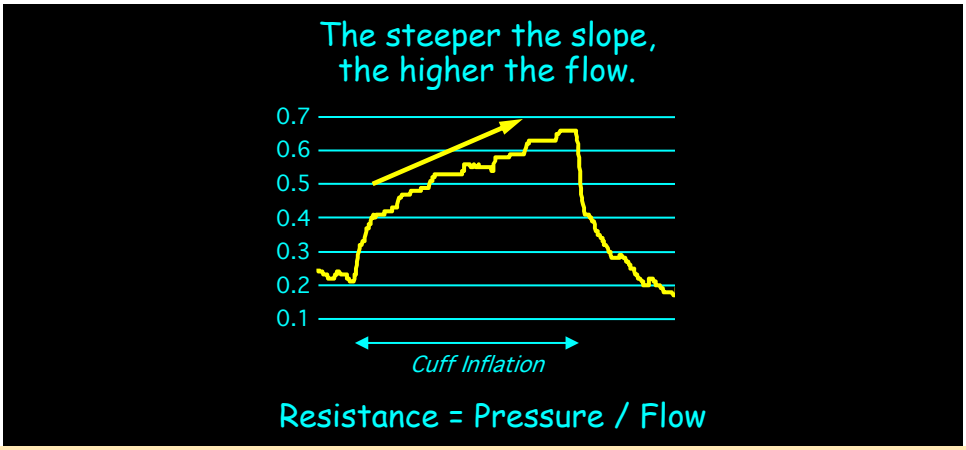


Fig. 240: Forearm blood flow. *One way to measure forearm blood flow is by a method called impedance plethysmography.*

can still enter the forearm and hand. The volume of the forearm expands slightly, and the strain gauge senses the increase in forearm circumference.

If the rate of blood flow into the forearm were high, then the volume of the forearm would increase rapidly after the cuff was

inflated; and if the rate of blood flow were low, then the volume of the forearm would increase more slowly. By a simple calculation you can estimate the blood flow into the forearm, from the rate of increase in the volume of the forearm after the cuff is inflated. Usually, measurement of forearm blood flow is done at least five times over about a minute, to obtain a reliable average value.

Once the rate of forearm blood flow (FBF) is known, the forearm vascular resistance (FVR) is calculated from the average blood pressure (mean arterial pressure, MAP) divided by the forearm blood flow. This is a similar calculation as for measuring total peripheral resistance (TPR) from the mean arterial pressure (MAP) divided by the cardiac output (CO).

When you stand up, the forearm vascular resistance normally increases. This is because of reflexive activation of the sympathetic noradrenergic system (SNS). When a person stands up or is tilted on a tilt table as part of tilt-table testing, the amount of blood ejected by the heart per minute falls, due to the force of gravity, which tends to pool blood in the legs and lower abdomen and pelvis and decreases venous return to the heart. The brain directs an increase in SNS outflows, norepinephrine is released from nerve terminals in blood vessel walls in the forearm and hand, and the forearm vascular resistance (FVR) goes up.

In sympathetic neurocirculatory failure the FVR doesn't increase like it or may not increase at all during orthostasis. In fainting, the FVR typically decreases, due to adrenaline-induced relaxation of blood vessels in skeletal muscle. In patients with low blood volume, FVR may be high even during

supine rest, as part of a compensation to maintain blood pressure.

Sympathetic Microneurography

One can monitor sympathetic noradrenergic system (SNS) outflow to skeletal muscle via a needle electrode inserted into the peroneal nerve, which is in the "funny bone" area outside and just below the knee. Sometimes the measurement is abbreviated MSNA, for muscle sympathetic nerve activity.

Bursts of MSNA are are tied to the heartbeat and are called "pulse-synchronous." When the blood pressure decreases, MSNA increases reflexively, due to activation of SNS outflow to the blood vessels in the skeletal muscles, and the frequency of pulse-synchronous bursts goes up.

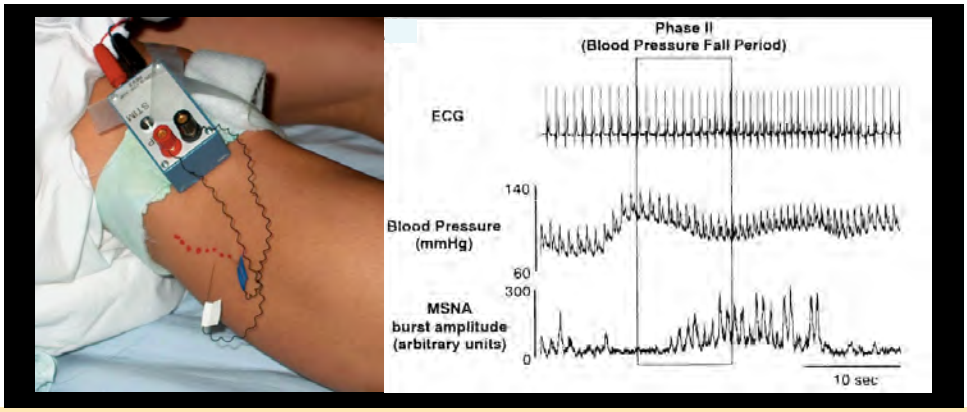


Fig. 241: Peroneal sympathetic microneurography. *During the Valsalva maneuver, the decrease in blood pressure in Phase II is associated with a reflexive increase in bursts of skeletal muscle sympathetic nerve traffic.*

An advantage of monitoring MSNA is the ability to track SNS

responses to a variety of stimuli rapidly and in real time; however, carrying out MSNA measurements requires substantial technical training and experience, and the measurements may not be covered by medical insurance. As with other physiological measures, MSNA cannot identify a problem with norepinephrine synthesis, storage, release, or recycling in sympathetic nerves.

Identifying nerve traffic as MSNA often requires assessing effects of baroreflex activation or inhibition on the signal, such as by breath holding or performing a Valsalva maneuver. In patients with chronic autonomic failure, MSNA can be difficult to measure because of the lack of baroreflex-mediated, pulse-synchronous bursts of nerve traffic.

Sympathetic noradrenergic outflow to the skin is not particularly sensitive to baroreflexes and is more responsive to psychological phenomenon such as startle.

Pupillometry

The pupils of the eyes receive both parasympathetic nervous system (PNS) and sympathetic noradrenergic system (SNS) innervation.

Pupil constriction evoked by PNS stimulation is mediated by acetylcholine acting at muscarinic receptors on iris sphincter muscle cells. The nerve fibers travel in the oculomotor nerve, which is the third cranial nerve, via the ciliary ganglion. The sphincter muscle cells are arranged circularly in the iris, and so when they contract the pupils get smaller.

The SNS innervation of the pupils is derived from pre-ganglionic neurons in the thoracic spinal cord. The nerve fibers synapse in the superior cervical ganglion in the neck and travel with the ophthalmic nerve, which is part of the fifth cranial nerve (the trigeminal nerve).

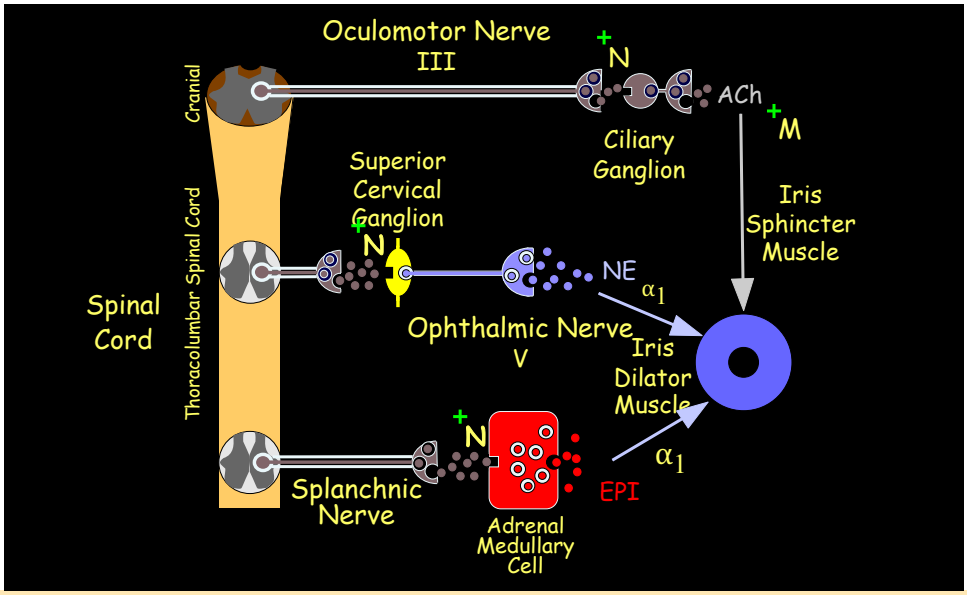


Fig. 242: Autonomic pupillomotor regulation. *Parasympathetic innervation of the pupils is derived from the Edinger-Westphal nucleus in the midbrain of the brainstem. The nerve fibers synapse in the ciliary ganglion and travel with the oculomotor nerve (the third cranial nerve) to the iris sphincter muscle. The SNS innervation of the pupils is derived from the superior cervical ganglion. The nerve fibers travel in the ophthalmic nerve (part of the trigeminal nerve, the fifth cranial nerve) to the iris dilator muscle. Circulating adrenaline also reaches adrenoceptors in the iris dilator muscle.*

The pupillary dilation evoked by SNS stimulation is mediated by norepinephrine acting at alpha-1 adrenoceptors on iris dilator muscle cells. The iris dilator cells are arranged radially (like

spokes on a bicycle wheel) in the iris, and so when they contract the pupils get larger.

Activation of the sympathetic adrenergic system (SAS), such as during distress, causes release of adrenaline into the bloodstream. Adrenaline also acts at the alpha-1 adrenoceptors on iris dilator muscle cells and dilates the pupils. SAS activation probably explains the pupillary dilation that occurs when people faint.

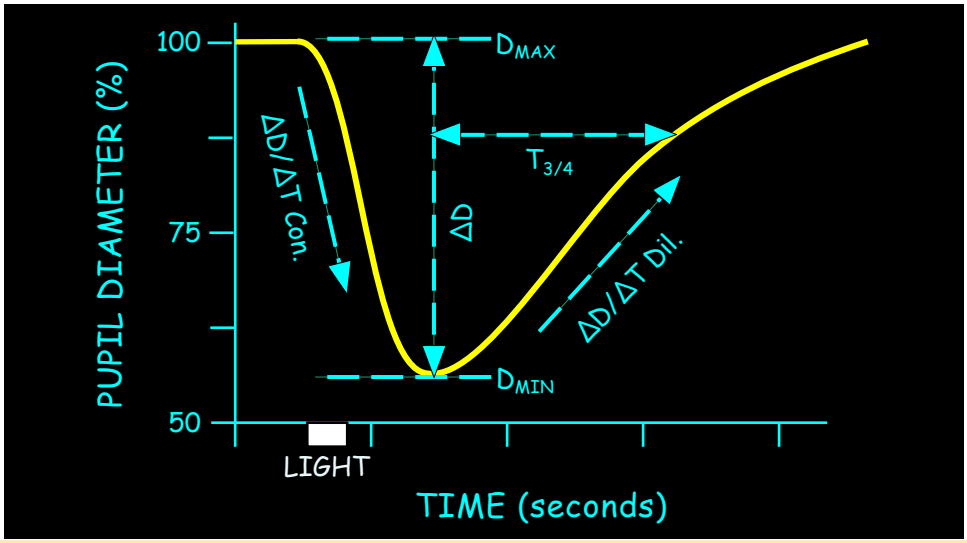


Fig. 243: Pupillometry parameters. *The rapid pupillary constriction after a brief light stimulus is directly related to parasympathetic cholinergic stimulation. The subsequent slow recovery of pupillary diameter is determined complexly and includes a contribution of the sympathetic noradrenergic system.*

Pupillometry involves tracking the dynamics of pupil size in response to a brief light stimulus. This is a simple, non-invasive autonomic function test.

In response to a brief light stimulus, the pupils constrict due to a rapid increase in parasympathetic nervous system (PNS) activity. After the light stimulus, the pupils slowly re-dilate. The re-dilation involves a contribution of the sympathetic noradrenergic system (SNS), since patients with Horner's syndrome (discussed below) not only have a small pupil but also have a delay in the return of pupil diameter toward baseline (prolonged $T_{3/4}$ in Fig. 243). The pupillary light reflex is too rapid to involve adrenaline.

How pupillometry results relate to abnormalities of particular components of the autonomic nervous system is a matter of current research.

HORNER'S SYNDROME

Horner's syndrome (also called Horner-Bernard and Bernard-Horner syndrome depending on your loyalty to Claude Bernard) involves the triad of ptosis (lid lag), miosis (constricted pupils), and anhidrosis (lack of sweating) on the affected side of the face.

Horner's syndrome usually reflects loss of input from the sympathetic noradrenergic system (SNS) and sympathetic cholinergic system (SCS), so that parasympathetic nervous system (PNS) effects on the pupils are unopposed.

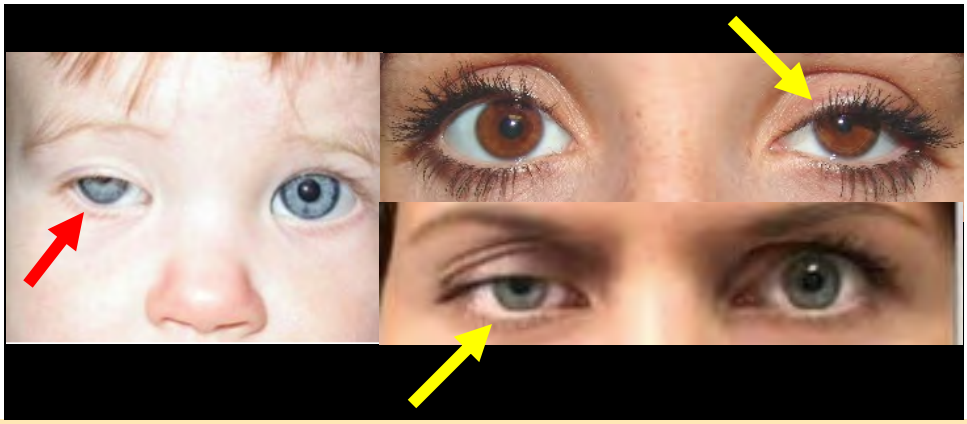


Fig. 244: Horner's syndrome (also called Horner-Bernard syndrome). *The syndrome consists of a droopy eyelid (ptosis), a smaller pupil (miosis), and decreased sweating on the side of the lesion (anhidrosis). The eye on the affected side also seems sunken in (enophthalmos).*

Sympathetic nerves to the face travel from the thoracic spinal cord through ganglia before ascending in the chest and neck to the head. A tumor in the chest or neck that impinges on the sympathetic chain can manifest clinically as Horner's syndrome.

ADIE'S PUPIL

In people with Adie's "tonic" pupil, the affected pupil is relatively large and constricts slowly in bright light. The condition begins gradually in one eye and often progresses to involve the other eye.

When Adie's pupil is associated with a loss of deep tendon reflexes, this is called Holmes-Adie syndrome. When in addition there is altered sweating, this is called Ross's syndrome.

As for the tonic pupil, in Holmes-Adie syndrome the loss of deep tendon reflexes (especially of the Achilles tendon) may occur first on one side of the body and then go on to involve the other side too. The eye and reflex symptoms may not appear at the same time. In Ross's syndrome, the loss of sweating can be associated with increased sweating and flushing on the other side of the face, in which case Ross's syndrome can overlap with the "harlequin syndrome," which is discussed elsewhere.

Ross's syndrome is thought to result from a viral infection that damages sensory neurons in the dorsal root ganglia and autonomic neurons in the ciliary ganglia. The complex involvement of skin sensory and autonomic innervation results in abnormal thermoregulatory changes in sweating and skin blood flow. The syndrome can be an isolated finding or occur with other conditions such as Sjogren's syndrome, migraine, or baroreflex failure. Once it develops, the syndrome is long-lasting or permanent.

Heart Rate Variability

THE SIGN OF A HEALTHY HEART

When you take in a slow, deep breath, your pulse rate increases, and when you then breathe out, your pulse rate falls. The wave-like rhythmic change in the heart rate due to breathing is called respiratory sinus arrhythmia.

Despite the word, arrhythmia, meaning "lacking rhythm,"

respiratory sinus arrhythmia is quite rhythmic and quite normal. The Dutch cardiologist Karel Frederik Wenckebach wrote in the early 1900s that a variable pulse rate is the sign of a healthy heart.

These changes result mainly from modulation of parasympathetic nervous system (PNS) outflow to the heart via the vagus nerve.

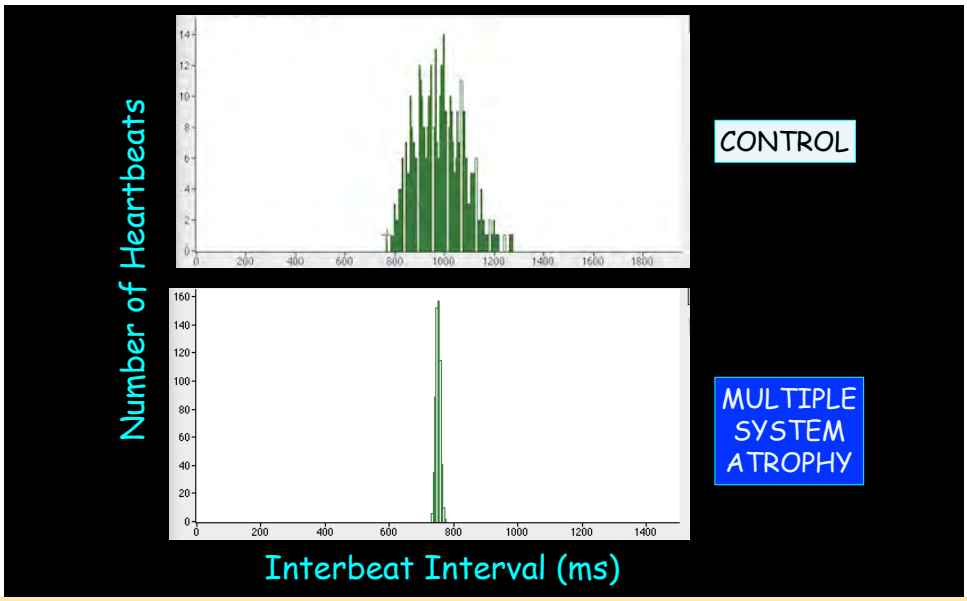


Fig. 245: Heart rate variability in the time domain. *Chronic autonomic failure syndromes such as multiple system atrophy involve low heart rate variability.*

If you recorded the cardiac interbeat interval across many heartbeats and graphed the number of beats in bins of interbeat intervals, you would see a bell-shaped curve, as in Fig. 245. The more variable the heart rate, the wider the bell-shaped curve. This is called analysis of heart rate variability in the time domain.

With aging, heart failure, and most forms of chronic autonomic failure, the heart rate becomes more stable. The bell-shaped curve becomes narrower. This is probably not from altered autonomic innervation of the heart but from decreased reflexive modulation of traffic in nerves supplying the heart.

POWER SPECTRAL ANALYSIS

Another form of analysis of heart rate variability is in the frequency domain. Power spectral analysis is simpler than the imposing name suggests.

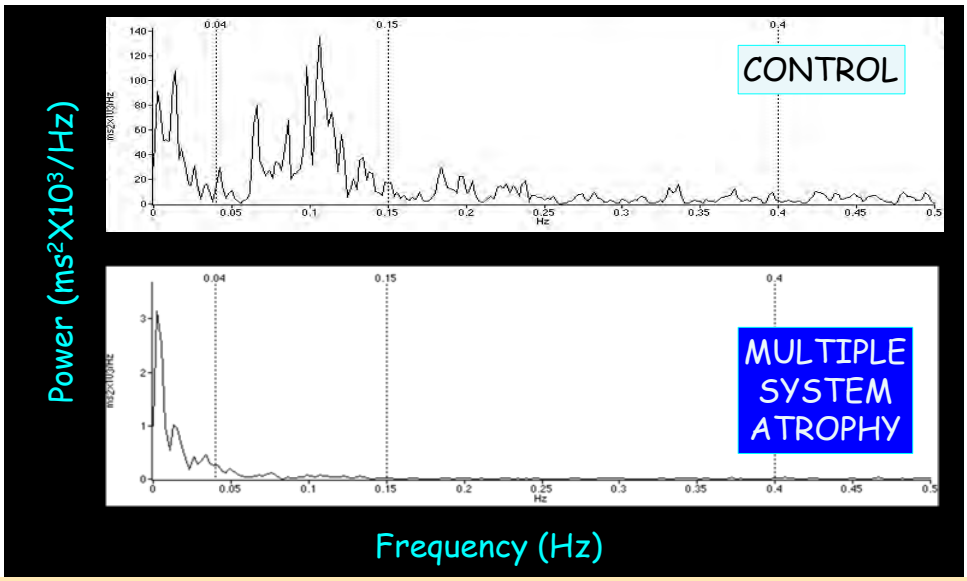


Fig. 246: Power spectral analysis of heart rate variability. *Here heart rate variability is being analyzed here in the frequency domain. At all frequencies there is low power in multiple system atrophy.*

Normally your heart rate increases when you breathe in and then decreases when you breathe out. This means that the beat-to-beat heart rate oscillates in a wave-like pattern.

If one graphed the size of the oscillation as a function of the frequency of the heartbeats, then at the frequency of breathing there would be a peak of "power." In people who have failure of the parasympathetic nervous system (PNS), there is little or no respiratory sinus arrhythmia, and so there is little or no peak of power at the frequency of breathing.

This sort of analysis typically reveals a second peak of power, at a lower frequency than the frequency of breathing. Some researchers have thought that low frequency (LF) power of heart rate variability is related to sympathetic nervous system influences on the heart.

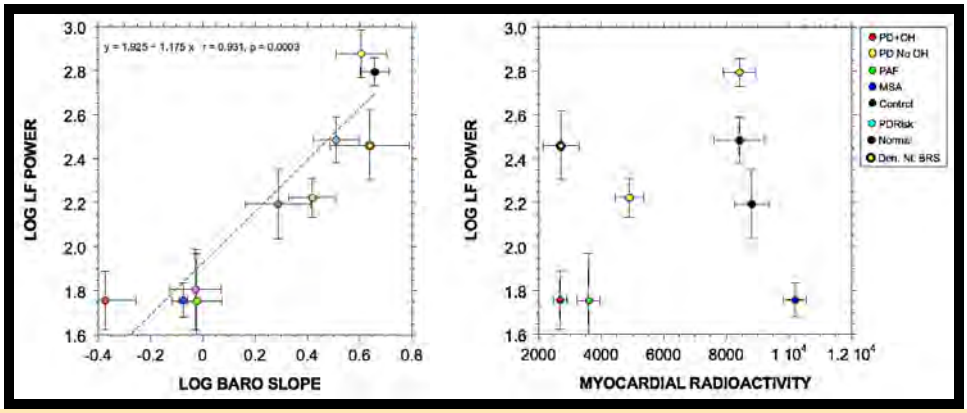


Fig. 247: Meaning of low frequency (LF) power of heart rate variability. *Across a variety of dysautonomias the log of LF power is related to the log of he baroreflex-cardiovagal gain but not to sympathetic innervation of the heart as indicated by myocardial ^{18}F-dopamine-derived radioactivity. LF power seems not to indicate cardiac autonomic "tone" so much as the ability to modulate that tone via baroreflexes.*

Others (myself included) have disagreed with the notion that

power spectral analysis of heart rate variability can assess sympathetic "tone" in the heart. Instead, LF power may be more of a measure of the ability to modulate autonomic outflows to the heart via baroreflexes.

Power spectral analysis of heart rate variability offers the advantages of being safe, technically easy, and fast. The main disadvantage is that the meanings of LF power (and of the low/high frequency ratio, proposed to reflect "sympathovagal balance") remain unsettled.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring, or ABPM, refers to automatic recording of blood pressure at pre-set time intervals during activities of daily life.

ABPM done over 24 hours can be valuable to assess whether the patient has the normal "dipping" of blood pressure that occurs during the night. Non-dipping often occurs in patients with neurogenic orthostatic hypotension, because during the day the patients have relatively low blood pressure when they are upright, and at night they have relatively high blood pressure when they are lying down (supine hypertension).

Ambulatory blood pressure monitoring can be useful to detect high blood pressure when the patient is lying down at night (nocturnal supine hypertension).

ABPM is quite useful to assess variability of blood pressure

over hours of observation. Patients with arterial baroreflex failure typically have large swings of blood pressure during the day and night.

Some patients have "white coat hypertension," meaning their blood pressures are high in the doctor's office but are normal at home. ABPM can also help diagnose white coat hypertension.

Gastric Emptying

Many autonomic, endocrine, and local factors regulate stomach emptying after ingestion of a meal. Some of these are diagrammed in Fig. 48.

The term, "gastroparesis," refers to delayed gastric emptying due to poor stomach motility.

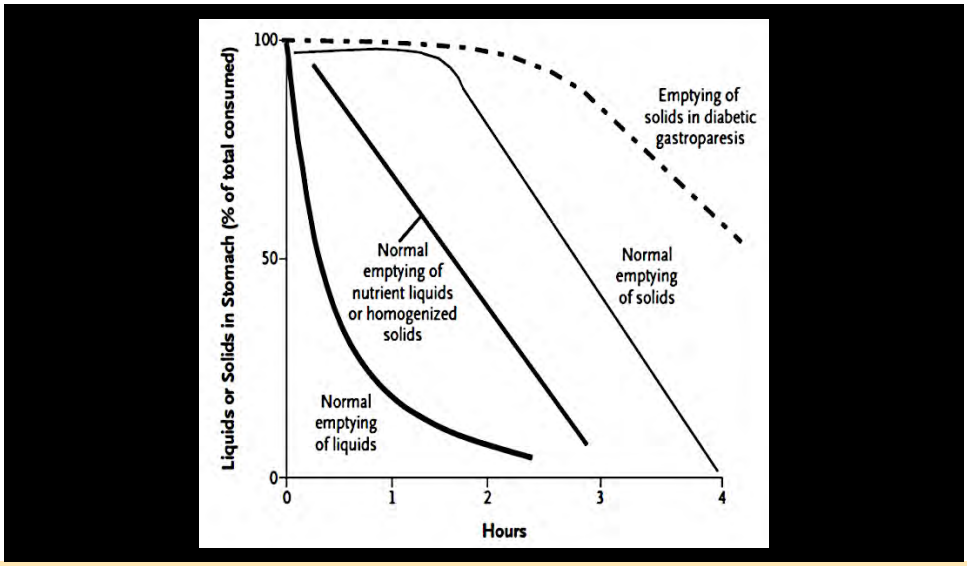


Fig. 248: Gastric emptying times. *Normally about ½ of ingested solid food passes through the stomach by 2-3 hours. Liquids pass through quicker.*

A decreased rate of gastric emptying can be a sign of parasympathetic nervous system (PNS) failure, sympathetic noradrenergic system (SNS) hyperactivity, increased circulating adrenaline levels, or any of a variety of endocrine or local enteric neuronal abnormalities.

One clinical test of gastric emptying is based on nuclear medical scanning after swallowing a substance tagged with radioactivity.

Probably the most common disorders involving gastroparesis are diabetes mellitus, Parkinson's disease, and multiple sclerosis. Gastroparesis can also result from damage during gastric surgery to branches of the vagus nerve that supply the stomach.

The Cold Pressor Test

In the cold pressor test, blood pressure is monitored when the patient dunks a hand into a bucket of ice-cold water and keeps the hand immersed. This rapidly increases the blood pressure by increasing activity of the sympathetic noradrenergic system (SNS). In a patient with baroreflex failure and an intact SNS, the cold pressor test would be expected to evoke an exaggerated increase in blood pressure, while in a patient with baroreflex failure and loss of sympathetic noradrenergic nerves the pressor response would be blunted.

The cold pressor test can only be done for a minute or two. The stimulus is complex and dynamic because of the rapid

development of pain, numbness, and distress. Patients with dysautonomia associated with chronic burning pain in the skin (erythromelalgia) can have a remarkable ability to tolerate prolonged cold pressor testing.

Composite Autonomic Severity Scale

A 10-point composite autonomic severity scale (CASS) allots 4 points for “adrenergic failure” and 3 points each for “sudomotor failure” and “cardiovagal” failure. Patients with a CASS score of 3 or less are thought to have no or mild autonomic failure, 4-6 moderate autonomic failure, and 7-10 severe autonomic failure.

This kind of lumped approach to autonomic failure may be more worthwhile for research purposes than for individual diagnosis. The CASS is insensitive to failure of single components of the autonomic nervous system, such as in dopamine-beta-hydroxylase (DBH) deficiency. The prevalence in the relevant population is not taken into account—constipation in the elderly is common, while pupillomotor dysfunction is uncommon. Within a particular domain, subtle differences can be crucial for differential diagnosis—urinary bladder dysfunction is found in both Parkinson’s disease with orthostatic hypotension (PD+OH) and in the parkinsonian form of multiple system atrophy (MSA-P), but urinary retention requiring self-catheterization is common in MSA-P and rare in PD+OH. The term, “adrenergic failure,” is misleading, since no measure of sympathetic adrenergic (as opposed to sympathetic noradrenergic) failure is included. The composite scale also depends importantly on the particular center. Neurochemical

and neuroimaging tests that can be more sensitive and informative than physiological tests are not included.

NEUROPHARMACOLOGIC (DRUG) TESTS

Tyramine

In the tyramine (TYR) infusion test, the drug tyramine is infused intravenously (IV). TYR that is taken up into the sympathetic nerves displaces norepinephrine (NE) from the

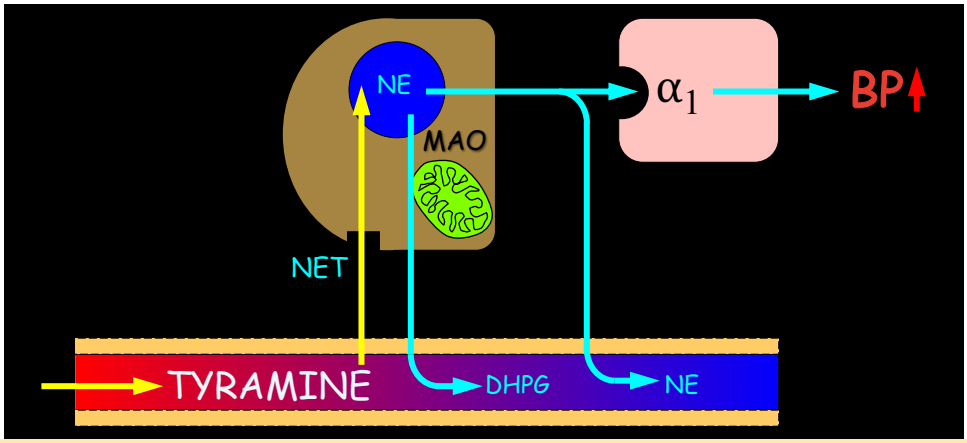


Fig. 249: Tyramine infusion test. *In the tyramine infusion test the drug is given IV for several minutes. Tyramine that is taken up into sympathetic nerves displaces norepinephrine (NE). One can measure both the physiological response (the increase in blood pressure) and the neurochemical responses (the increases in plasma levels of NE and its neuronal metabolite 3,4-dihydroxyphenylglycol (DHPG)).*

vesicles. Some of the NE reaches its receptors on vascular smooth muscle cells, and the blood pressure goes up. Plasma NE and its breakdown product 3,4-dihydroxyphenylglycol (DHPG) may also be measured.

If a patient had autonomic failure due to a loss of sympathetic

nerves, tyramine would not release norepinephrine from the nerves, because there would be no norepinephrine to displace. In such a patient tyramine would not increase the blood pressure by as much as if the patient had an intact sympathetic noradrenergic system. In addition, such a patient would have relatively small increases in levels of norepinephrine and related compounds, such as DHPG, in the plasma.

Ganglion Blockade

Trimethaphan, pentolinium, and hexamethonium are ganglion blockers—that is, they block transmission of nerve signals in the ganglia. The control signals are relayed in the ganglia by release of the chemical messenger, acetylcholine, which binds to nicotinic receptors on the post-ganglionic neurons. These drugs inhibit ganglionic transmission by blocking the neuronal nicotinic receptors.

Blockade of transmission of nerve impulses in ganglia produces effects on a variety of body functions. When a person stands up, the ability to maintain blood pressure depends importantly on reflexes that tighten blood vessels by way of increased sympathetic noradrenergic nerve traffic. Ganglion blockers always produce a fall in blood pressure when the person is upright—orthostatic hypotension—and blunt or eliminate reflexive increases in heart rate.

Probably the most noticeable effect of ganglion blockade in someone who is lying down is a dry mouth. This is because of blockade of the parasympathetic nervous system (PNS), which is responsible for production of watery saliva.

In the ganglion blockade test, a ganglion blocker drug is given by vein at a dose calculated so as not to decrease the blood pressure excessively. The blood pressure and pulse rate are monitored frequently or continuously, and blood may be sampled from an indwelling catheter in an arm vein, for measurements of plasma levels of norepinephrine or other neurochemicals.

If a patient had autonomic failure due to a loss of sympathetic post-ganglionic nerves, ganglion blockade would not decrease the blood pressure. But if a patient had baroreflex failure due to a brain disease in which there was an inability to regulate sympathetic nerve traffic to intact terminals, there might be ongoing, unregulated release of norepinephrine from the nerve terminals. In such a patient ganglion blockade would decrease the blood pressure substantially. The ganglion blockade test therefore can provide information about whether autonomic failure is associated with a loss of sympathetic nerve terminals or from failure of the brain to regulate sympathetic nerve traffic appropriately.

In some patients with long-term high blood pressure, the hypertension reflects an overall increase in the rate of nerve traffic in the sympathetic noradrenergic system (SNS). This increases delivery of norepinephrine to its receptors in the heart and blood vessels, causing an increase in the output of blood by the heart (cardiac output) and tightening of blood vessels (vasoconstriction). By either or both mechanisms, the blood pressure is high because of the high rate of delivery of norepinephrine to its receptors. Some investigators have called this hypernoradrenergic hypertension. In a patient with hypernoradrenergic hypertension, administration of a ganglion

blocker would be expected to decrease the rate of norepinephrine release from the sympathetic nerves, and the extent of the fall in the plasma norepinephrine level would be related to the extent of the fall in blood pressure. In a patient with an equal amount of hypertension but with a normal rate of nerve traffic in the SNS, ganglion blockade would not be expected to decrease the blood pressure so much.

Unfortunately, ganglion blockers are not available commercially any more.

Clonidine

Clonidine (brand name Catapres™) is an imidazoline that stimulates alpha-2 adrenoceptors in the brain, in blood vessel walls, and on sympathetic nerves. Clonidine decreases blood pressure by two mechanisms—inhibiting sympathetic noradrenergic system (SNS) outflows and inhibiting norepinephrine release for a given amount of SNS traffic. Although stimulation of alpha-2 adrenoceptors on vascular smooth muscle cells would be expected to increase blood pressure, but this effect usually is overwhelmed by the other effects, and except in rare situations clonidine drops the blood pressure.

The clonidine suppression test is based on effects of the drug on blood pressure and on plasma levels of norepinephrine. If a patient had excessive activity of the sympathetic noradrenergic system, then clonidine would produce large decreases in blood pressure and plasma norepinephrine levels. Clonidine suppression testing therefore can identify long-term high blood

pressure associated with increased release of norepinephrine from sympathetic nerve terminals—hypernoradrenergic hypertension.

Clonidine suppression testing is used mainly to evaluate possible pheochromocytoma, a tumor that produces catecholamines. In pheochromocytoma the plasma norepinephrine levels fails to decrease after clonidine administration, due to continuous, unregulated norepinephrine secretion by the tumor.

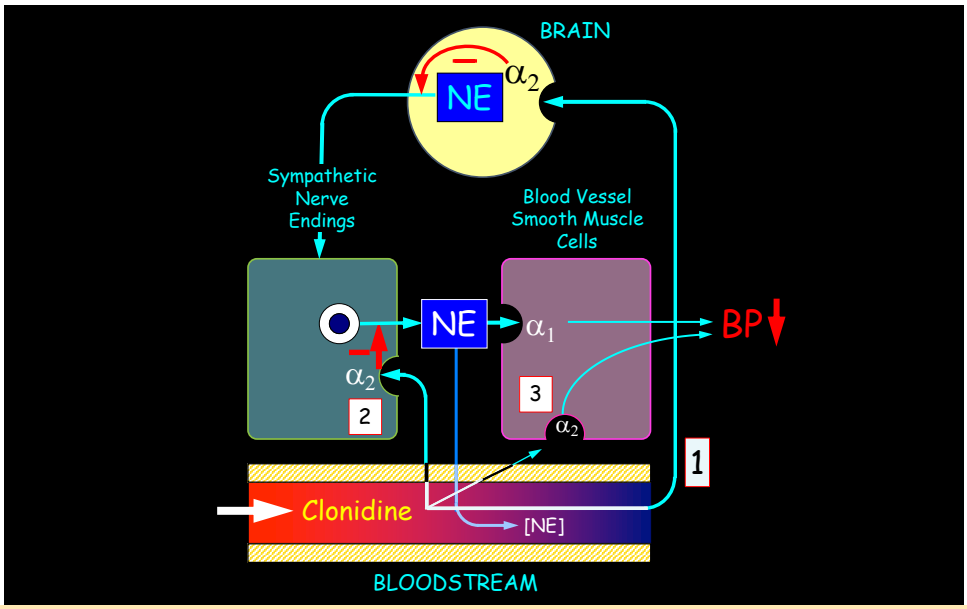


***Fig. 250:* Clonidine effects.** *Clonidine decreases blood pressure by inhibiting sympathetic noradrenergic system (SNS) outflows (1) and inhibiting norepinephrine release for a given amount of SNS traffic (2). The drug also stimulates alpha-2 adrenoceptors on vascular smooth muscle cells (3), but this effect usually is overwhelmed by the other effects.*

Isoproterenol

The isoproterenol infusion test can help identify causes of abnormal heart rate or inability to tolerate prolonged standing.

Isoproterenol (brand name Isuprel™) is a catecholamine that stimulates all types of beta-adrenoceptors. Because of this action, isoproterenol has several effects in the body. Stimulation of beta-adrenoceptors in the heart increases the rate and force of the heartbeat and increases the output of blood by the heart per minute (cardiac output).

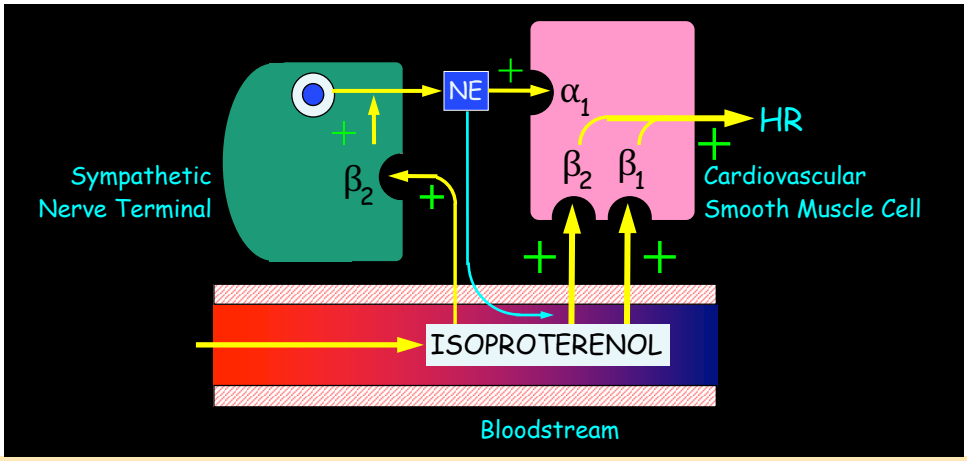


Fig. 251: Isoproterenol infusion test. *Isoproterenol stimulates beta-adrenoceptors. This increases the rate and force of heart contraction. By way of norepinephrine release, isoproterenol also indirectly stimulates alpha-adrenoceptors.*

Stimulation of beta-adrenoceptors relaxes smooth muscle cells that line bronchioles, the small airway tubes in the lungs. Isoproterenol and related drugs therefore can reverse bronchoconstriction in acute asthma attacks. Stimulation of beta-adrenoceptors in the liver converts stored energy in the

form of glycogen to immediately available energy in the form of glucose. Stimulation of beta-adrenoceptors on vascular smooth muscle cells in skeletal muscle relaxes the blood vessels, and this decreases the resistance to blood flow in the body as a whole (total peripheral resistance). Stimulation of beta-adrenoceptors on sympathetic nerves increases the release of norepinephrine.

The isoproterenol infusion test can help identify causes of abnormal heart rate or inability to tolerate prolonged standing.

In the hyperdynamic circulation syndrome the patient has a relatively fast pulse rate, high cardiac output, variable blood pressure that tends to be increased, susceptibility to panic or anxiety attacks, and improvement by treatment with the beta-adrenoceptor blocker, propranolol. The same phenomena occur in a proportion of young adults with early, borderline hypertension. Patients with the hyperdynamic circulation syndrome or borderline hypertension can have excessive increases in heart rate during isoproterenol infusion. Patients with the postural tachycardia syndrome (POTS) can have a fast pulse rate even when they are lying down. In POTS, isoproterenol administration can also produce excessive increases in heart rate or evoke panic.

Isoproterenol given by vein is also sometimes used as part of tilt table testing in patients with orthostatic intolerance or chronic fatigue. During upright tilting, infusion of isoproterenol can bring on a rapid fall in blood pressure or loss of consciousness, converting a negative to a positive tilt table test.

Isoproterenol infusion as part of provocative tilt table testing is now rarely done because of the high likelihood of false-positive test results.

Isoproterenol releases norepinephrine from sympathetic nerves. Patients with a form of dysautonomia associated with a loss of sympathetic nerves would be expected to have a blunted increase in the plasma norepinephrine level in response to isoproterenol. This is what happens, for instance, in Parkinson's disease with orthostatic hypotension.

The effects of isoproterenol wear off rapidly within minutes of stopping the infusion. Since it is a catecholamine, the drug does not cross the blood-brain barrier, and so usually there are little if any behavioral or emotional effects. Isoproterenol can increase the rate or depth of respiration, produce trembling, or bring on abnormal heart rhythms or abnormal heartbeats. These side effects disappear rapidly after the drug is stopped.

Glucagon

Glucagon is one of the body's three main hormones regulating glucose levels.

When given intravenously (IV) as a bolus, glucagon stimulates release of adrenaline from the adrenal medulla. In patients with an adrenal gland tumor that produces catecholamines (pheochromocytoma, or "pheo"), glucagon challenge testing can evoke a large increase in blood pressure.

Glucagon challenge testing is also used in the evaluation of

patients who seem to have a pheo clinically but who don't actually harbor the tumor. These patients are thought to have "pseudopheochromocytoma," or "pseudopheo." The condition can resemble postural tachycardia syndrome, arterial baroreflex failure, or hyperdynamic circulation syndrome. Glucagon administration in pseudopheo patients can evoke a large increase in plasma adrenaline levels. This constitutes a positive glucagon challenge test.

^{131}I-Albumin to Measure Blood Volume

Blood volume is the total volume of blood in the body. Most of the blood volume is in the veins. If the blood volume were low, then during standing, because of gravitational blood pooling in veins of the abdomen, pelvis, or legs there could be enough of a decrease in venous return to the heart and cardiac output that the person could feel lightheaded or faint. Therefore, hypovolemia can be a cause of orthostatic intolerance.

There are different ways to measure blood volume. A commercially available test is based on intravenous (IV) injection of albumin that is tagged with a trace amount of radioactive iodine (^{131}I-albumin). Albumin is the main protein in the blood. In the ^{131}I-albumin blood volume test, an exact, known amount of ^{131}I-albumin is injected. Blood is then drawn through the IV at various time points over about a half hour, and the concentration of ^{131}I in the plasma is measured.

By definition, the concentration of a substance is the amount of that substance per unit of volume. Since the amount of ^{131}I injected is known, and the plasma concentration of ^{131}I is

measured in the laboratory, by algebra the plasma volume is the ^{131}I concentration divided by the amount of injected ^{131}I. From the plasma volume divided by the hematocrit (the percent of the blood that is red blood cells), the blood volume is then calculated.

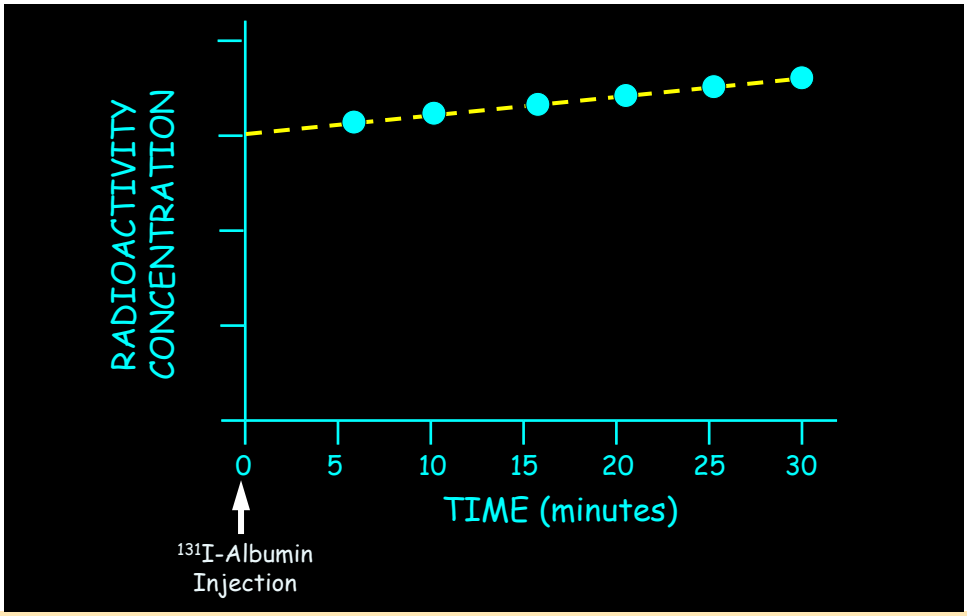


Fig. 252: ^{131}I-Albumin to measure blood volume. *In the ^{131}I-albumin blood volume test, blood volume is calculated from the amount of injected ^{131}I, the concentration of ^{131}I in the plasma, and the hematocrit.*

Most of the injected ^{131}I-albumin stays in the bloodstream. Because the concentration of ^{131}I-albumin in the blood may change slightly over time (such as by leakage of fluid out of the blood vessels), blood is sampled at several time points, and by extrapolation to the y-axis the estimated concentration at time=0 is used for the calculation of blood volume.

In selected patients with chronic orthostatic intolerance (COI),

measurement of blood volume may be indicated. If the blood volume were low, this could be a starting point for further testing that could pinpoint a treatable cause of the COI. Moreover, in this setting a drug such as fludrocortisone and a high salt diet could be beneficial by increasing the blood volume.

BIOCHEMICAL TESTS

Neurochemical tests of autonomic nervous system functions are mainly done to examine activities of the sympathetic noradrenergic system (SNS) and the sympathetic adrenergic system (SAS). This is because the main chemical messengers of these systems, norepinephrine and adrenaline (epinephrine), can be measured in the plasma. The main chemical messenger of the parasympathetic nervous system (PNS), acetylcholine, undergoes rapid enzymatic breakdown after it is released and cannot be measured in the plasma.

The Cat Comes Back

In the diagnostic evaluation of patients with known or suspected dysautonomias, measurement of plasma catechols is rarely diagnostic but often is informative.

Human plasma normally contains at least 7 catechols. Three are the catecholamines norepinephrine, adrenaline, and dopamine. Another is 3,4-dihydroxyphenylalanine (DOPA), which is the precursor of the catecholamines and the immediate product of the rate-limiting enzyme in catecholamine biosynthesis, tyrosine hydroxylase (TH). DOPA is converted to dopamine by the enzymatic action of L-aromatic-amino-acid decarboxylase (LAAAD).

3,4-Dihydroxyphenylglycol (DHPG, DOPEG) is the main intra-neuronal metabolite of norepinephrine, and 3,4-dihydroxyphenylacetic acid (DOPAC) is the main intra-neuronal metabolite of DA. Both are formed from the

enzymatic action of monoamine oxidase (MAO) on cytoplasmic catecholamines.

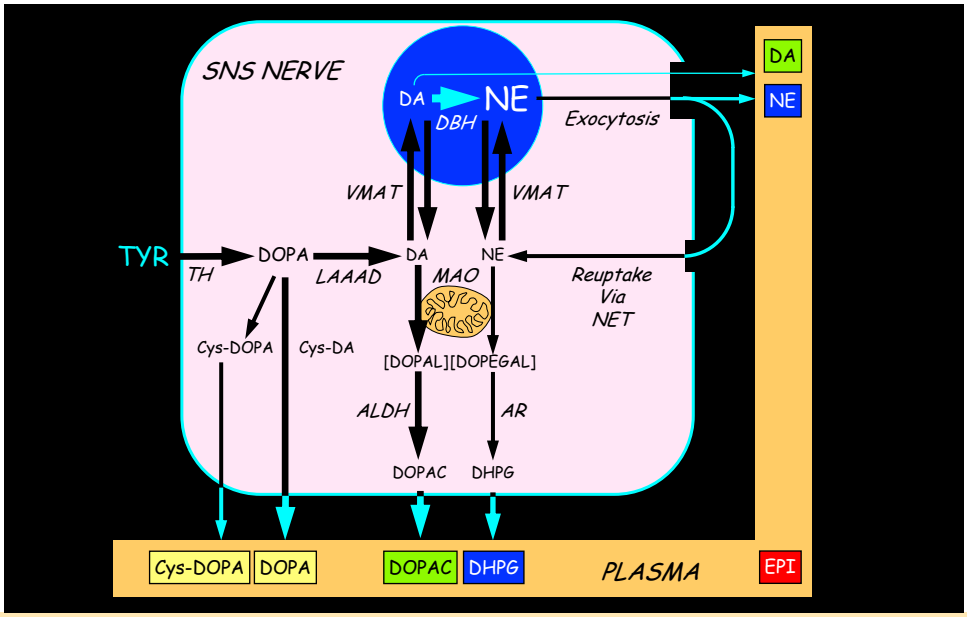


Fig. 253: Plasma catechols. *Several catechols can be measured in the plasma. This diagram shows how they are related to processes in nerves of the sympathetic noradrenergic system (SNS). Epinephrine (EPI) is the hormone secreted by the adrenal medulla.*

Plasma epinephrine (EPI, adrenaline) is derived from the adrenal medulla.

Another endogenous catechol typically found in human plasma is 5-S-cysteinylDOPA (Cys-DOPA). Cys-DOPA is formed from covalent bonding of DOPA with cysteine (or with glutathione, followed by enzymatic conversion of glutathione to cysteine).

Measurements of plasma catechols are rarely diagnostic but

often are informative. Measurements of the intra-neuronal metabolites with the parent compounds can greatly enhance the information compared to measuring the catecholamines alone.

Condition	Catechol Pattern
DBH deficiency	Low NE, DHPG
	High DA, DOPAC
Menkes disease	High DOPA/DHPG
	High DA/NE
LAAAD deficiency	High DOPA/DOPAC
	High DOPA/DA
HSAN III (FD)	High DOPA/DHPG

Fig. 254: Diagnostic patterns of plasma catechols. *Plasma catechol patterns are diagnostic in some rare diseases.*

Condition	Catechol Pattern
Diabetic autonomic neuropathy	Low DHPG/NE
POTS	High upright NE
Neurally mediated hypotension	High EPI/NE during tilt
PD+OH	Blunted orthostatic %ΔNE
Diabetic autonomic neuropathy	Low DHPG/NE
DLB	Blunted orthostatic %ΔNE
Takotsubo cardiopathy	High EPI
PAF	Low NE, DHPG, blunted ortho. %ΔNE
Pseudopheo	High EPI after glucagon
Famil. amyloid. polyneuropathy	Low NE, blunted ortho. %ΔNE
HSAN IV	Low NE
Pheo	High NE, blunted clonidine suppression

Fig. 255: Supportive plasma catechol patterns. *Measuring plasma catechol patterns can be informative in many dysautonomias. (ortho.=orthostatic; %Δ=percent change)*

Plasma Norepinephrine (NE)

Since norepinephrine (NE) is the main chemical messenger of the sympathetic noradrenergic system (SNS), the plasma NE level has often been used as an index of SNS "activity" in the body as a whole. In people who are resting lying down, plasma NE levels normally range from about 100 to about 500 pg/mL.

Plasma norepinephrine is used to test the part of the sympathetic nervous system that regulates the heart and blood vessels—the sympathetic noradrenergic system (SNS).

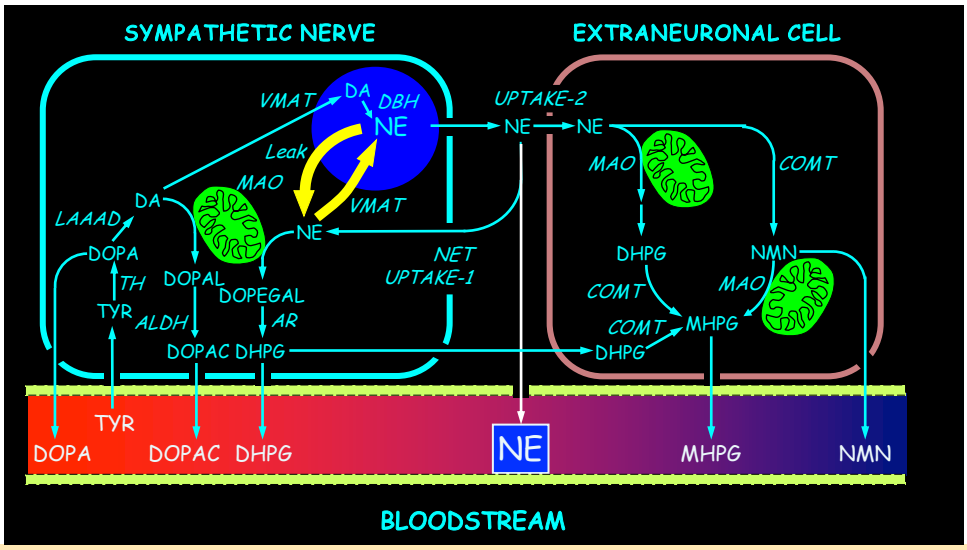


Fig. 256: Plasma NE determinants. *Many processes affect plasma NE levels.*

The relationship between the rate of sympathetic nerve traffic and the concentration of norepinephrine in the plasma is complex and indirect and is influenced by many factors. The

blood sample should be obtained under carefully controlled or monitored conditions, and the plasma NE level should be interpreted by an expert.

In using plasma norepinephrine levels to indicate activity of the sympathetic noradrenergic system, several complicating factors should be taken into account.

Here is a brief description of some of the complexities involved:

First, only a small percent of the NE released from sympathetic nerves actually makes its way into the bloodstream. Most is recycled back into the nerve terminals, by the Uptake-1 process mediated by the cell membrane NE transporter, or NET. This means that a person might have a high plasma NE level, despite a normal rate of sympathetic nerve traffic, if the NET were dysfunctional due to a disease or were blocked by a drug.

Second, the plasma NE level is determined not only by the rate of entry of norepinephrine into the plasma but also by the rate of removal of norepinephrine from the plasma. Norepinephrine is cleared from the plasma extremely rapidly (half-time about 1.5 minutes). This means that a person might have a high plasma NE level because of a problem with the ability to remove NE from the plasma, such as in kidney failure.

One way to estimate the rate of NE entry into the bloodstream ("spillover"), after taking plasma clearance into account, is based on intravenous (IV) infusion of a tracer-labeled form of

norepinephrine.

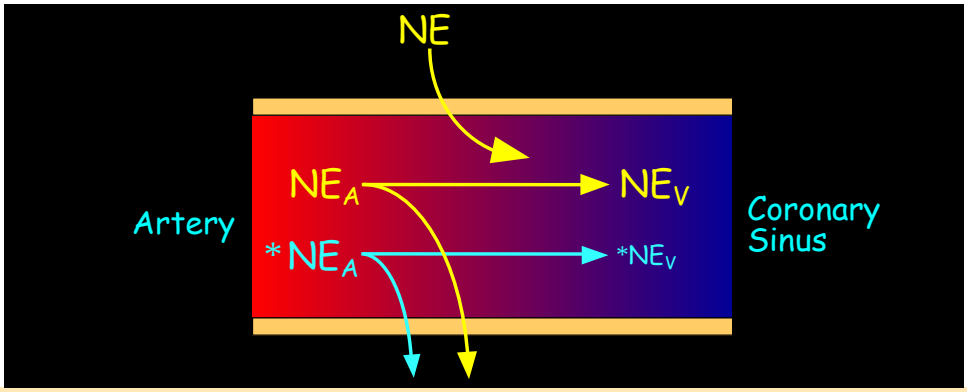


Fig. 257: Norepinephrine (NE) spillover. *One can estimate the rate of entry of NE into the bloodstream by infusing tracer-labeled NE and sampling arterial and venous (in this case coronary sinus) blood.*

The person's own NE, which is not labeled, dilutes the tracer-labeled NE. The more dilution of the tracer, the greater the NE spillover.

The tracer dilution technique cannot distinguish release from reuptake as determinants of NE spillover. Simultaneous measurement of levels of tracer-labeled NE and DHPG can do this. To the extent neuronal uptake of the tracer-labeled NE were decreased, formation of tracer-labeled DHPG would be decreased. If there were an increase in NE release without a change in reuptake, then the rate of NE spillover would be increased without a change in formation of tracer-labeled DHPG.

Third, NE is produced in sympathetic nerve terminals by the action of three enzymes, in concert with other required chemicals such as vitamin C, vitamin B6, and oxygen. In

addition, NE is produced in, stored in, and released from tiny bubble-like vesicles in sympathetic nerves; and for norepinephrine to be produced in the vesicles requires another transporter, the vesicular monoamine transporter (VMAT). If there were a problem with any of these enzymes, co-factors, or the VMAT, decreased NE production could result, and there would be a low plasma NE level regardless of the rate of sympathetic nerve traffic.

Fourth, the plasma NE level usually is measured in a blood sample drawn from a vein in the arm. Because the skin and skeletal muscle in the forearm and hand contain sympathetic nerves, the plasma NE level in blood from an arm vein is determined not only by the amount of NE release from sympathetic nerves in the body as a whole but also by release locally in the forearm and hand.

Fifth, the plasma NE level depends importantly on the posture of the person at the time of blood sampling (the level normally approximately doubles within 5 minutes of standing up from lying down), the time of day (highest in the morning), whether the person has eaten recently (higher plasma NE after meal ingestion), the temperature of the room (higher plasma NE in a cold room), dietary factors such as salt intake, and any of a large number of commonly used over-the-counter and prescription drugs or herbal remedies. These factors often are not controlled or recorded.

Plasma Adrenaline (Epinephrine, EPI)

Compared to the plasma NE level, which is complexly and indirectly related to overall sympathetic noradrenergic system

(SNS) activity in the body as a whole, the plasma EPI (adrenaline) level is a fairly direct indicator of activity of the sympathetic adrenergic system (SAS).

Plasma adrenaline (epinephrine, EPI) is used to test the sympathetic adrenergic system (SAS).

Nevertheless, some factors can complicate interpreting plasma EPI levels. When the blood flow in the arm or hand is slow, there is greater extraction of the arterial EPI during its passage through the tissues. In the setting of high forearm vascular resistance, the EPI level in the antecubital venous plasma underestimates the level in the arterial plasma.

A large number of common and difficult to control life experiences influence activity of the sympathetic adrenergic system. These include drugs, alterations in blood glucose levels (such as after a meal), body temperature, posture, and especially emotional distress.

Plasma EPI is probably the most sensitive biochemical indicator of distress.

An additional problem is technical. Because adrenaline is a very powerful hormone, the plasma level normally is very low–so low that it is often below the limit of detection of commercially available laboratory assays. In a healthy person lying down, plasma EPI levels can be as low as a few picograms (a millionth of a millionth of a gram) per milliliter.

Finally, other chemicals besides adrenaline can interfere with the measurement. This can especially be a problem in people who drink a lot of coffee, even if it is decaffeinated, because of chemicals in the plasma that can mimic adrenaline in the assay procedure.

Plasma DHPG

3,4-Dihydroxyphenylglycol (DHPG, DOPEG) is the main intra-neuronal metabolite of norepinephrine (NE). In people who are at rest lying down, plasma DHPG averages about 500-1,200 pg/mL.

Plasma DHPG levels can provide important supplementary information in assessing the sympathetic noradrenergic system.

Plasma DHPG levels have different determinants from plasma NE levels. Plasma NE levels are determined importantly by exocytotic release of NE in response to sympathetic nerve traffic and by neuronal reuptake via the cell membrane norepinephrine transporter (NET) via the Uptake-1 process. Under resting conditions, plasma DHPG levels are determined mainly by the net leakage into the cytoplasm of NE stored in vesicles and by monoamine oxidase (MAO) activity in sympathetic noradrenergic nerves. Plasma DHPG is better than plasma NE as a measure of the stores of NE in the sympathetic noradrenergic system (SNS). In the setting of loss of SNS terminals there is a loss of NE stores, and plasma DHPG levels are decreased.

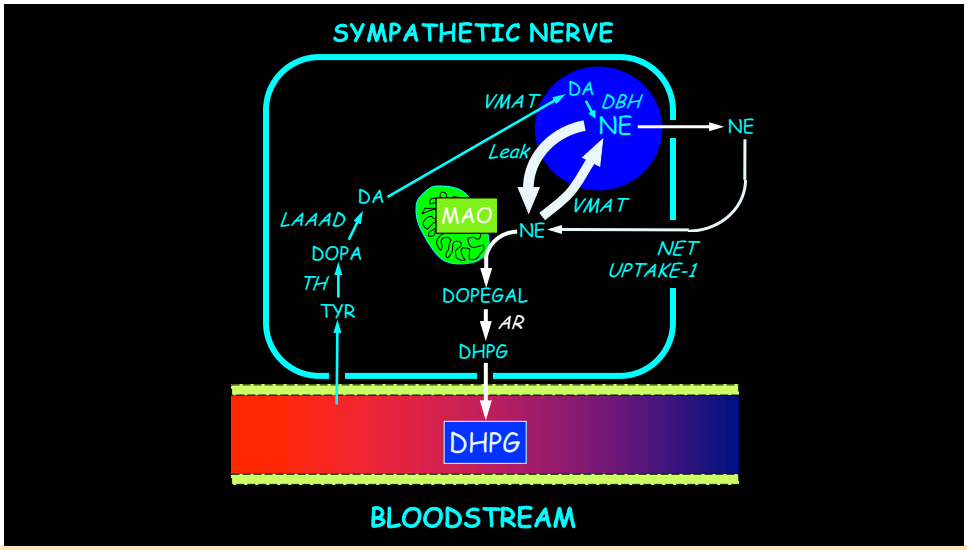


Fig. 258: Determinants of plasma dihydroxyphenylglycol (DHPG) levels. *Plasma DHPG is indirectly related to the turnover of stores of norepinephrine in sympathetic nerves.*

In the setting of increased sympathetic noradrenergic system (SNS) activity, the increase in NE release results in an increase in plasma NE levels. This is what happens, for instance, during standing up (orthostasis). Plasma NE levels normally double within 5 minutes of standing up from lying down (normal increase at least 60%). Plasma DHPG levels also increase, due to reuptake of some of the released NE, but the percent increases is smaller than the percent increase in plasma NE.

Inhibition of neuronal reuptake of NE, such as by tricyclic anti-depressants, some amphetamines, cocaine, and inhibitors of the cell membrane NE transporter (NET), decreases plasma DHPG levels more than plasma NE levels. When there is decreased NET activity, then during orthostasis the increase in plasma NE is larger than the increase in plasma DHPG, and the plasma DHPG/NE ratio is increased.

Since DHPG is a product of the enzymatic oxidation of NE catalyzed by monoamine oxidase (MAO), MAO inhibition decreases plasma DHPG levels without affecting plasma NE levels. Although MAO-A is the type of MAO in sympathetic noradrenergic nerves, treatment with an MAO-B inhibitor can decrease plasma DHPG levels.

Plasma DOPA

DOPA (3,4-dihydroxyphenylalanine, levodopa) is the immediate product of the rate-limiting enzymatic step in the synthesis of the catecholamines—hydroxylation of tyrosine catalyzed by tyrosine hydroxylase (TH).

Plasma levels of DOPA average about 1,000-2,000 pg/mL, which is higher than levels of any of the catecholamines. This probably reflects the lower rate of clearance of DOPA from the plasma rather than a higher rate of production. Patients treated with levodopa/carbidopa, such as for Parkinson's disease, can have plasma DOPA levels a thousand times higher than found endogenously.

One determinant of plasma DOPA is TH activity in sympathetic noradrenergic nerves. Patients with generalized sympathetic noradrenergic denervation therefore have decreased plasma DOPA levels.

DOPA is converted to dopamine by the enzyme L-aromatic-amino-acid decarboxylase (LAAAD). In conditions involving low LAAAD activity, plasma DOPA levels are increased with

respect to those of dopamine, norepinephrine, and their metabolites.

Plasma DOPAC

DOPAC (3,4-dihydroxyphenylacetic acid) is the main neuronal metabolite of dopamine. Plasma DOPAC levels are much higher than plasma dopamine levels, averaging about 1,000-2,000 pg/mL, probably because of slower clearance of DOPAC than of dopamine from the plasma.

Since DOPAC is a deaminated metabolite of dopamine, patients on monoamine oxidase inhibitors have low plasma DOPAC levels. The sources and meanings of plasma DOPAC levels have not been systematically studied. It is likely that there are important dietary influences on plasma DOPAC levels.

Plasma Metanephrines

In a patient with symptoms or signs suggestive of a pheochromocytoma, such as episodic hypertension, sweating, pallor, and headache, the most efficient screening test is measurement of plasma levels of free (unconjugated) metanephrines.

The term, “metanephrines,” refers to the O-methylated metabolite of norepinephrine (normetanephrine, NMN)) and the O-methylated metabolite of epinephrine (metanephrine, MN).

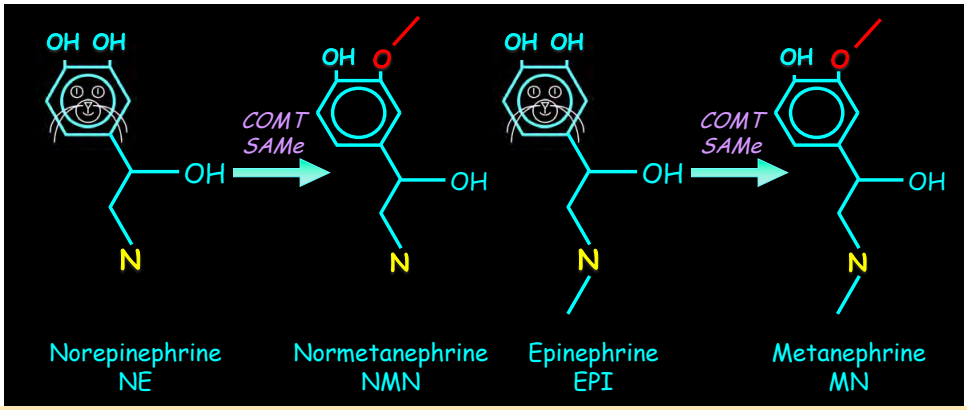


Fig. 259: Catecholamines and metanephrines. *Catechol-O-methyltransferase (COMT) catalyzes the conversion of norepinephrine to normetanephrine and of epinephrine to metanephrine.*

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. The H of one of the hydroxyl groups is replaced by a CH_3 group.

Unlike sympathetic noradrenergic nerves, the catecholamine-producing cells of 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 form normetanephrine (NMN). Plasma NMN therefore provides a more sensitive, specific test for pheo than does plasma NE.

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.

3-Methoxytyramine is the O-methylated metabolite of dopamine. 3-Methoxytyramine isn't considered to be a metanephrine, for reasons that escape me. A high plasma 3-methoxytyramine level is a sensitive biomarker of metastatic pheochromocytoma or of paraganglioma.

Antibody Tests

One mechanism by which autonomic nerves can be damaged or destroyed is autoimmunity. In autonomic autoimmunity proteins expressed in the autonomic nervous system are targeted by antibodies or immune cells.

Probably the most well characterized form of autoimmune attack is autoimmune autonomic neuropathy from a circulating antibody to the neuronal nicotinic receptor. Since ganglionic neurotransmission depends on this receptor, autoimmune autonomic neuropathy manifests with decreased functions of post-ganglionic nerves. In autoimmune autonomic ganglionopathy (AAG), the attack is sufficiently severe and generalized to cause all components of the autonomic nervous system to fail clinically—a "pandysautonomia." In AAG, the titer of the antibody to the neuronal nicotinic receptor correlates with the severity of the patient's symptoms and signs.

Cancer cells can produce antibodies to proteins expressed by autonomic nerves ("paraneoplastic syndrome"). Anti-Hu

antibodies (also known as Type 1 anti-neuronal nuclear antibody, ANNA-1) are especially common in small cell lung cancers.

A variety of infectious diseases can result in autonomic neuropathies, such as mononucleosis, herpes simplex, and Coxsackie B.

Lambert-Eaton myasthenic syndrome is an autoimmune disorder of neuromuscular transmission characterized by antibodies directed against presynaptic, voltage-gated calcium channels, impairing acetylcholine release. This syndrome is most commonly associated with symptoms and signs of parasympathetic nervous system failure.

Several diseases can include autonomic neuropathy that may have an autoimmune mechanism, such as diabetes, Guillain-Barré syndrome, Sjogren's syndrome, lupus, and amyloidosis. In general, there is no specific test to identify the specific offending antibody. These are discussed later in this book.

Other antibodies are included in commercially available panels. Some associated with autonomic neuropathies are antinuclear antibody and Rheumatoid factor.

It should be noted that the presence of an antibody, such as to the neuronal nicotinic receptor, does not mean that the antibody is pathogenic and causes or contributes to dysautonomia. It can be very difficult to make this determination with confidence. One way to assess this possibility is by plasma exchange. In this procedure, the patient's blood is drawn into a machine that separates the cells from the plasma, removes the plasma, and

infuses the patient's cells back into the patient, along with saline, albumin, and electrolytes. Plasma exchange temporarily decreases circulating levels of all antibodies. Rapid improvement in the patient's symptoms and signs would indicate that one or more antibodies are pathogenic, but it would not identify the specific antibody.

NEUROIMAGING TESTS

Neuroimaging is a way to see nervous system tissue. This section is divided into macroscopic and microscopic neuroimaging. Macroscopic neuroimaging in autonomic medicine is mainly to see the sympathetic noradrenergic innervation of the heart. In patients with autonomic failure and a parkinsonian movement disorder there is also a role for imaging of the striatum in the brain. Microscopic neuroimaging is mainly to see autonomic fibers in skin biopsy specimens.

Overview of Cardiac Sympathetic Neuroimaging

Sympathetic neuroimaging is based on injection of tracer-labelled compounds that radiolabel sites of the cell membrane norepinephrine transporter (NET) or that are taken up into sympathetic nerves via the NET and radiolabel intra-neuronal catecholamine storage sites.

Detection of the radioactivity is increasingly by tomographic radionuclide imaging.

Tomography is a type of scanning based on slices.

Tomography refers to slices. Imagine you had a radioactive object in a box. You could determine if there were something radioactive inside by using a detector, such as a Geiger counter. Now suppose you had a large number of little Geiger counters all around the box. Tomographic scans are two-dimensional

images, or slices. Tomographic slices would allow you to see what was inside the box at any level. If the object were small, most of the slices would be empty. Eventually, at the level of the object, you would see an image of the object in the slice. The sites of radioactivity inside the body can be seen in horizontal slices across the body (transaxial), from front to back (coronal), or from side to side (sagittal).

The heart stands out among body organs in terms of the intensity of radiolabeling of sympathetic nerves, and virtually all of sympathetic neuroimaging focuses on the main pumping muscle of the heart, the left ventricular myocardium.

Sympathetic nerves to the heart travel with the coronary arteries that deliver blood to the heart muscle. The nerves then dive into the muscle and form mesh-like networks that surround the heart muscle cells. Because all radioactive neuroimaging tests have a limit of resolution of at least a few millimeters, the imaging does not show individual nerves but gives a general picture. Since the nerves are found throughout the heart muscle, the picture looks very much like a scan of the heart muscle itself.

The radioactive drugs used for imaging the sympathetic nerves in the heart are given by injection into a vein, and they are delivered to the heart muscle by way of the coronary arteries.

Sympathetic neuroimaging is rarely done as part of autonomic function testing in the United States, although this is done commonly in Europe and Japan and has been for decades. The discrepancy is due mainly to issues related to approvals by regulatory agencies and third party payers.

In general there are two types of cardiac sympathetic neuroimaging agent, one type a sympathomimetic amine and the other a catecholamine. A sympathomimetic amine is a type of chemical that mimics effects of catecholamines. The sympathomimetic amines used in cardiac sympathetic neuroimaging are taken up into sympathetic nerves in the heart via the cell membrane norepinephrine transporter (NET) and once inside the nerves are taken up into vesicles via the vesicular monoamine transporter (VMAT).

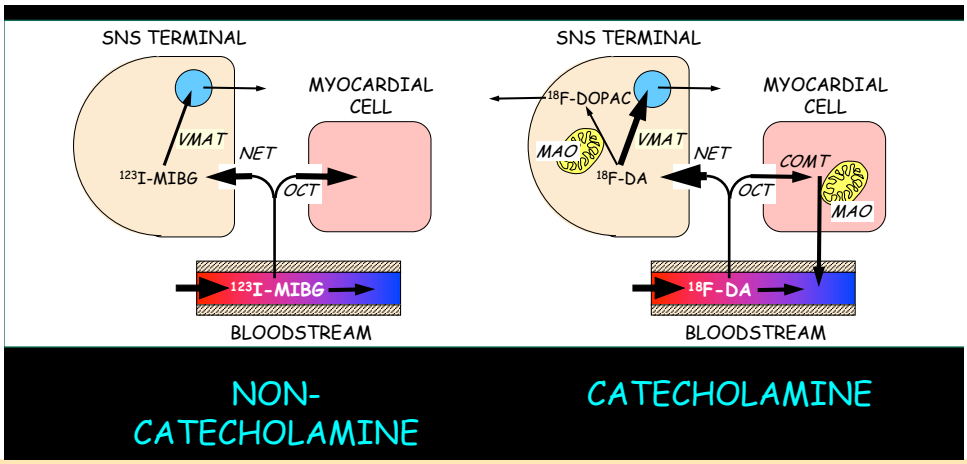


Fig. 260: Two types of sympathetic imaging agent. *Non-catecholamine sympathomimetic amines (e.g., ^{123}I-MIBG) and catecholamines (e.g., ^{18}F-dopamine) share the property of being taken up into sympathetic nerves and within the nerves being translocated in vesicles. The intra-neuronal fates differ.*

^{123}I-MIBG, ^{11}C-meta-hydroxyephedrine, and other radiolabeled sympathomimetic amines are not substrates for either MAO or COMT. They are better substrates than catecholamines for extra-neuronal uptake via the Uptake-2 process mediated by organic cation transporters (OCT). Little is

known about the metabolic fate of these tracers in myocardial cells. This means that there is more non-specific radioactivity with these tracers than with radiolabeled catecholamines.

^{123}I-MIBG is also not as good as catecholamines as a substrate for the NET or the vesicular monoamine transporter (VMAT). Nevertheless, from the point of view of detecting sympathetic noradrenergic denervation, both types of agents work well because of the shared feature of being substrates for the NET and VMAT.

^{123}I-MIBG Scanning

The most commonly used cardiac sympathetic neuroimaging agent world-wide is ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG). To detect the radioactivity and form a tomographic image, single photon emission tomographic scanning (SPECT) is done. ^{123}I-MIBG SPECT scanning is used routinely in Europe and East Asia in the diagnostic evaluation of neurogenic orthostatic hypotension, to distinguish Lewy body diseases (e.g., Parkinson's disease with orthostatic hypotension, pure autonomic failure) from non-Lewy body diseases (e.g., multiple system atrophy) in selected cases and to distinguish dementia with Lewy bodies from Alzheimer's disease.

In the United States ^{123}I-MIBG scanning is FDA-approved for evaluation of pheochromocytoma and some forms of heart failure but not for the above differential diagnostic purposes, despite extensive and long-standing experience with ^{123}I-MIBG scanning outside the USA and on compelling literature.

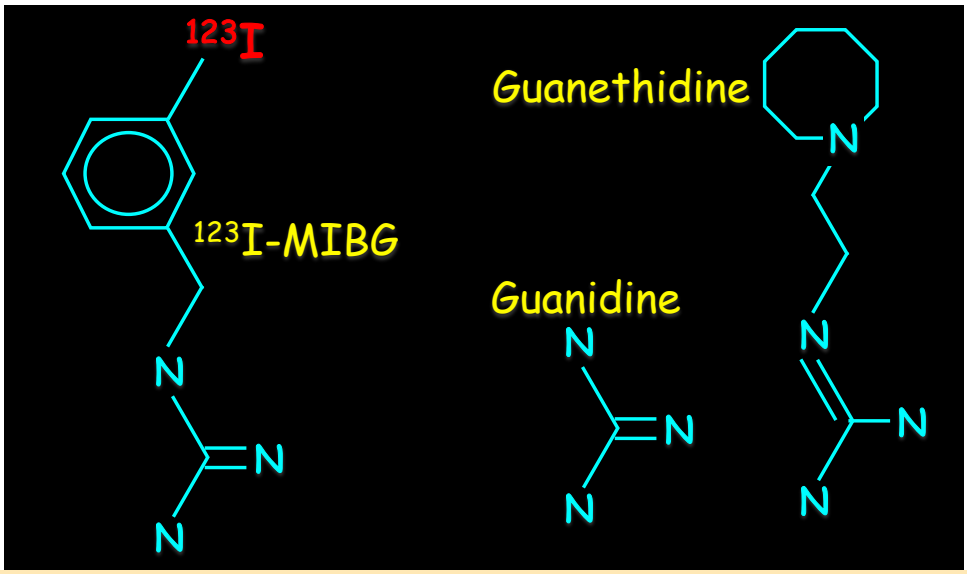


Fig. 261: MIBG & guanethidine. *^{123}I-Metaiodobenzylguanidine (^{123}I-MIBG) is a sympathomimetic amine that is structurally analogous to guanethidine. ^{123}I-MIBG is not an analog of norepinephrine.*

Almost all ^{123}I-MIBG scanning studies involve calculation of the heart/mediastinum (h/m) ratio of radioactivity. This is because absolute concentrations of ^{123}I-MIBG-derived radioactivity cannot be measured accurately.

The h/m ratios are calculated during an "uptake" phase of about 15-30 minutes and a subsequent "washout" phase after a few hours. The relatively long scanning intervals in typical ^{123}I-MIBG scanning render the meaning of "uptake" at best complicated. Because of the extremely rapid exit of injected sympathomimetic amines from the bloodstream, neuronal uptake via the NET, and vesicular uptake via the VMAT, the "uptake" phase probably actually corresponds to a period when not only uptake but also loss of the radioactivity is occurring.

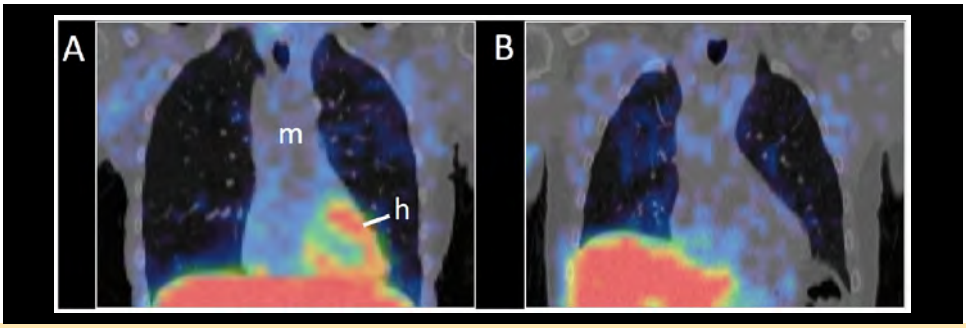


Fig. 262: The h/m ratio in MIBG scanning. *^{123}I-MIBG scanning as usually done does not involve measurement of the absolute amount of radioactivity in the heart but the ratio of radioactivity in the heart (h) to that in the mediastinum (m). Panel A shows a normal image; panel B shows an abnormal image typical of that in patients with Lewy body diseases (Figure reproduced with permission of P. Borghammer.)*

^{18}F-Dopamine Scanning

6-[^{18}F]fluorodopamine, or ^{18}F-dopamine, is a radioactive form of the catecholamine dopamine. ^{18}F-Dopamine scanning for cardiac sympathetic neuroimaging offers advantages over ^{123}I-MIBG SPECT scanning but is available only at the NIH Clinical Center.

After injection of ^{18}F-dopamine into a vein, the drug is taken up by sympathetic nerves, and the radioactivity is detected by a positron emission tomographic scanning, or PET scanning. Because there are so many sympathetic nerves in the heart, PET scans of the heart after injection of ^{18}F-dopamine basically look like images of the heart itself.

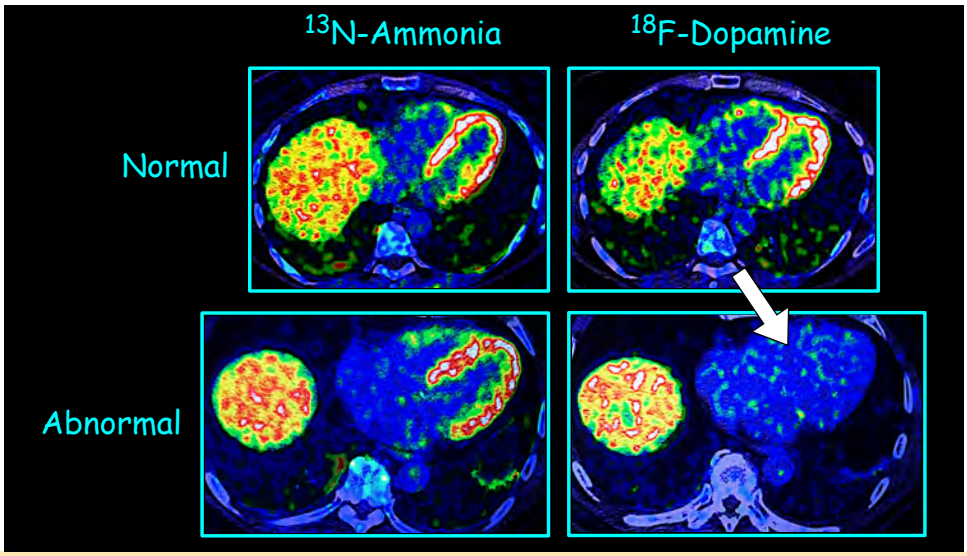


Fig. 263: ^{13}N-Ammonia and ^{18}F-dopamine PET/CT scans in (left) a control subject and (right) a patient with a Lewy body form of neurogenic orthostatic hypotension (nOH). *Both patients have normal myocardial ^{13}N-ammonia perfusion scans. In the patient with the abnormal ^{18}F-dopamine scan (arrow) the liver is seen well, but the left ventricular myocardium is not seen at all (white arrow).*

Different forms of dysautonomia can produce remarkably different pictures of the sympathetic nerves in the heart by ^{18}F-dopamine scanning. Probably the most striking images are obtained in Lewy body forms of neurogenic orthostatic hypotension such as pure autonomic failure and Parkinson's disease with orthostatic hypotension. Even when the blood flow to the heart muscle is normal, often there is no heart visible in the patient's chest!

Analysis of the rate of decline of ^{18}F-dopamine-derived radioactivity over time during a scanning session can provide valuable information about how the sympathetic nerves are functioning. This is a matter of active research interest now.

^{18}F-DOPA Brain Scanning

^{18}F-Dopamine does not pass through the "blood-brain barrier." This means that ^{18}F-dopamine PET scanning of the brain cannot visualize brain structures (unless there is a deficient blood-brain barrier). ^{18}F-DOPA can penetrate the blood-brain barrier and delineate catecholaminergic centers.

^{18}F-DOPA in the brain is converted to ^{18}F-dopamine, and the radioactivity is concentrated in regions that store monoamines such as dopamine, norepinephrine, and serotonin.

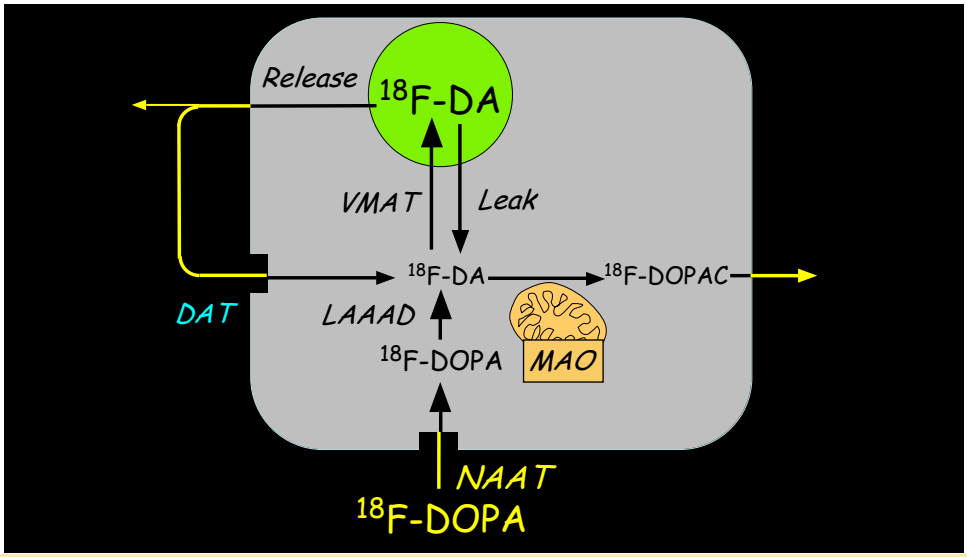


Fig. 264: Fate of ^{18}F-DOPA. *^{18}F-DOPA neuroimaging is based on uptake of ^{18}F-DOPA via the neutral amino acid transporter (NAAT), conversion of radioactive ^{18}F-DOPA to ^{18}F-dopamine (^{18}F-DA) in the neuronal cytoplasm, and uptake of the ^{18}F-DA into vesicles via the vesicular monoamine transporter (VMAT), radiolabeling the vesicles.*

The striatum in the brain consists of the caudate and putamen.

In a ^{18}F-DOPA PET scan the striata on the two sides of the brain look like slugs, or like a sad clown's eyes. The clown's beady eyes correspond to the head of the caudate. The "eye liner" corresponds to the putamen, which is the major site of damage in Parkinson's disease (PD). As you'll learn later, in PD the eye liner seems washed away.

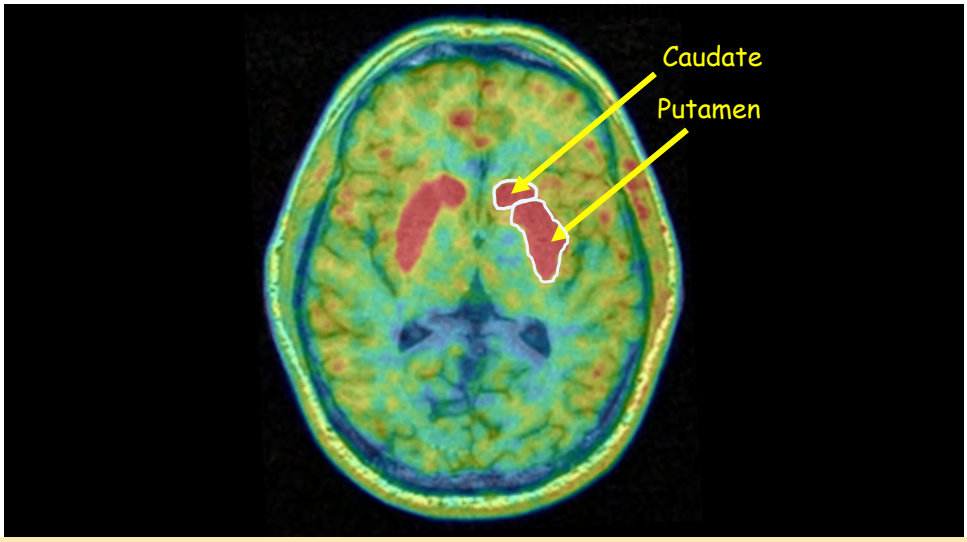


Fig. 265: ^{18}F-DOPA PET/MRI scan. *The ^{18}F-DOPA PET image superimposed on the person's MRI scan shows the dopamine-containing terminals in the striatum (caudate and putamen). See the "sad clown's eyes?*

As for cardiac ^{18}F-dopamine-derived radioactivity, analysis of the rate of decline of putamen ^{18}F-DOPA-derived radioactivity over time during a scanning session can provide valuable information about how the dopaminergic terminals are functioning.

DAT Scanning

There are other imaging agents that can be used like ^{18}F-DOPA to visualize abnormalities of the nigrostriatal dopamine system in the brain. A related type of scan is called a "DAT" scan. DAT stands for the cell membrane dopamine transporter. Since transporters for dopamine are found on the terminals in the striatum, a DAT scan can detect loss of dopamine terminals such as in Parkinson's disease.

Skin Biopsies

The dermis of the skin contains three constituents that receive post-ganglionic sympathetic innervation—sweat glands, *arrector pili* (pilomotor) muscles, and blood vessels. There have been major recent advances in visualizing the nerves supplying these structures and using the images as biomarkers of specific forms of dysautonomia.

The sweat glands in the skin receive sympathetic cholinergic nerve fibers. These post-ganglionic, non-myelinated, slow-conducting fibers release acetylcholine. The acetylcholine binds to muscarinic receptors, evoking sweat secretion. In skin biopsy samples, one can identify the sympathetic cholinergic fibers by their contents of vasoactive intestinal peptide (VIP) or choline acetyltransferase (ChAT).

The hair follicles have small muscles attached to them called pilomotor or *arrector pili* muscles. The pilomotor muscles are responsible for the hair standing up, or piloerection, when you are exposed to cold or when you are distressed. The muscles

receive sympathetic noradrenergic nerve fibers relatively specifically. The nerves release norepinephrine, which binds to alpha-adrenoceptors on the *arrector pili* muscles, and the hair stands up. In skin biopsy samples, one can identify sympathetic noradrenergic fibers by their contents of dopamine-beta-hydroxylase (DBH) or tyrosine hydroxylase (TH).

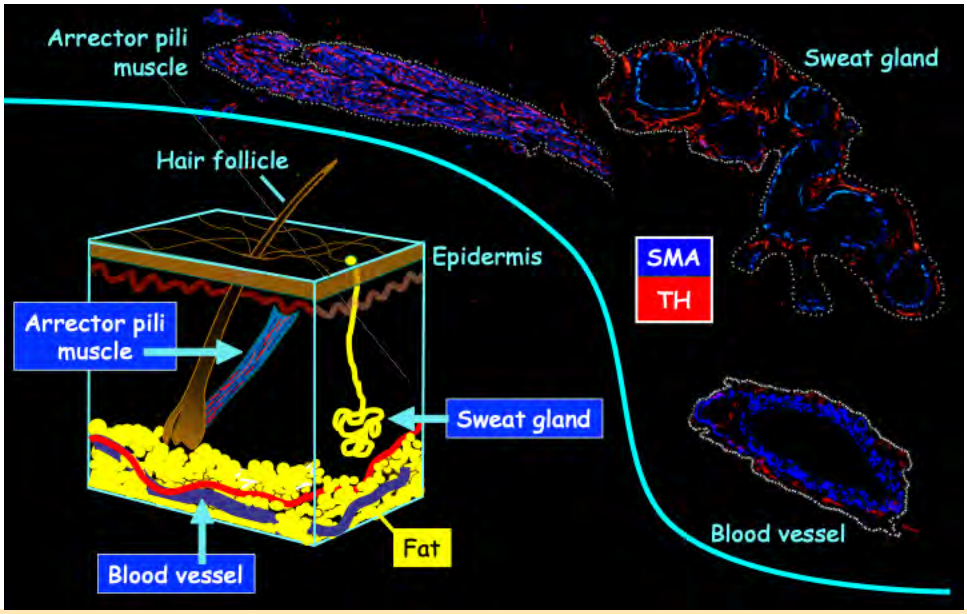


Fig. 266: Sympathetic noradrenergically innervated skin constituents. *The dermis contains 3 structures—arrector pili (pilomotor) muscles, blood vessels, and sweat glands—that receive sympathetic noradrenergic innervation, as indicated by immunoreactive tyrosine hydroxylase (TH, red). These structures also contain smooth muscle actin (SMA, blue). The images are not shown to the same scale. Brightness and contrast have been manipulated to emphasize the different arrangements of TH with respect to SMA. Regions of interest for quantifying signal intensities are outlined with white dots. (Images provided by R. Isonaka)*

Since the ***arrector pili*** muscles and the walls of blood vessels receive purely sympathetic noradrenergic innervation, PGP 9.5 staining can identify sympathetic noradrenergic nerves in these structures, even though PGP 9.5 reacts with all forms of small nerve fibers, not just post-ganglionic autonomic fibers.

STARS IN THE DYSAUTONOMIAS UNIVERSE

This part presents several examples of conditions in the "dysautonomias universe."

The approach here is not meant to be exhaustive or encyclopedic. The conditions are described in line with the chronological sequence from pediatric to adult to geriatric.

Recall the definition of dysautonomia as a condition in which altered functions of one or more components of the autonomic nervous system adversely affect health. The old man who suffers a heart attack while shoveling snow exemplifies damage because of an interaction of the autonomic nervous system (ANS) with an independent pathologic state—ischemic heart disease. Common, chronic disorders such as diabetes, heart failure, kidney failure, pulmonary failure, liver failure, and neurodegenerative diseases are all associated with dysautonomias of one kind or another. Drugs and other treatments for any of a variety problems, from hypertension to benign prostatic hypertrophy to cancer to the common cold, can cause harm by stimulating or inhibiting parts of the ANS. In this section, however, the focus is on disorders in the dysautonomias universe (Fig. 194).

PEDIATRIC INHERITED DYSAUTONOMIAS

Several inherited or congenital diseases feature a form of dysautonomia (Fig. 195). The following discussion describes some of them. Most are severe and become manifest in infancy or childhood.

Pediatric inherited forms of dysautonomia are rare but can be severe or lethal.

HSANs

HSAN stands for hereditary sensory and autonomic neuropathy. This is a family of inherited conditions that all feature decreased ability to sense pain. Because of the sensory loss, the patients can self-mutilate. All forms of HSAN are rare. The most common is familial dysautonomia (HSAN III), followed by congenital insensitivity to pain with anhidrosis (CIPA), which is HSAN IV.

FAMILIAL DYSAUTONOMIA (HSAN III)

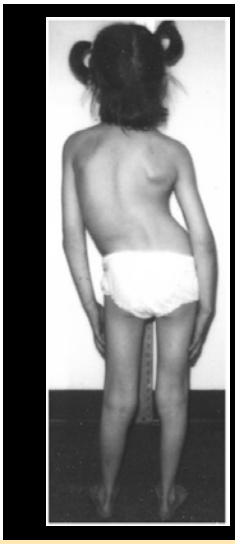
The prototype of an inherited dysautonomia is familial dysautonomia (FD), also known as Riley-Day syndrome and hereditary sensory and autonomic neuropathy type III (HSAN III). FD is a rare inherited disease that features abnormalities in sensation and in functions of the autonomic nervous system. FD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

The cause of FD is a mutation of the gene, *IKBKAP*. The mutation 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 non-myelinated sensory fibers and post-ganglionic sympathetic noradrenergic nerves. 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 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, the patients are at high risk of burns of the mouth or esophagus due to drinking scalding hot liquid.



"Crises"
(vomiting, sweating, agitation, variable BP)

Kyphoscoliosis

Corneal lesions

Aspiration & GERD (Nissen fundoplication)

Burns, corneal lesions, Charcot joints

Oro-dental self-mutilation

Neurogenic orthostatic hypotension

Fig 267: FD complications. *FD patients are susceptible to many complications.*

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

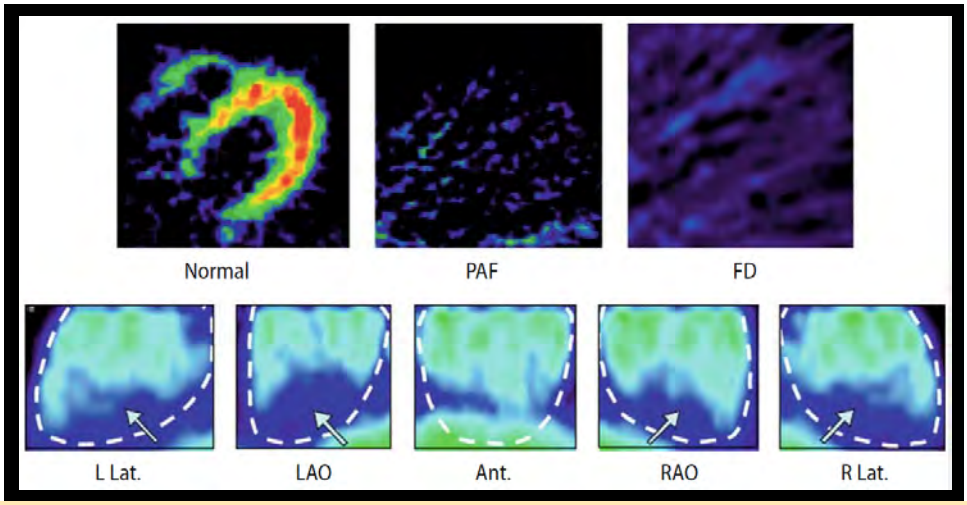


Fig. 268: Incomplete SNS development in FD. *Familial dysautonomia involves decreased cardiac noradrenergic innervation at the bottom of the heart.*

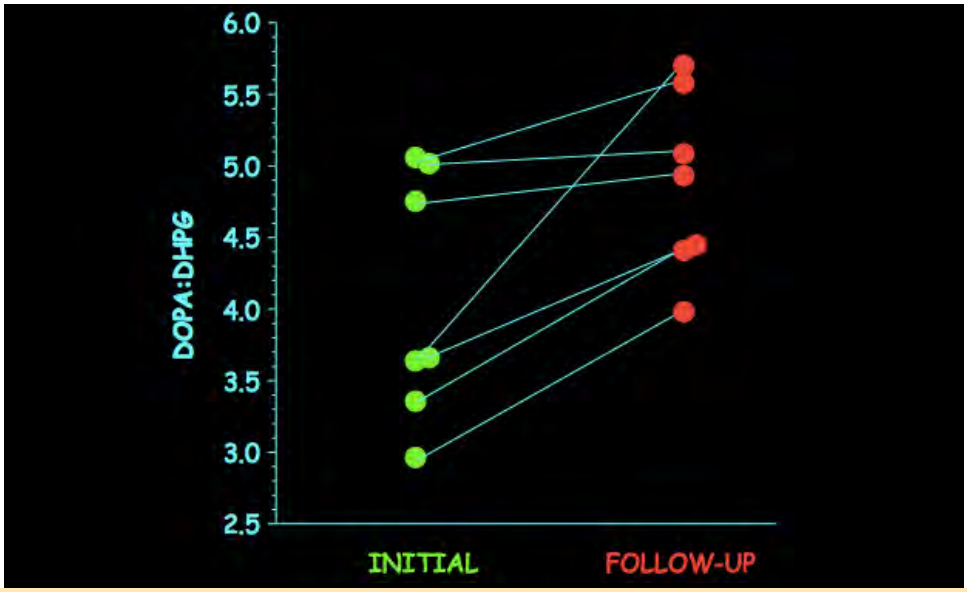


Fig. 269: Progressive neurodegeneration in FD. *There is evidence for progressive neurodegeneration of sympathetic noradrenergic neurons over many years.*

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.

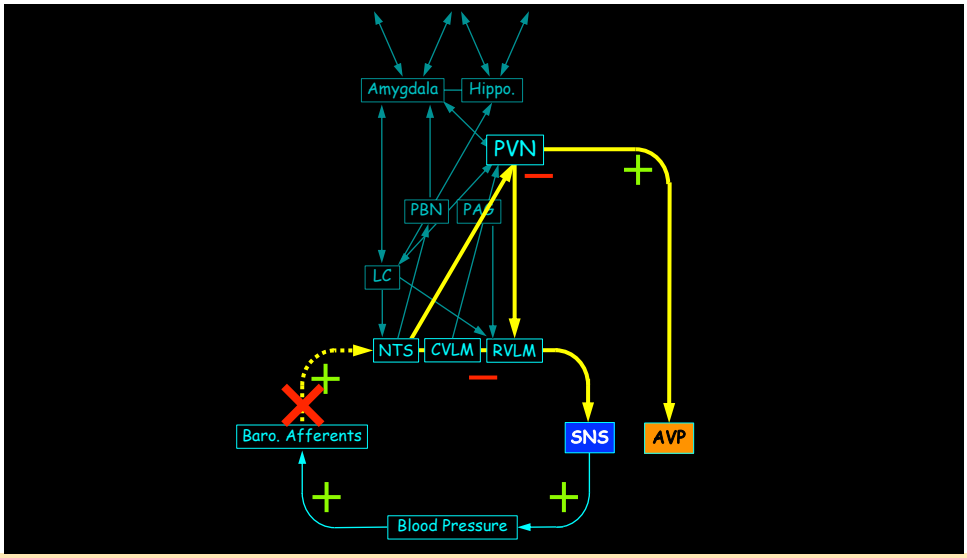


Fig. 270: Afferent baroreflex failure in FD. *Because of afferent baroreflex failure FD patients have withdrawal of the sympathetic noradrenergic system (SNS) from baroreflex restraint and have blunted arginine vasopressin (AVP) responses to orthostasis.*

FD patients have labile blood pressure. This has been attributed to baroreflex failure, due to decreased information coming to the brain from baroreceptors—an afferent lesion that would fit generally with the concept of a hereditary sensory and

autonomic neuropathy. Consistent with an afferent lesion, FD patients have attenuated responses of both plasma NE and AVP levels during orthostasis.

CONGENITAL INSENSITIVITY TO PAIN WITH ANHIDROSIS

In congenital insensitivity to pain with anhidrosis (HSAN IV) the patients often have self-mutilation. The disease can be caused by mutation of the gene encoding tropomyosin receptor kinase-A (TRK-A), also known as neurotrophic tropomyosin kinase receptor type 1 (NTRK1) and the high affinity nerve growth factor (NGF) receptor. NTRK1 is a receptor that normally is phosphorylated in response to nerve growth factor (NGF). Because of the lack of phosphorylation, there is a deficiency in the neurotrophin signaling pathway that is responsible for the development and maintenance of autonomic and sensory fibers.

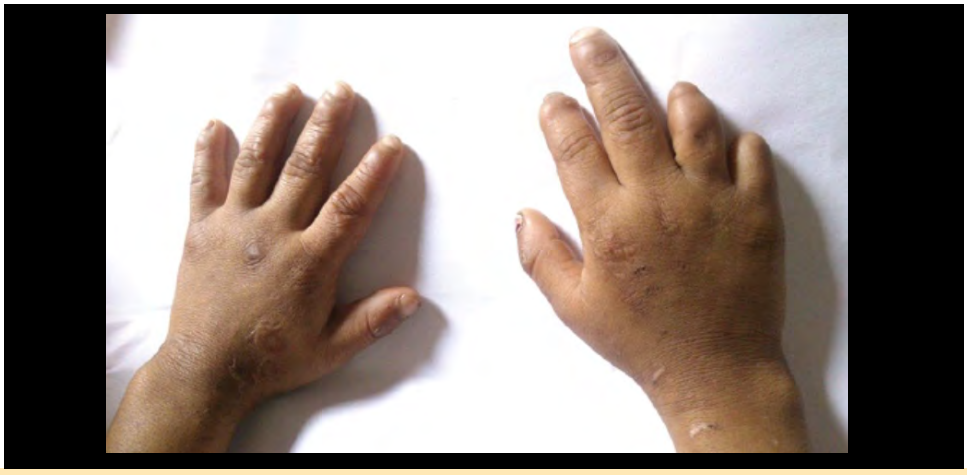


Fig. 271: Self-mutilation in HSAN IV. *Self-mutilation in HSAN IV reflects lack of pain sensation.*

As one might predict, in HSAN IV plasma levels of norepinephrine (NE) are extremely low and fail to increase during orthostasis. Blood pressure responses may be only mildly affected, possibly because of denervation supersensitivity. Heart rate responses to head-up tilting are normal in HSAN IV, which makes sense in that NGF is not thought to be required for parasympathetic nervous system (PNS) development.

The associated finding of normal plasma epinephrine (EPI) levels in HSAN IV is consistent with a mechanism separate from NGF participating in development and functioning of the sympathetic adrenergic system (SAS).

Congenital Central Hypoventilation Syndrome (CCHS)

Congenital central hypoventilation syndrome (CCHS) has been called “Ondine’s curse.” According to an old myth, the sea nymph Ondine (“unda” is Latin for “wave”) falls in love with and marries a mortal, but he commits adultery, and as punishment he is cursed in that if he ever fell asleep he would stop breathing and die. There are other versions of the story, but it is the striking peculiarity of the curse that is sticky.

The main manifestation of CCHS is apnea (lack of breathing) during sleep. The patients breathe normally while awake, but they hypoventilate during sleep. The drop in blood oxygen tension and buildup of carbon dioxide do not stimulate ventilation.

In most cases the causative gene of CCHS is in the pairedlike homeobox gene *(PHOX2B)*. Mutation in this gene is

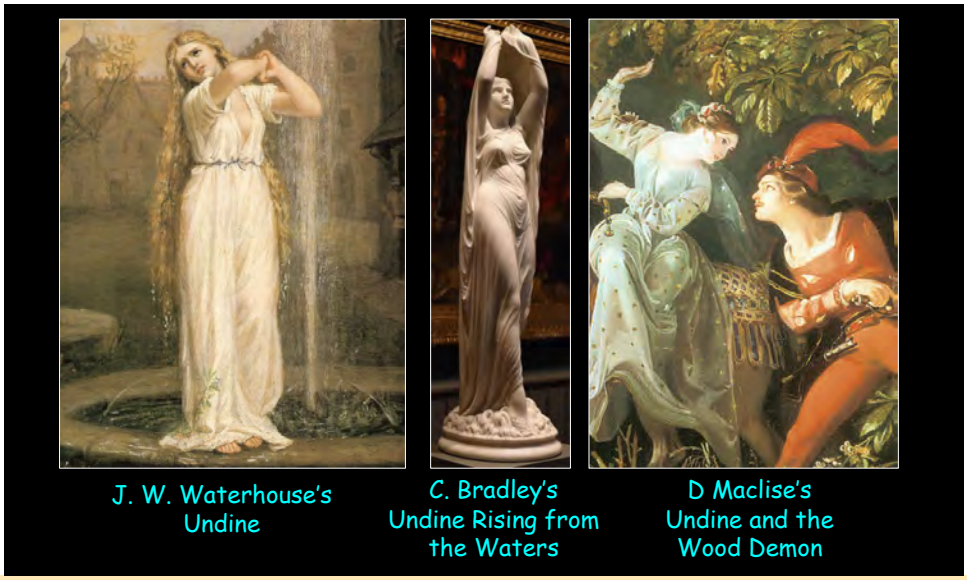


Fig. 272: Ondine. *Artists' depictions of the sea nymph Ondine (Undine).*

now required to diagnose CCHS. Normally, *PHOX2B* contains a 20-alanine coding repeat region. An increased number of polyalanine repeats in this region is referred to as polyalanine repeat expansion mutation (PARM). Over 90% of patients with CCHS carry a PARM in the *PHOX2B* gene. The remaining 10% have non-polyalanine repeat mutations, such as from missense, nonsense, or frameshift mutations.

The protein encoded by *PHOX2B* is a transcription factor responsible for regulating expression of genes involved with development of the autonomic nervous system. Phox2B is expressed in brainstem centers involved in regulation of autonomic outflows and ventilation, such as the retrotrapezoid nucleus (RTN). The RTN plays a key role in ventilatory

responses to carbon dioxide buildup (hypercarbia) or decreased pH. CCHS also seems to involve loss of neurons in the locus ceruleus, the main source of norepinephrine in the brain and an important center for arousal and vigilance.

CCHS is associated commonly—but not always—with manifestations of autonomic failure, including pupillary abnormalities, hypothermia, decreased sweating, decreased heart rate variability, episodes of sinus arrest, and Hirschsprung's disease.

CCHS patients share some subtle facial features.

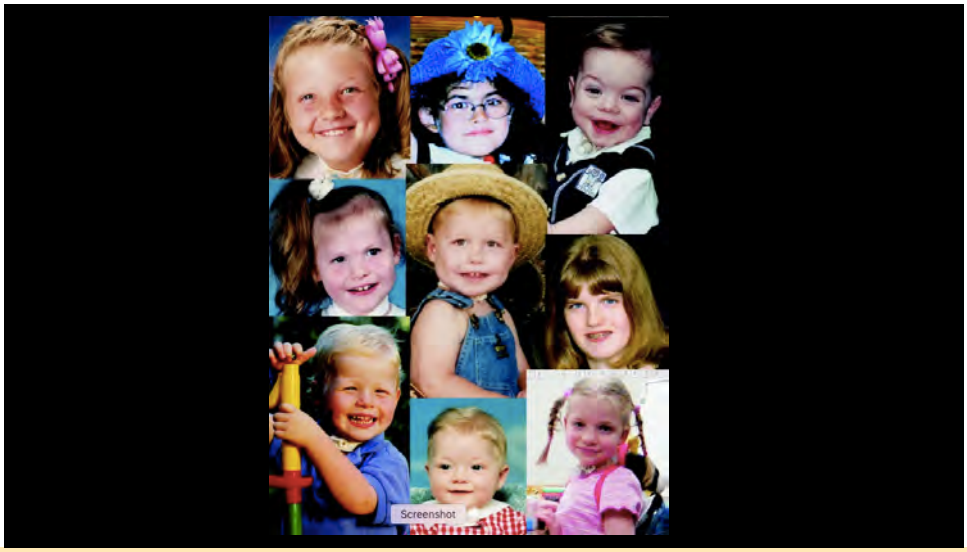


Fig. 273: Facial features in CCHS. *Shared aspects are increased upper lip height, increased biocular width and upper facial height, and nasal tip protrusion.*

CCHS is associated with poor cognitive development, which may be attributed to repeated prolonged bouts of cerebral hypoxia. CCHS can now be diagnosed in neonates. Thanks to

early institution of artificial ventilation, CCHS patients can now live into adulthood with better neurocognitive outcome.

Diseases of Catecholamine Synthesis

PKU

If you have read the label on a can of diet soda that contains the sweetener, aspartame, you have seen 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 phenylalanine can lead to a buildup of phenylalanine; 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 might be harmful.

For phenylalanine hydroxylase to function requires a co-factor called tetrahydrobiopterin (BH_4). Since BH_4 is also a required co-factor for tyrosine hydroxylase (TH), BH_4 is necessary for synthesizing catecholamines in the body. BH_4 is also a co-factor for the synthesis of serotonin and nitric oxide.

In dihydropteridine reductase deficiency there is an inability to recycle BH_4. This causes an atypical form of PKU in which even restricting phenylalanine does not protect the infant from

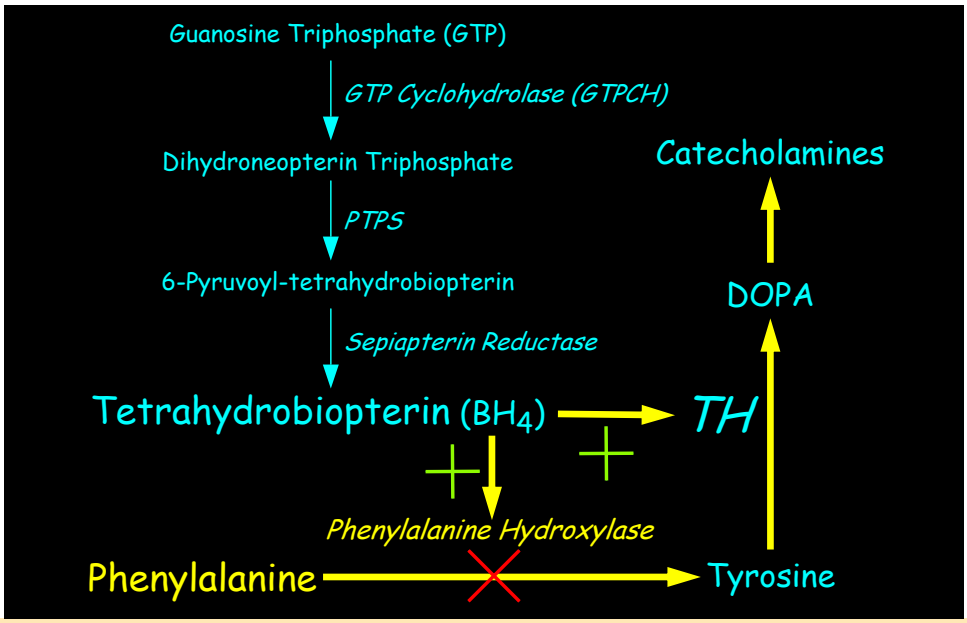


Fig. 274: Phenylketonuria (PKU). *PKU results from phenylalanine hydroxylase deficiency. Levodopa treatment is ineffective, because the damage is from phenylalanine buildup.*

developing a neurodegenerative disease, and death occurs in childhood.

TH Deficiency

Tyrosine hydroxylase (TH) is the rate-limiting enzyme in the biosynthesis of the catecholamines.

TH deficiency is a rare genetic disorder transmitted as an autosomal recessive trait. The deficiency results in a wide spectrum of abnormalities, from a mild parkinsonian movement disorder developing during childhood to a life-threatening neurological disorder in infancy. As for Segawa's disease (discussed in the next section), patients with TH deficiency respond to levodopa treatment.

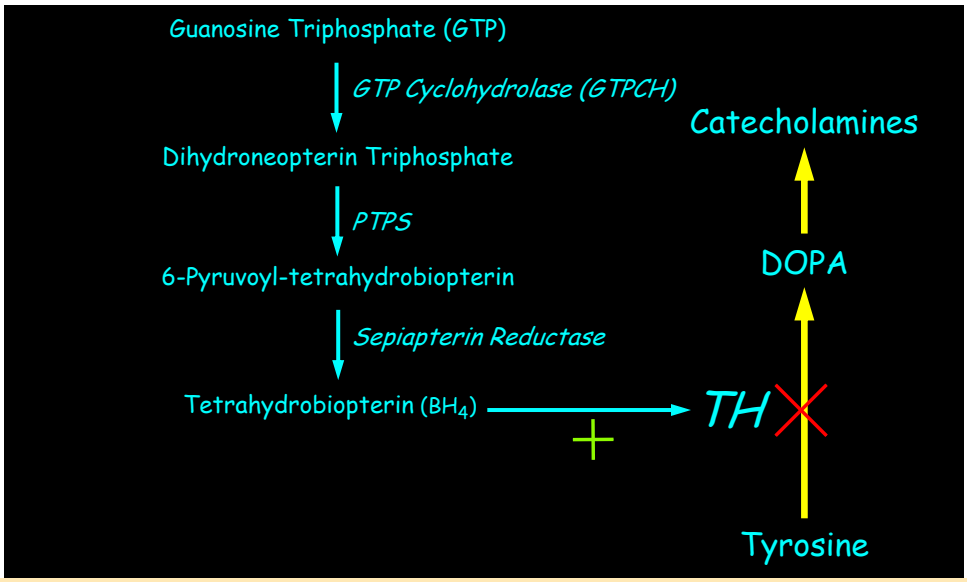


Fig. 275: Tyrosine hydroxylase (TH) deficiency. *In TH deficiency there is decreased ability to synthesize DOPA and therefore catecholamines. Levodopa treatment is effective.*

DOPA-Responsive Dystonia

GTP cyclohydrolase (GTPCH) is the first enzyme in the synthetic cascade leading to tetrahydrobiopterin (BH_4). Since BH_4 is a co-factor for tyrosine hydroxylase (TH), GTPCH deficiency manifests as a form of parkinsonism with dystonia (DOPA-responsive dystonia, or Segawa's disease). The symptoms get worse as the day goes on.

Mutation of the gene encoding GTPCH produces an autosomal dominantly inherited form of DOPA-responsive dystonia. Autosomal-recessive forms of the disease arise from mutations of the genes encoding sepiapterin reductase or TH. The disease usually manifests in childhood.

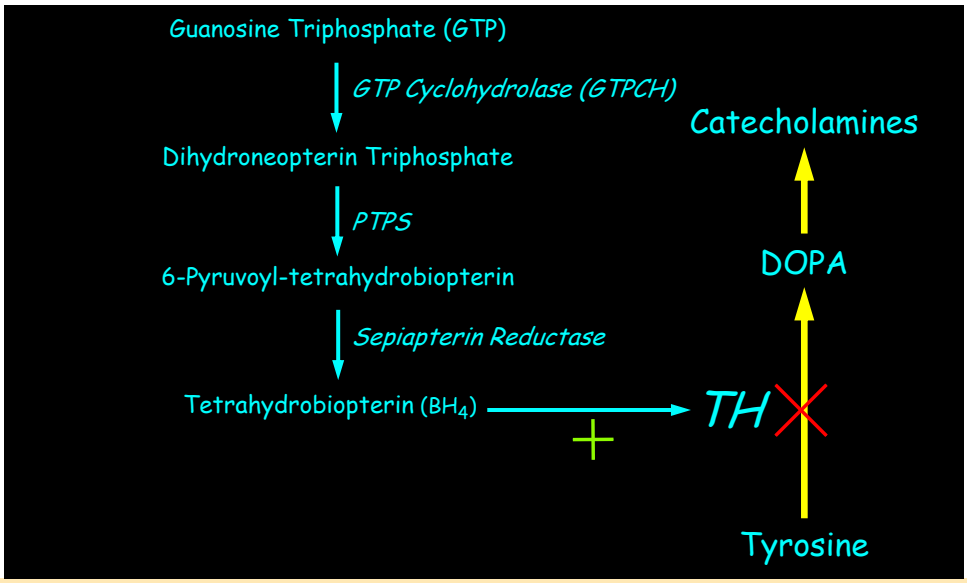


Fig. 276: GTPCH Deficiency. *Deficiency of GTP cyclohydrolase (GTPCH) results in decreased DOPA synthesis and manifests with DOPA-responsive dystonia.*

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.

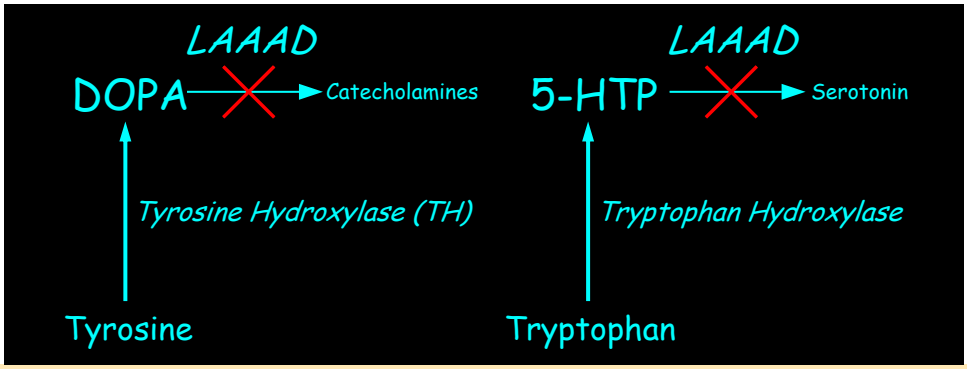


Fig. 277: L-aromatic-amino-acid decarboxylase (LAAAD) deficiency. *LAAAD deficiency results in decreased production of the catecholamines and of serotonin.*

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 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. Recently it has been found that the patients can benefit markedly from a form of gene therapy based on administration into the brain of an adeno-associated virus that increases LAAAD activity.

DBH Deficiency

Dopamine-beta-hydroxylase (DBH) catalyzes the conversion of dopamine to norepinephrine. 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 post-ganglionic sympathetic innervation of the heart and blood vessels is present.

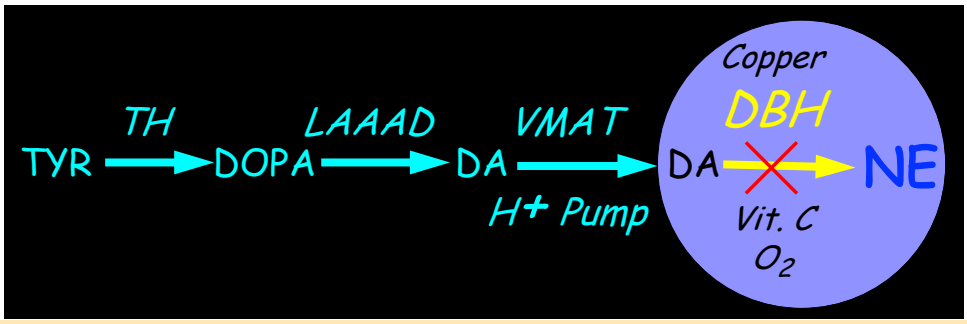


Fig. 278: Dopamine-beta-hydroxylase (DBH) deficiency. *Patients with DBH deficiency have decreased synthesis of norepinephrine.*

Sympathetic cholinergic system function is intact in patients with DBH deficiency. Therefore, the patients have normal sweating, even though they have sympathetic neurocirculatory failure. Treatment with L-dihydroxyphenylserine (droxidopa, L-DOPS) bypasses the enzyme deficiency and results in remarkable improvement that is virtually curative in DBH deficiency.

Decreased DBH activity can be the result of a mutation in the gene *CYB561*, which leads to a shortage of vitamin C (ascorbic acid), a required DBH co-factor.

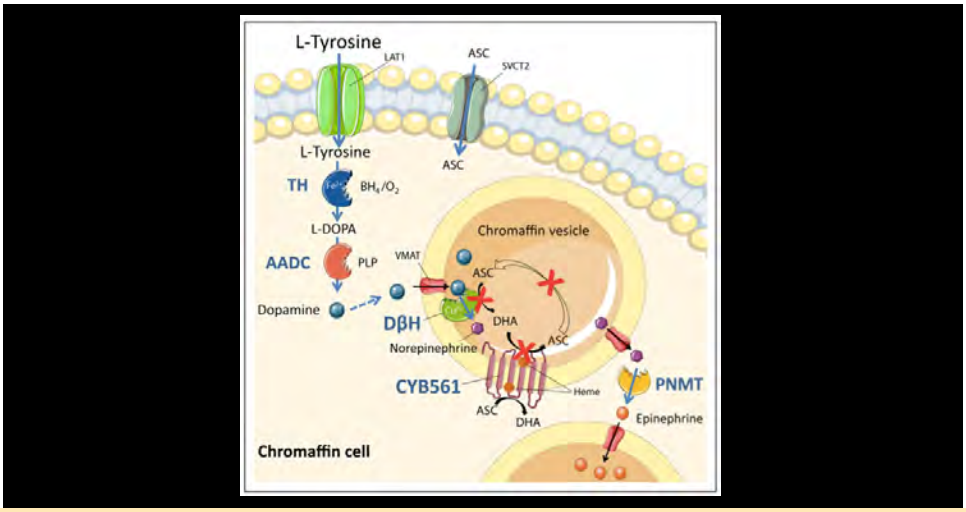


Fig. 279: Functional DBH deficiency from* CYB561 *gene mutation. *Mutation of the* CYB561 *gene decreases ascorbic acid in vesicles, resulting in a form of neurogenic orthostatic hypotension from functional DBH deficiency. There is no actual deficiency of DBH enzyme itself in this rare disease.*

Mice with knockout of the DBH gene do not survive to birth. How it is that people with DBH deficiency survive and, with norepinephrine precursor treatment, can thrive remains a medical scientific mystery.

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.

Fig. 280: Menkes disease. *Menkes disease is also known as "kinky hair disease."*

The baby soon fails to meet developmental milestones, deteriorates neurologically, and dies in childhood.

The gene that regulates copper metabolism and is mutated in Menkes disease is located on the X-chromosome. This means that the disease is confined virtually exclusively to boys.

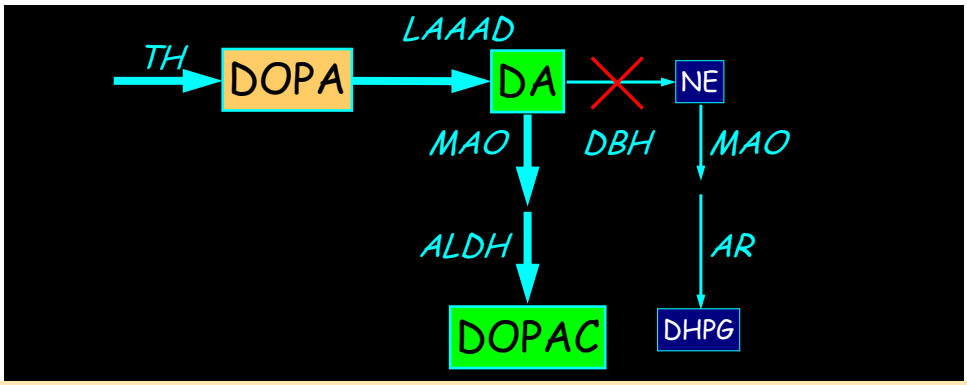


Fig. 281: Plasma catechols in Menkes disease. *Menkes disease results from abnormal copper handling in the body. DBH is a copper enzyme. Plasma levels of catechols proximal to DBH are built up, and levels distal to DBH are decreased. Plasma DOPA/DHPG, DOPAC/DHPG, and DA/NE ratios are always high in Menkes disease*

DBH contains—and its activity absolutely requires—copper. In at-risk newborns one can diagnose Menkes disease by the pattern of plasma catechols. Catechols proximal to the DBH step are built up and those distal to DBH are decreased. Plasma DOPA, DA, and DOPAC levels are high, and plasma NE and DHPG levels are low, resulting in a pattern of high DOPA/DHPG, DOPAC/DHPG, and DA/NE ratios.

Detecting this pattern has so far proven perfectly sensitive and specific in diagnosing the disease in at-risk newborns, enabling successful early copper treatment. 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.

Fig. 282: Successful treatment of Menkes disease. *Early copper treatment can markedly improve outcome in Menkes disease, if treatment is begun soon enough after birth.*

ADOLESCENT/ADULT DYSAUTONOMIAS

There are many forms of dysautonomia in adolescents or adults (Fig. 195). In general, the more common they are, the more mysterious their causes and disease mechanisms.

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.

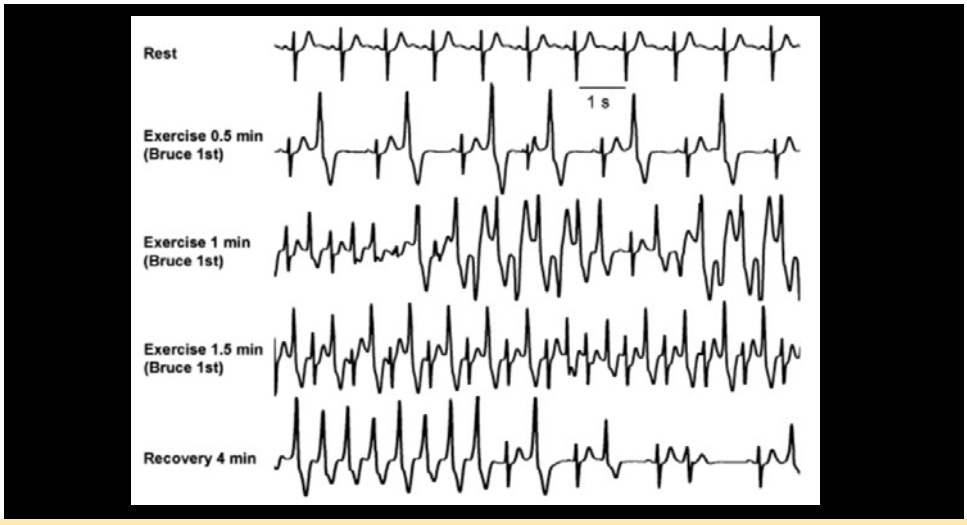


Fig. 283: Catecholaminergic polymorphic ventricular tachycardia. *These tracings show exercise-induced ventricular tachycardia in a patient with CPVT.*

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.

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

There are two modes of inherited transmission of CPVT, a more common autosomal dominant form avnd 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. Autosomal dominantly transmitted CPVT is from mutations of the cardiac ryanodine receptor, which is 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 stellate ganglionectomy.

Fabry Disease

Fabry disease is a chronic disease caused by deficiency of the enzyme alpha-galactosidase A. The disease is transmitted as an X-linked trait and therefore mainly affects males.

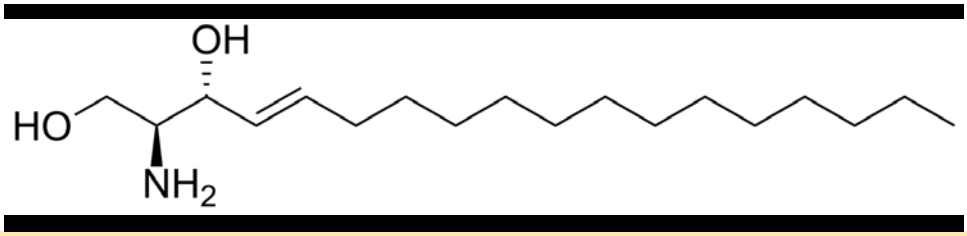


Fig. 284: Chemical structure of sphingosine. *Fabry disease involves accumulation of sphingolipids, which are derived from sphingosine.*

Alpha-galactosidase A is needed to metabolize lipids, fatty substances that include oils, waxes, and fatty acids. The enzyme deficiency causes accumulation of a type of lipid called sphingolipid. Sphingolipids are fatty acid derivatives of sphingosine.

Symptoms of Fabry disease usually begin in childhood or adolescence. There are burning sensations in the arms and legs that are exacerbated by exercise and heat exposure.
The lipid storage problem in Fabry disease can produce clouding of the corneas, increased risk of heart attack or stroke, heart enlargement, kidney failure, and gastrointestinal abnormalities.

Fabry disease is characterized by angiokeratomas, which are benign tumors of skin capillaries. The tumors appear as small, raised reddish-purple skin blemishes.

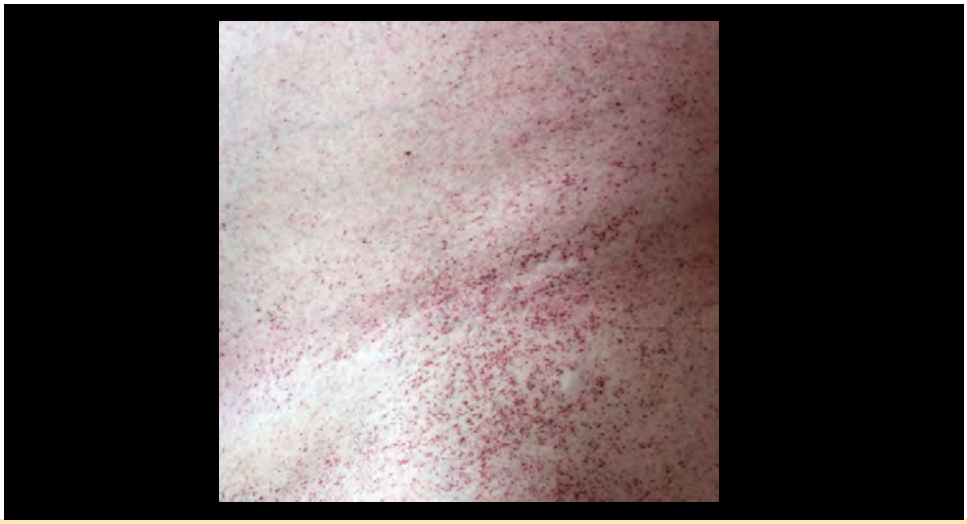


Fig. 285: Fabry disease skin. *Angiokeratomas and dry skin are characteristic skin findings in Fabry disease.*

Fabry disease also features anhidrosis (lack of sweating). One can detect anhidrosis in Fabry disease by the quantitative sudomotor axon reflex test (QSART). An abnormal QSART result in this setting does not necessarily point to a form of sympathetic cholinergic neuropathy, since the sweat secretion apparatus itself might be dysfunctional.

Amyloidosis

Amyloidosis refers to a variety of disorders that have in common deposition of a mis-folded protein called amyloid in body organs. Normally the protein is soluble, but 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, even in his hospital bed at the NIH Clinical Center, in an effort to decrease his distressing "pins and needles" sensations.

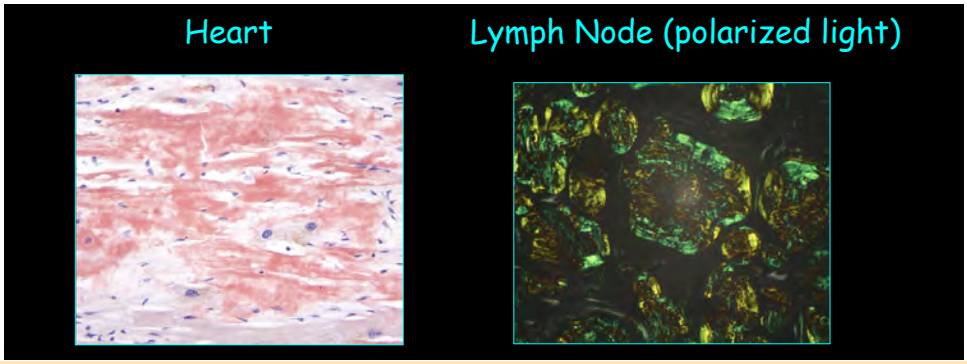


Fig. 286: Microscopic pathology in amyloidosis. *Congo red staining reveals amyloid deposits in organs such as the heart and lymph nodes.*

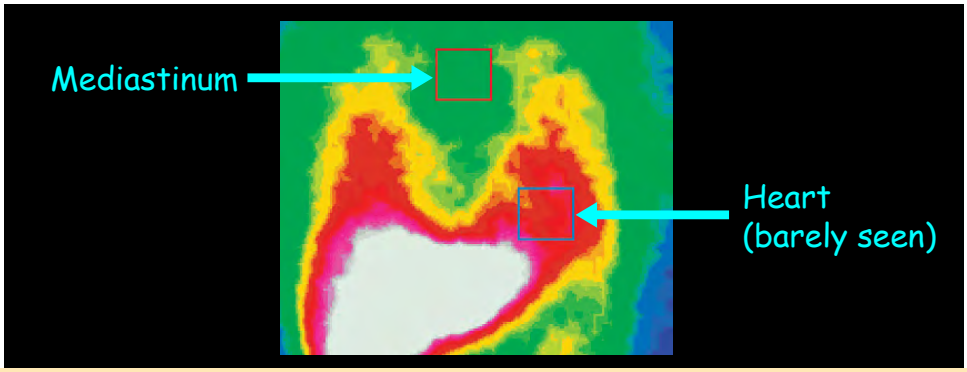


Fig. 287: Cardiac sympathetic neuroimaging in amyloidosis. *This ^{123}I-MIBG scan indicates amyloidosis-associated cardiac sympathetic denervation. The heart should appear white, like the liver. Instead, the heart is barely visible.*

One can diagnose amyloidosis by biopsying mucus membranes (rectal, buccal) or abdominal fat pad tissue and looking under a

microscope for deposits of the amyloid material. Congo red staining, especially when combined with polarized light, demonstrates the proteins microscopically.

Patients with amyloidosis can have a marked reduction of myocardial noradrenergic nerves, as indicated by cardiac sympathetic neuroimaging.

HEREDITARY TRANSTHYRETIN AMYLOIDOSIS

Hereditary transthyretin amyloidosis is a rare but clinically and scientifically important cause of chronic autonomic failure. It is important clinically, because if left untreated the disease progresses to lethality at a young age, and correct diagnosis and timely treatment can prolong life. It is important scientifically, because the disease seems to exemplify a class of progressive neurodegenerative disorders that are associated with abnormal deposition of proteins, analogous to alpha-synuclein deposition in Parkinson's disease and tau deposition in progressive supranuclear palsy.

In other diseases the pathogenic role of the abnormal protein is a matter for research, but in hereditary transthyretin amyloidosis there is no doubt. The disease results from extracellular deposition of the mutated protein, transthyretin (TTR), in a variety of organs and tissues—especially the liver, heart, gut, and peripheral nerves.

Normally TTR exists as a tetramer, but the abnormal protein tends to dissociate to monomers that misfold and aggregate to form insoluble fibrils. The US FDA has approved patisiran, an

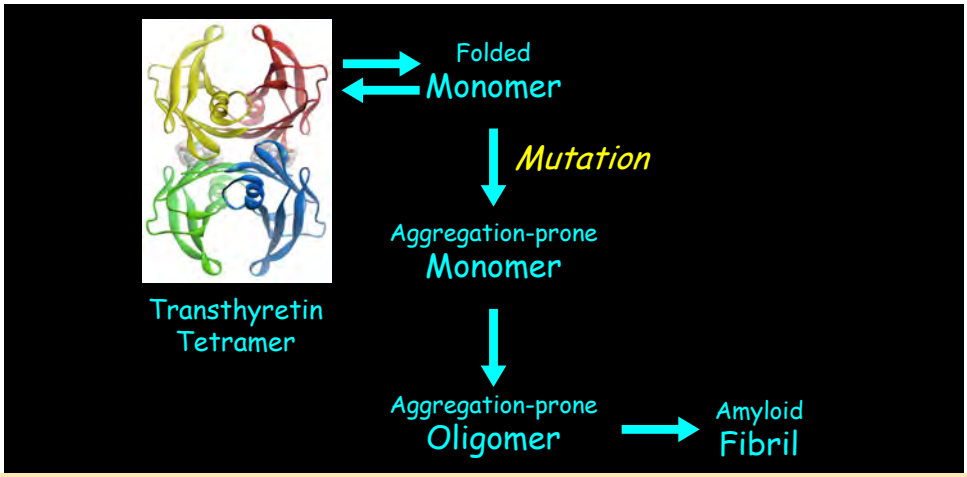


Fig. 288: Transthyretin (TTR) and amyloidosis. *The pathogenetic schema relates TTR gene mutation to familial amyloidotic polyneuropathy.*

RNA interference drug that reduces TTR production. Another drug, tafamidis, inhibits the dissociation of TTR tetramers into monomers.

When presenting mainly as sensory, autonomic, and motor polyneuropathy, the term familial autonomic polyneuropathy (FAP) has been used, and when presenting mainly as cardiomyopathy, familial amyloid cardiomyopathy (FAC) has been used. A mixed form also can occur. The disease is transmitted as an autosomal dominant trait.

FAP at first predominantly involves small unmyelinated nerve fibers and manifests with sensory loss mainly affecting pain and temperature sensation. Later, involvement of motor fibers causes progressive weakness and gait abnormalities.
The amyloid fibrils are extracellular, and the neurotoxic mechanism producing length-dependent polyneuropathy in FAP is poorly understood. It has been proposed that mutated TTR

exerts adverse effects at neuronal cell membranes.

In the central nervous system, amyloid is found in the choroid plexuses and around blood vessels—cerebral amyloid angiopathy. Although there is no intra-neuronal amyloid deposition, there are diffuse metabolic changes in brain that may be related to axonal damage.

In FAC the cardiomyopathy involves amyloidotic infiltration of the myocardium, arrhythmias or heart block, and autonomic denervation. A major feature of FAC is cardiac dysautonomia, which is associated with worse survival.

The exact mechanisms of amyloid-related autonomic failure are unknown.

Erythromelalgia

The term, “erythromelalgia,” comes from the Latin for red, painful extremities. Patients with erythromelalgia have redness, swelling, and an intense burning sensation in the extremities or face. The symptoms worsen with exposure to heat or exercise and are relieved by local cooling of the skin.

The striking red skin coloration reflects excessive local accumulation of blood in dilated blood vessels. The skin feels warm. Elevation of the affected extremity temporarily reverses the redness. Why the blood accumulates remains mysterious.

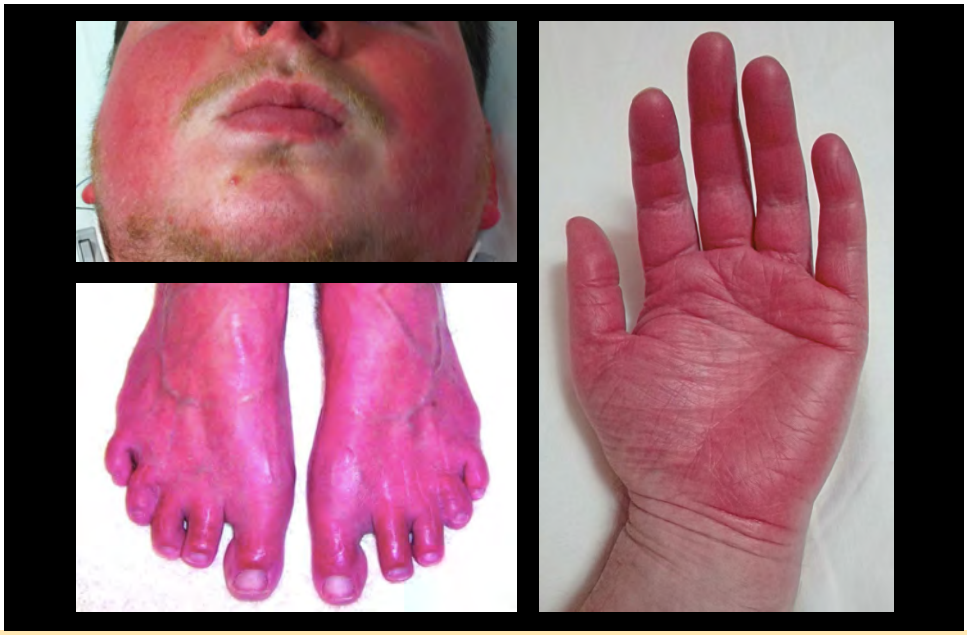


Fig. 289: Erythromelalgia. *These photos illustrate the dramatic skin changes found in erythromelalgia.*

Secondary forms of erythromelalgia are associated with other conditions, such as myeloproliferative diseases, autoimmune disorders, Fabry disease, or hypercholesterolemia, or drugs such as fluoroquinolones (a class of antibiotics), bromocriptine (a dopamine receptor blocker), pergolide (a dopamine receptor agonist), verapamil (a calcium channel blocker), and ticlopidine (an anti-platelet drug). Mechanisms of secondary erythromelalgia are also poorly understood.

Primary erythromelalgia has no known cause. Rarely, erythromelalgia is inherited as an autosomal dominant trait and results from hyperexcitability of nociceptor C-fibers in the dorsal root ganglion. The dorsal root ganglion neurons relay pain impulses to the spinal cord. The hyperexcitability can results from mutation of the gene encoding a subunit of the voltage-gated sodium channel, NA(v)17. The channels are

activated at more hyperpolarized trans-membrane electrical potentials than normal, so that the channels are open for prolonged periods.

Sympathetic neurons in ganglia express the same NA(v)17 channel; however, whether erythromelalgia involves abnormal sympathetic neurocirculatory regulation is poorly understood.

Between flare-ups of erythromelalgia microcirculatory flow is actually decreased, and there is blunting of reflexive responses of microcirculatory flow to the Valsalva maneuver and cooling of the opposite extremity. These abnormalities have been interpreted in terms of decreased cutaneous perfusion combined with reflexive sympathetically mediated vasoconstriction, due to small fiber sympathetic neuropathy and denervation hypersensitivity; however, only a small minority of erythromelalgia patients have small fiber sympathetic neuropathy based on analyses of skin biopsies.

Patients with erythromelalgia wish to stay in a cool environment. Patients I have seen have brought with them small fans to blow against their skin. The condition can be socially isolating and depressing. I had a patient who had no complaints dunking her feet in ice cold water. This should not be used as a form of treatment, however, because of damage to the skin.

There is no known consistently effective treatment of erythromelalgia. Tramadol, amitriptyline, mexiletine (a non-selective voltage-gated sodium channel blocker), or opioids may give relief.

Diabetic Autonomic Neuropathy

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.

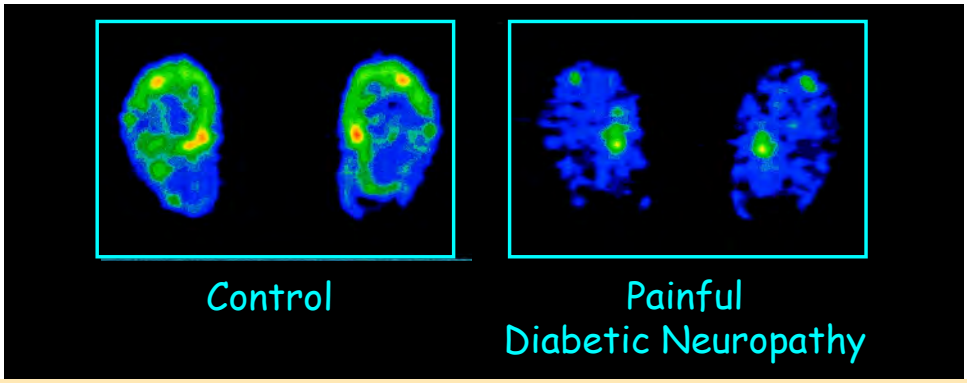


Fig. 290: Painful diabetic neuropathy. *^{18}F-Dopamine scans at the same level of the feet in a control subject and in a patient with painful diabetic neuropathy. The patient has neuroimaging evidence of loss of sympathetic noradrenergic innervation.*

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 myocardial noradrenergic 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 patchy loss of sympathetic innervation from locally decreased delivery of the tracer.

Mechanisms of diabetic autonomic neuropathy are poorly understood.

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

INSULIN NEURITIS

Another form of neuropathy in diabetes is caused by insulin treatment and has been called insulin neuritis. Insulin neuritis is brought on by a rapid improvement in glucose levels in the setting of long-term high glucose levels (hyperglycemia). In

diabetics who have a greater than 4% decrease in their hemoglobin A1c level over 3 months, the risk of developing insulin neuritis exceeds 80%.

The pattern of pain in insulin neuritis follows a “stocking and glove” distribution, with more proximal involvement as the condition worsens. Unlike the usually painful diabetic neuropathy in chronic diabetes, pain in insulin neuritis comes on abruptly. Pathologically, insulin neuritis is a small fiber neuropathy that affects autonomic and sensory non-myelinated fibers. There is also evidence of microvascular disease, as reflected by retinopathy and excretion of albumin in the urine.

In addition to pain, patients with insulin neuritis have a high frequency of orthostatic hypotension, lightheadedness, or syncope. In men, erectile failure is also usually present.

Autonomic function testing in insulin neuritis reveals decreased heart rate responses to deep breathing or the Valsalva maneuver and abnormal beat-to-beat blood pressure responses during Phase II and Phase IV of the Valsalva maneuver. These findings fit with baroreflex-cardiovagal and baroreflex-sympathoneural failure.

HYPOGLYCEMIA UNAWARENESS

In healthy people hypoglycemia rapidly activates the sympathetic adrenergic system (SAS). The high circulating epinephrine concentrations help restore glucose levels. Epinephrine exerts many noticeable effects, such as pallor, sweating, trembling, and a fast pulse rate and augments the

experience of distress.

Epinephrine and glucagon are the body's two main glucose counter-regulatory hormones. Patients with type 1 diabetes or severe, insulin-dependent type 2 diabetes have a lack of glucagon release in response to hypoglycemia.

In hypoglycemia unawareness there is a failure of hypoglycemia to trigger epinephrine secretion. Because of this, the patient does not experience the characteristic warning symptoms of low blood glucose levels. There can be prolonged, severe hypoglycemia that results in seizures, syncope, or brain damage.

Hypoglycemia unawareness goes away after 2 to 3 weeks of careful avoidance of hypoglycemia.

The mechanism by which hypoglycemia shifts the threshold for SAS activation to lower plasma glucose concentrations is unknown.

Spinal Cord Transection

Traumatic accidents that cut the spinal cord (spinal cord transection) results in a particular form of dysautonomia.

The vagus nerve is derived from the brainstem, which would be above the level of spinal cord transection. Spinal cord transection disrupts the pathways descending from the central autonomic network to the sympathetic and the sacral

parasympathetic nerves.

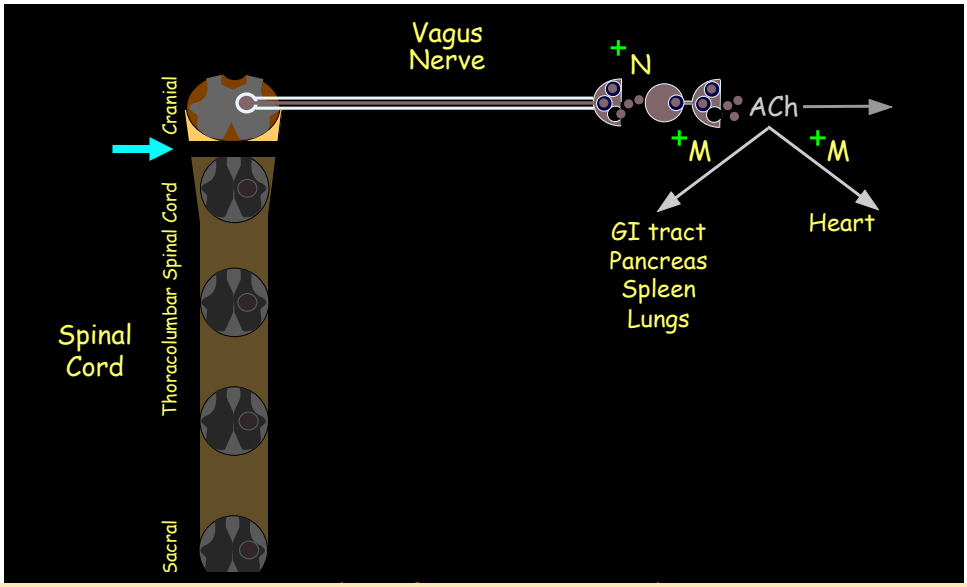


Fig. 291: Autonomic effects of spinal cord transection. *Spinal cord transection does not affect the vagus nerve but disconnects the sympathetic nerves and the sacral parasympathetic nerves from the brain.*

In patients with spinal cord transection, the nervous connections between the autonomic pre-ganglionic neurons in the intermediolateral columns of the spinal cord and the ganglia and post-ganglionic neurons remain intact. This sets the stage for a phenomenon called “autonomic dysreflexia.”

When the urinary bladder (or the rectum) is distended, sympathetic noradrenergic outflow to the cardiovascular system increases via a spinal reflex. Because of the disruption of the baroreflexes, there is no buffering of the increase in blood pressure.

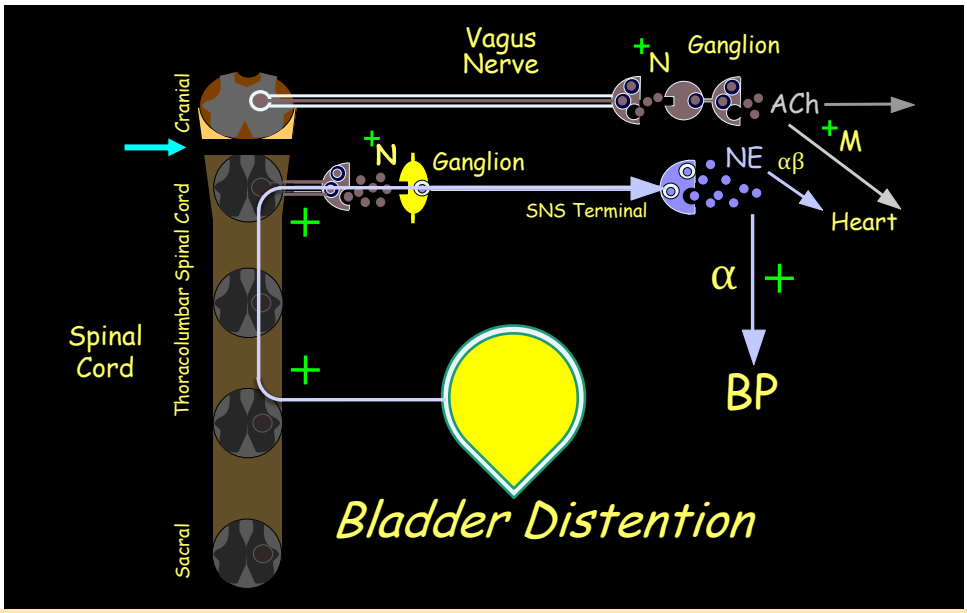


Fig. 292: Autonomic dysreflexia. *In patients with spinal cord transection, distention of the urinary bladder (or the rectum) can evoke a paroxysmal increase in blood pressure.*

In patients with spinal cord transection, distention of the urinary bladder or of the rectum can evoke a dangerous increase in blood pressure.

Afferent Baroreflex Failure

In afferent baroreflex failure the brain does receive afferent traffic from baroreceptors, and the sympathetic noradrenergic system is activated inappropriately because of release from baroreceptor restraint.

Afferent baroreflex failure is associated with excessive variability of blood pressure.

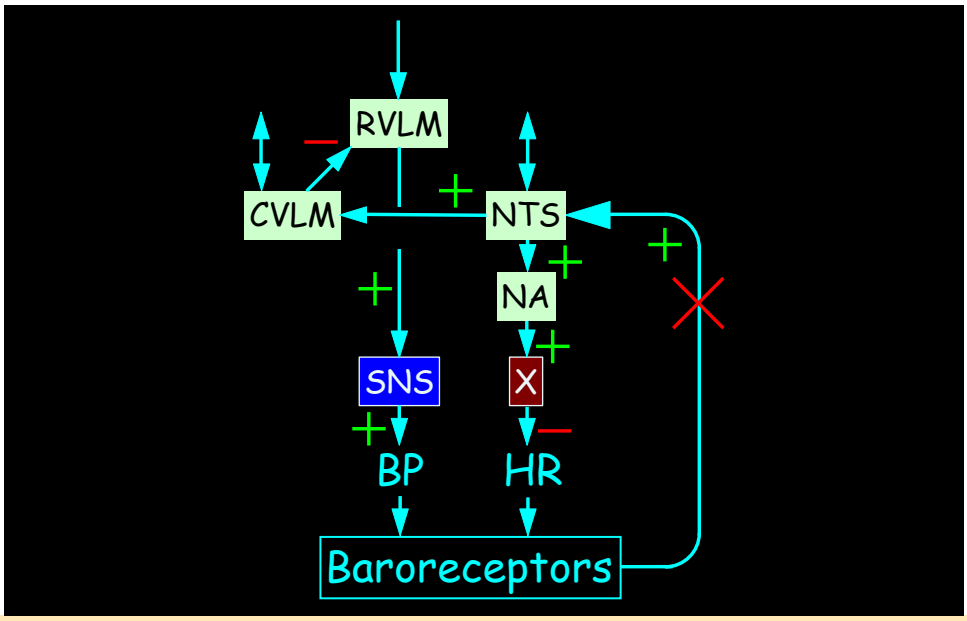


Fig. 293: Afferent baroreflex failure. *Baroreflex failure can result from an afferent lesion.*

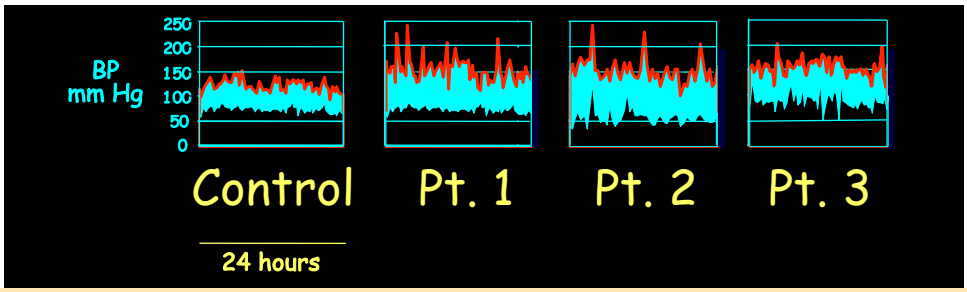


Fig. 294: Increased variability of blood pressure in afferent baroreflex failure. *Excessive blood pressure variability can be documented by 24-hour ambulatory blood pressure monitoring in patients with arterial baroreflex failure.*

Orthostatic intolerance in afferent baroreflex failure is associated with large swings of 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.

Baroreflex failure can result from tumors or neurosurgery that involve the dorsal medulla. Baroreflex failure also is a common correlate of congestive heart failure. These represent central rather than afferent lesions.

Failure of the arterial baroreflex can produce orthostatic intolerance.

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 hypothesized—correctly—that baroreflex failure linked neck irradiation in the distant past with cardiovascular instability years later.

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 were encased in a rigidified carotid sinus, such as due to arteriosclerosis after neck irradiation, then arterial baroreflex failure could result. Because of the “debuffering” the blood pressure is allowed to increase and decrease excessively.

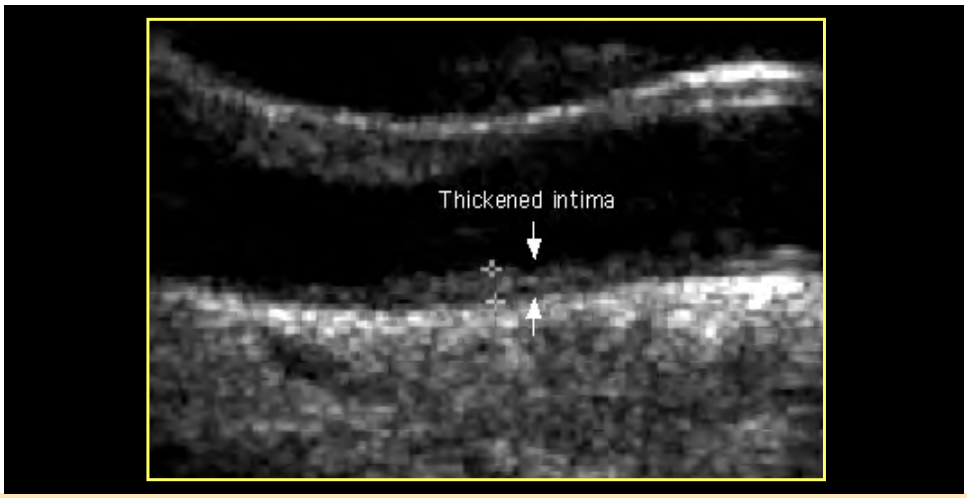


Fig. 295: Carotid arteriosclerosis in baroreflex failure after neck irradiation. *In this patient baroreflex failure developed years after therapeutic irradiation of the neck. There is carotid arterial intimal wall thickening.*

Baroreflex failure is often very difficult to treat. Some patients have improvement with clonidine. A carotid sinus stimulator that could be switched on and off when needed might be helpful, but this hasn't been studied.

Harlequin Syndrome

This dramatic but rare syndrome involves the sudden onset of facial flushing and sweating on one side of the head after exercise or heat exposure. The cause is disruption of sympathetic nerve fibers, which ascend in the chest and neck alongside the carotid artery.

The flushing and sweating occur on the side opposite the sympathetic lesion, presumably because of a form of compensatory activation of the intact sympathetic pathway. The

affected side remains relatively dry and pale.

Rarely, Horner's syndrome and the harlequin syndrome occur together; when this happens ptosis and miosis occur on the same side as the lesion, while the flushing and sweating occur on the opposite side.

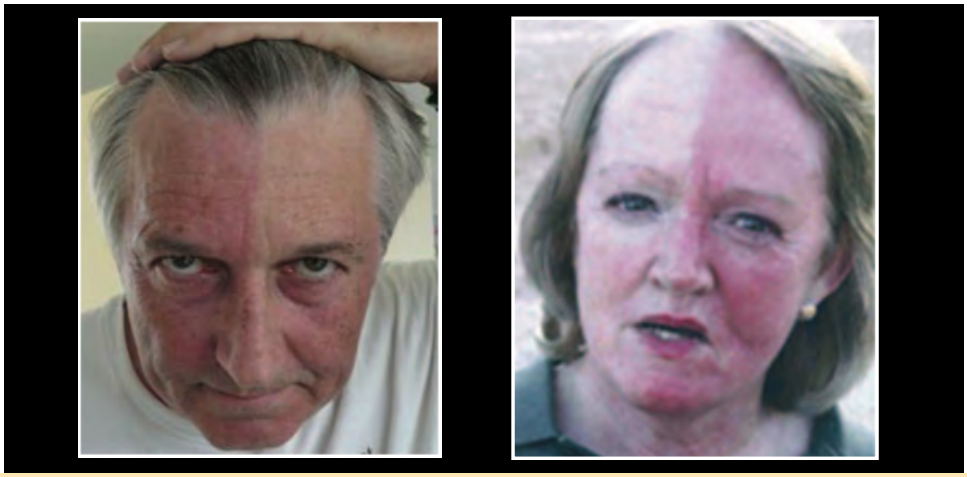


Fig. 296: Harlequin syndrome. *There is flushing and sweating on the side opposite the sympathetic lesion.*

Post-ETS Syndrome

Bilateral endoscopic thoracic sympathectomy (ETS) is done at several centers world-wide. There has been aggressive marketing of the procedure as a safe cure for hyperhidrosis; however, there can be long-term side effects.

These include "compensatory hyperhidrosis" below the level of the surgery (in the abdomen, back, groin, or feet). The mechanism of compensatory hyperhidrosis is unknown. This might represent a form of activation of a portion of the

sympathetic cholinergic system when another portion is disabled.

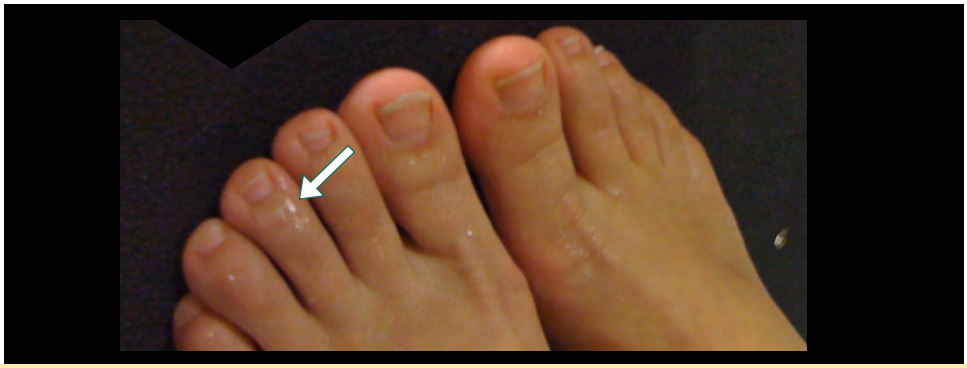


Fig. 297: Post-ETS compensatory hyperhidrosis. *Hyperhidrosis below the level of the surgery can be a long-term side effect of endoscopic thoracic sympathectomy (ETS).*

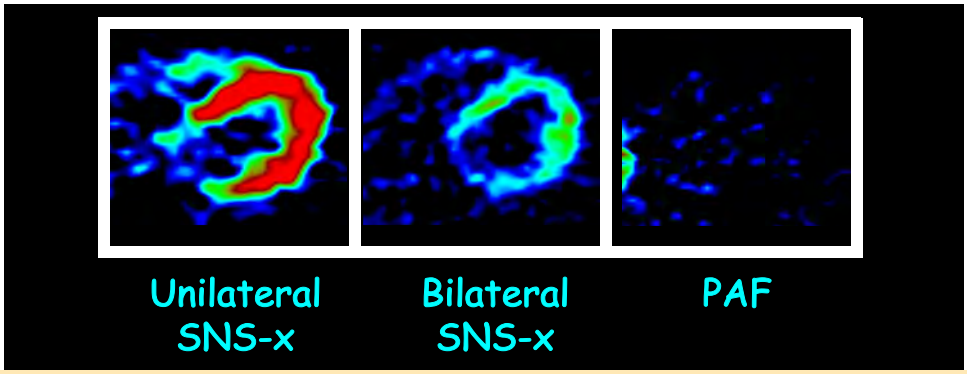


Fig. 298: Post-ETS partial cardiac denervation. *Partial cardiac sympathetic denervation is revealed here by ^{18}F-dopamine scanning in a patient who had undergone bilateral endoscopic thoracic sympathectomies for hyperhidrosis.*

After undergoing ETS some people experience a "post-ETS" syndrome that includes decreased exercise tolerance, insomnia, decreased heart rate responsiveness, and apathy. One may speculate that these non-specific symptoms are related to effects of partial cardiac denervation.

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 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, cigarette smoking, and co-morbidities such as coronary artery disease, diabetes, or obesity.

The blood pressure is determined by numerous interactions among the central nervous system, heart, kidneys, adrenal glands, and blood vessels.

The body has many effectors that mediate these interactions. You probably recognize some of the effectors in the diagram in Fig. 299. The parasympathetic nervous system (PNS) and the sympathetic noradrenergic system (SNS) use the neurotransmitters acetylcholine and norepinephrine, the sympathetic adrenergic system (SAS) uses the hormone epinephrine, and the renal DOPA/dopamine system (DDA) uses dopamine as an autocrine/paracrine substance. Other effectors include the renin-angiotensin-aldosterone (RAS) system, the

hypothalamic-pituitary-adrenocortical (HPA) system, arginine vasopressin (AVP), atrial natriuretic peptide (ANP), nitric oxide (NO), cytokines (CTK), and prostaglandins (PG).

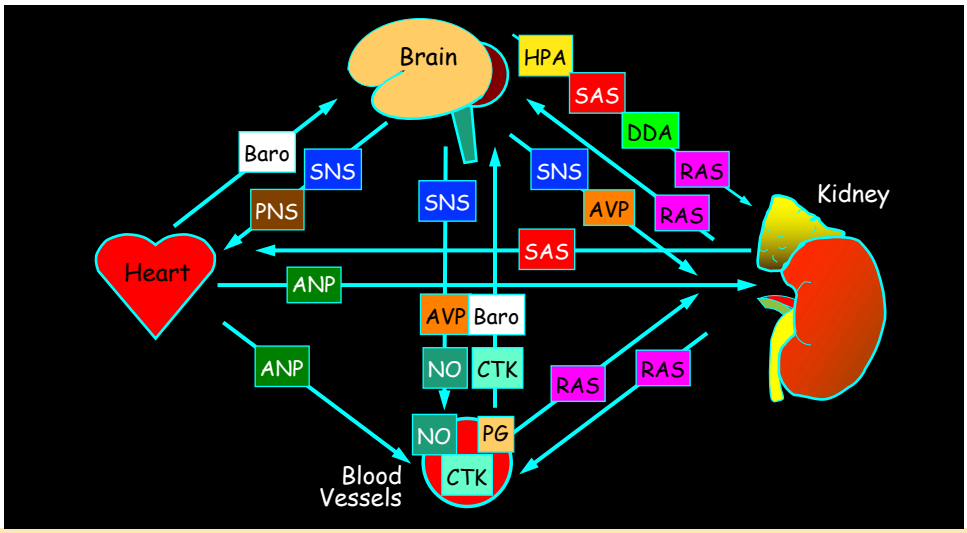


Fig. 299: Multiple determinants of blood pressure. *The central nervous system, heart, kidneys, and blood vessels interact to determine the blood pressure.*

Baroreflex afferents from the heart and large blood vessels (especially the carotid sinus region in humans) to the brain provide inhibitory inputs that initiate multiple negative feedback loops.

A complex network involving many chemical messengers acts as if there were a "barostat" that keeps blood pressure within bounds.

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 role in the maintenance of sodium balance in the body. Dietary sodium restriction stimulates RAS activity;

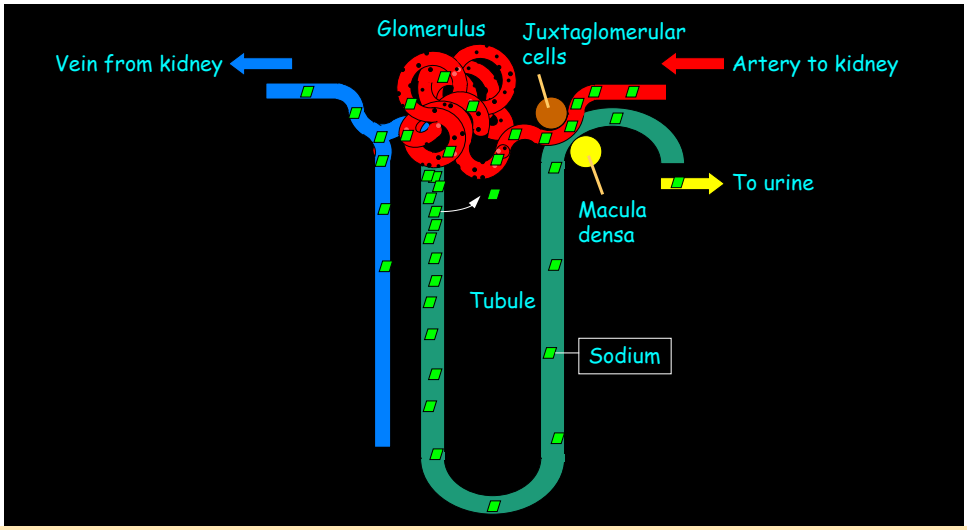


Fig. 300: A kidney nephron. *Emphasized here is involvement of the juxtaglomerular apparatus in renal sodium handling.*

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 return it the bloodstream. The sodium that escapes this recycling stays in the filtrate and eventually leaves the body in the excreted urine.

Specialized tubule cells called the macula densa (from the Latin for “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. Renin is the first station in a negative feedback loop.

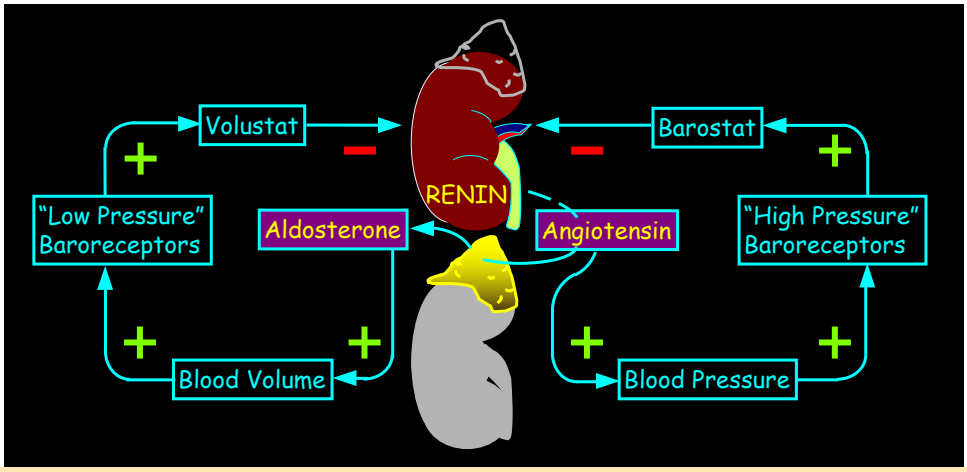


Fig. 301: Homeostats and the RAS. *Depicted here are hypothesized relationships of components of the renin-angiotensin-aldosterone system to the “volustat” and “barostat.”*

The juxtaglomerular cells act as sensors themselves. They detect stretch, and therefore the distending pressure, in the blood vessels to the kidneys. A fall in the distending pressure leads to release of renin. This means that at least two homeostats regulate the RAS by negative feedback. The variables that are kept within bounds are the pressure in the blood vessels approaching the glomeruli and the concentration of sodium in the glomerular filtrate.

Stretch receptors in two places outside the kidneys also contribute to regulation of renin release. “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 a potent vasoconstrictor. Angiotensin II therefore increases blood pressure. Predictably, both ACE inhibitors and angiotensin II receptor blockers are effective to treat hypertension. Another key effect of angiotensin II, which establishes the RAS as the body’s main system for regulating sodium balance, is to stimulate the adrenal cortex to release aldosterone. Aldosterone increases reabsorption of sodium from the tubules in the kidneys.

Activation of the RAS therefore increases the blood pressure by constricting blood vessels, via the vasoconstrictor effect of angiotensin II, and by increasing the blood volume, via the sodium-retaining effect of aldosterone. Thus, one can conceptualize the RAS as an effector for both the barostat and the volustat.

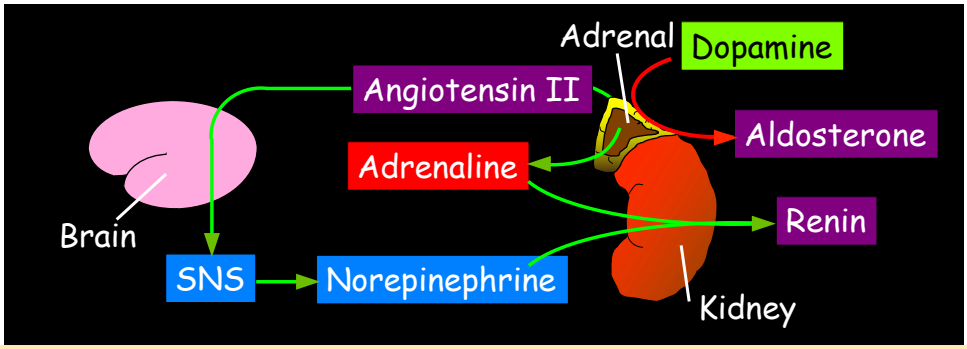


Fig. 302: Catecholamine-RAS relationships. *Catecholamine systems interact in several ways with the renin-angiotensin-aldosterone system (RAS).*

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

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 internal 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 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.

PHEOCHROMOCYTOMA (PHEO)

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

"Pheos" are rare tumors of cells that make catecholamines.

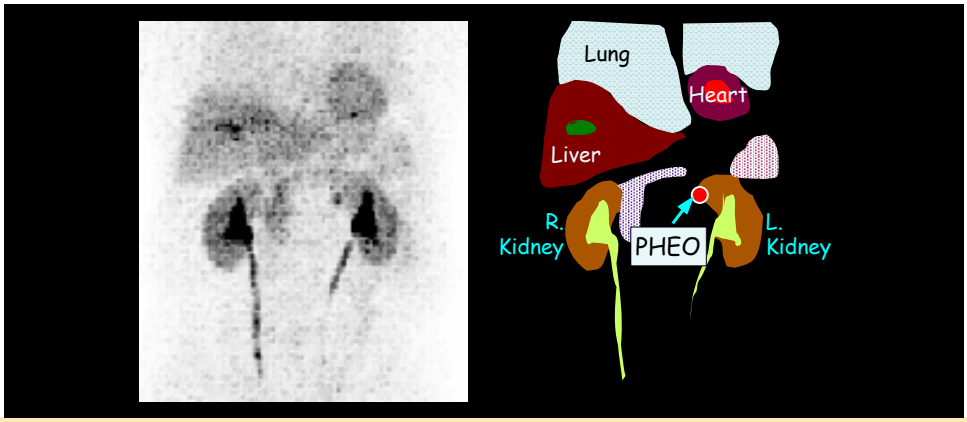


Fig. 303: Pheochromocytoma. *Pheochromocytomas ("pheos") usually are located in the adrenal gland.*

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

Most pheos are benign and can be removed surgically. This means that pheos represent a potentially curable form of 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 in a symptomatic patient, pheo is ruled out.

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, ^{18}F-dopamine) may be done.

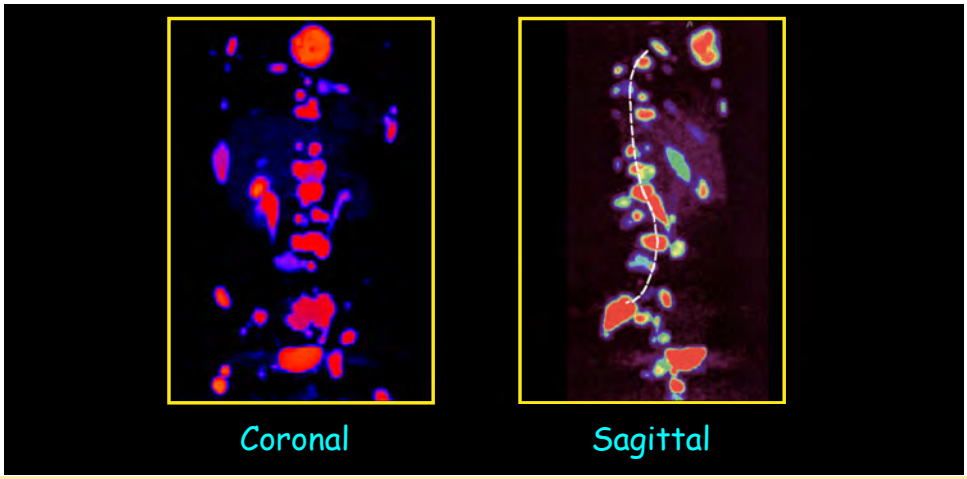


Fig. 304: Metastatic pheochromocytoma. *Multiple foci of ^{18}F-dopamine-derived radioactivity are revealed in this patient with pheochromocytoma that has metastasized widely to bone.*

Clonidine decreases sympathetic noradrenergic system (SNS) outflows and thereby decreases plasma norepinephrine (NE) levels. If a patient had high blood pressure due to high SNS 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.

Rarely, pheochromocytoma is malignant and metastasizes. Metastatic pheo can be detected by a variety of specialized imaging agents and also biochemically by measuring plasma levels of 3-methoxytyramine, the O-methylated metabolite of dopamine.

Stress Cardiopathy in a Senator

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

I know of the case of a U.S. Senator who 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, adrenaline was infused IV. Unexpectedly, this worsened his heart failure, and the patient almost died. The infusion was stopped, and gradually he recovered.

He then underwent a workup for pheo that included ^{18}F-dopamine PET scanning and measurement of plasma metanephrines. Both tests were positive. A pheo was identified surgically and removed safely. 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 suspicion of pheo. Second, increases in plasma levels of catecholamines by a pheo can be sufficiently massive to cause a form of heart failure from stress cardiopathy (described later). 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"

Pheochromocytomas (pheos) are rare. Most patients who undergo a diagnostic workup for a pheo prove not to have the tumor. The term, “pseudopheochromocytoma,” or “pseudopheo,” 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 tachycardia syndrome.

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

Glucagon injection into pseudopheo patients produces a disproportionately large increase in plasma adrenaline levels. This type of reaction 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.

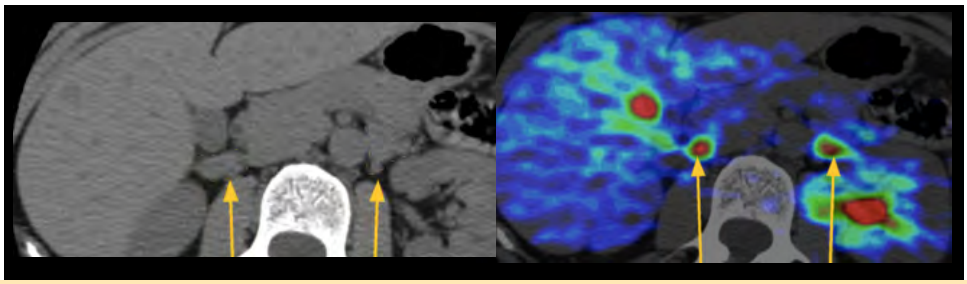


Fig. 305: Bilateral adrenomedullary hyperplasia in pseudopheo. *The arrows point to enlarged adrenal medullas (bilateral adrenomedullary hyperplasia) in this patient with pseudopheo.*

I know of a case of pseudopheo and postural tachycardia syndrome where the patient had bilateral adrenomedullary hyperplasia. There was marked improvement after adrenalectomy on one side and selective adrenal medullectomy on the other side.

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. The situation in heart failure provides a good example.

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

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.

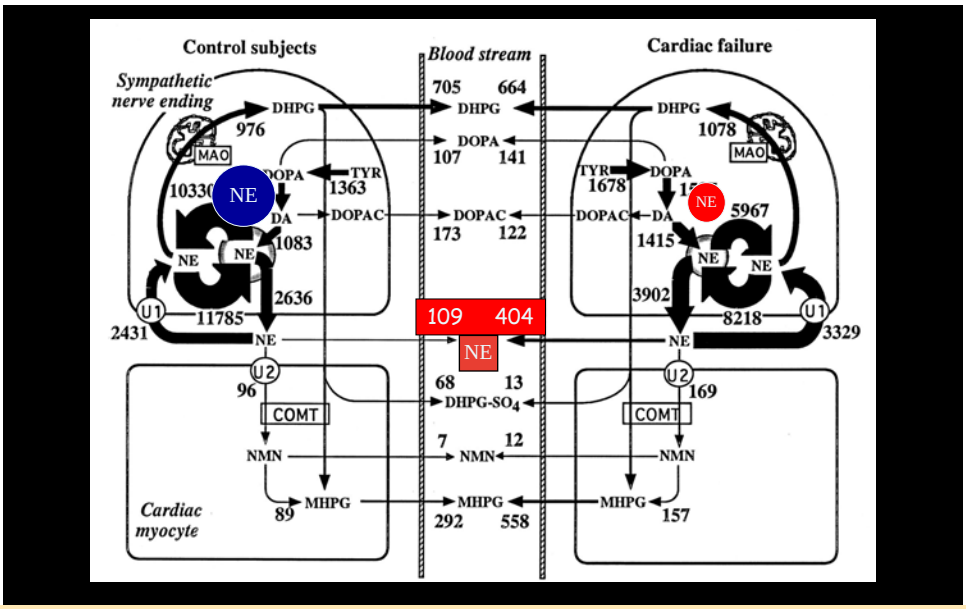


Fig. 306: Cardiac sympathetic stimulation in heart failure. *Heart failure involves increased norepinephrine release from sympathetic nerves at the same time that there is depletion of norepinephrine stores.*

Although this can improve the pump function of the heart, 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.

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.

Thinking in homeostatic terms one can grasp the development and progression of autonomic abnormalities in heart failure. Suppose a person was born with 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 sympathetic noradrenergic system (SNS) from baroreceptor restraint, the brain would direct a compensatory increase in cardiac SNS outflow. Increased norepinephrine (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. This is an allostatic state, and there is a progressive accumulation of allostatic load. 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 abnormal heart rhythms (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 also result in buildup of catecholamines in the cytosol, where they can be rendered "autotoxic" by spontaneous and enzymatic oxidation. 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 symptomatic 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

activation of the sympathetic adrenergic system (SAS) and adrenomedullary release of adrenaline. Rather than augmenting left ventricular myocardial contractility, too much adrenaline is toxic to myocardial cells. Myocardial contractility would decrease further, "stress cardiopathy" would set in, and the pulmonary edema would worsen.

In several ways, physiologic negative feedback loops would have now 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.

Stress Cardiopathy

All emotions entail changes in heart functions. As noted previously, this fact was recognized by one of the giants in the history of medicine and physiology, William Harvey, in the 1600s (Fig. 174).

Pathological studies about how distress can produce sudden death were not done until the past century. In 1907, about a dozen years after the discovery of the cardiovascular stimulatory effects of adrenaline, it was demonstrated that infusion of adrenaline can lead to the death of heart muscle. The heart muscle cells rupture and die of overstraining. A particular microscopic change called "contraction band necrosis" develops.

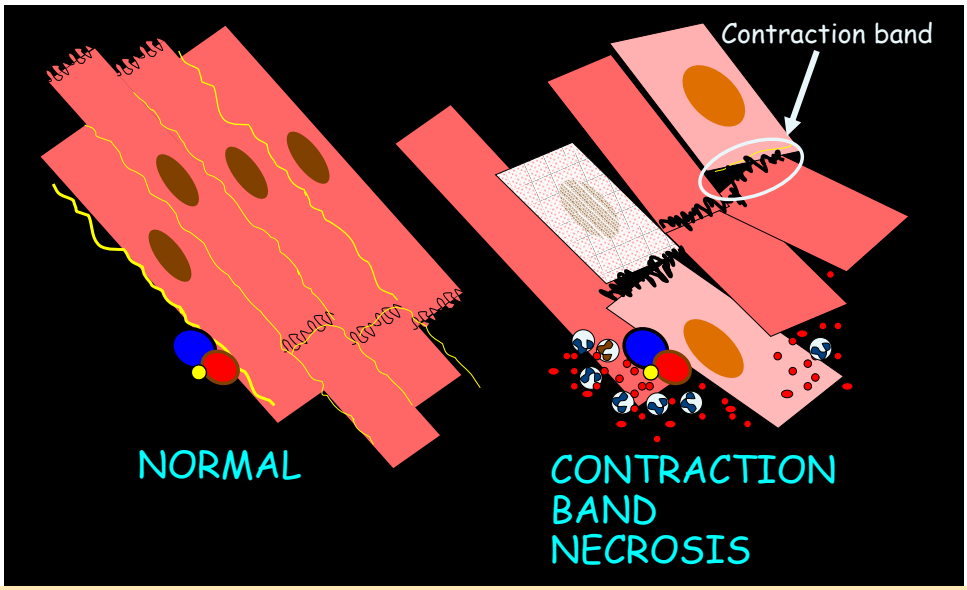


Fig. 307: Contraction band necrosis. *Contraction band necrosis of heart muscle cells is a typical microscopic post-mortem finding in stress cardiopathy.*

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

TAKOTSUBO CARDIOPATHY

A relatively recently described form of distress-induced acute heart failure is *takotsubo* cardiopathy, so named because of a peculiar abnormal shape of the heart in most 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, at least in this respect, 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

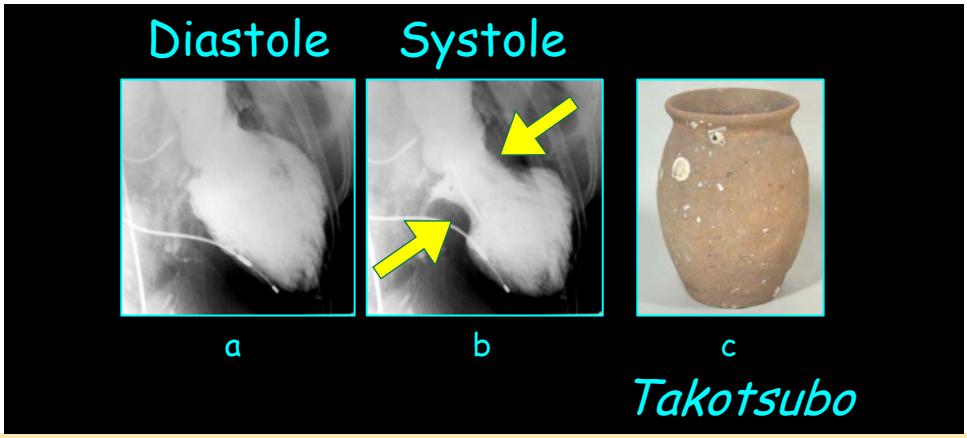


Fig. 308: Takotsubo cardiopathy. *In takotsubo cardiopathy, during systole the apex of the heart balloons out, while the base of the heart contracts normally (yellow arrows), giving the appearance of a takotsubo.*

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.

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 IV 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.

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 adenyl 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 toxic metabolites that interfere with the functions of numerous proteins required for cellular integrity. Third, adrenaline-mediated increased entry of ionized calcium into the cytoplasm could so contract the cells that they rupture—hence the term, "contraction band necrosis."

Stroke

Stroke from intra-cranial bleeding (intracerebral hemorrhage or subarachnoid hemorrhage) is associated with a high frequency of electrocardiographic abnormalities. The most common of these is prolongation of the heart rate-corrected QT interval (the

QTc interval). Large, inverted T waves and U waves also occur.

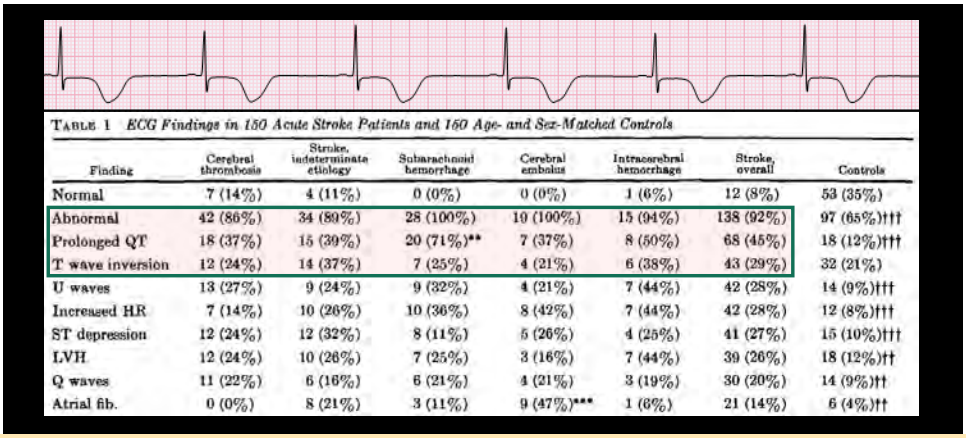


TABLE 1 *ECG Findings in 150 Acute Stroke Patients and 150 Age- and Sex-Matched Controls*

Finding	Cerebral thrombosis	Stroke, indeterminate etiology	Subarachnoid hemorrhage	Cerebral embolus	Intracerebral hemorrhage	Stroke, overall	Controls
Normal	7 (14%)	4 (11%)	0 (0%)	0 (0%)	1 (6%)	12 (8%)	53 (35%)
Abnormal	42 (86%)	34 (89%)	28 (100%)	10 (100%)	15 (94%)	138 (92%)	97 (65%)†††
Prolonged QT	18 (37%)	15 (39%)	20 (71%)**	7 (37%)	8 (50%)	68 (45%)	18 (12%)†††
T wave inversion	12 (24%)	14 (37%)	7 (25%)	4 (21%)	6 (38%)	43 (29%)	32 (21%)
U waves	13 (27%)	9 (24%)	9 (32%)	4 (21%)	7 (44%)	42 (28%)	14 (9%)†††
Increased HR	7 (14%)	10 (26%)	10 (36%)	8 (42%)	7 (44%)	42 (28%)	12 (8%)†††
ST depression	12 (24%)	12 (32%)	8 (11%)	5 (26%)	4 (25%)	41 (27%)	15 (10%)†††
LVH	12 (24%)	10 (26%)	7 (25%)	3 (16%)	7 (44%)	39 (26%)	18 (12%)††
Q waves	11 (22%)	6 (16%)	6 (21%)	4 (21%)	3 (19%)	30 (20%)	14 (9%)††
Atrial fib.	0 (0%)	8 (21%)	3 (11%)	9 (47%)***	1 (6%)	21 (14%)	6 (4%)††

Fig. 309: EKG abnormalities that are new at the time of a stroke. *Acute stroke is associated with several EKG abnormalities. The most common new abnormality is QTc prolongation, especially in stroke from intra-cranial bleeding.*

These EKG abnormalities are also associated with elevations of cardiac-specific enzymes and with subendocardial necrosis. It seems likely that this reflects substantial sympathetic noradrenergic and adrenergic stimulation, as in stress cardiopathy.

Subendocardial necrosis does not correspond to coronary anatomy. Recall that the sympathetic nerves to the heart travel with the epicardial coronary arteries and then dive into the myocardium from the outside. Local release of norepinephrine at the level of the delicate nerve terminals could exert toxic effects on the nearby myocardial cells.

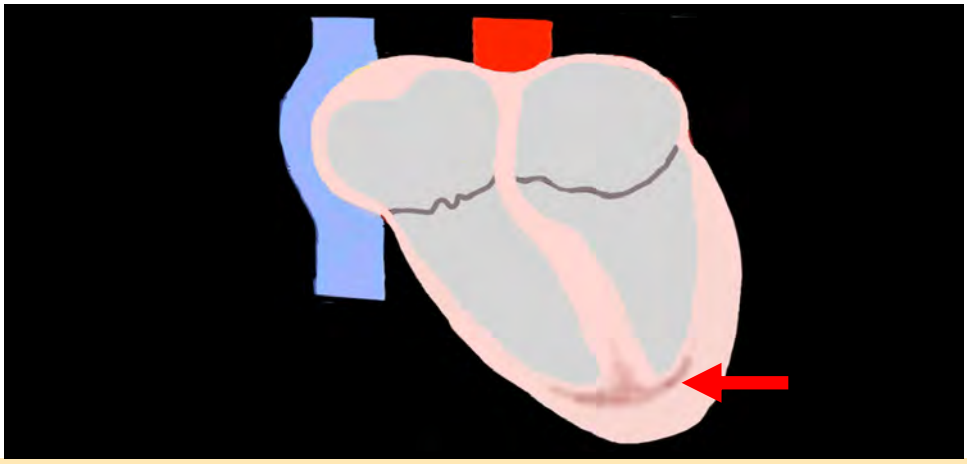


Fig. 310: Subendocardial necrosis. *Subendocardial necrosis can occur in stroke from intra-cranial bleeding.*

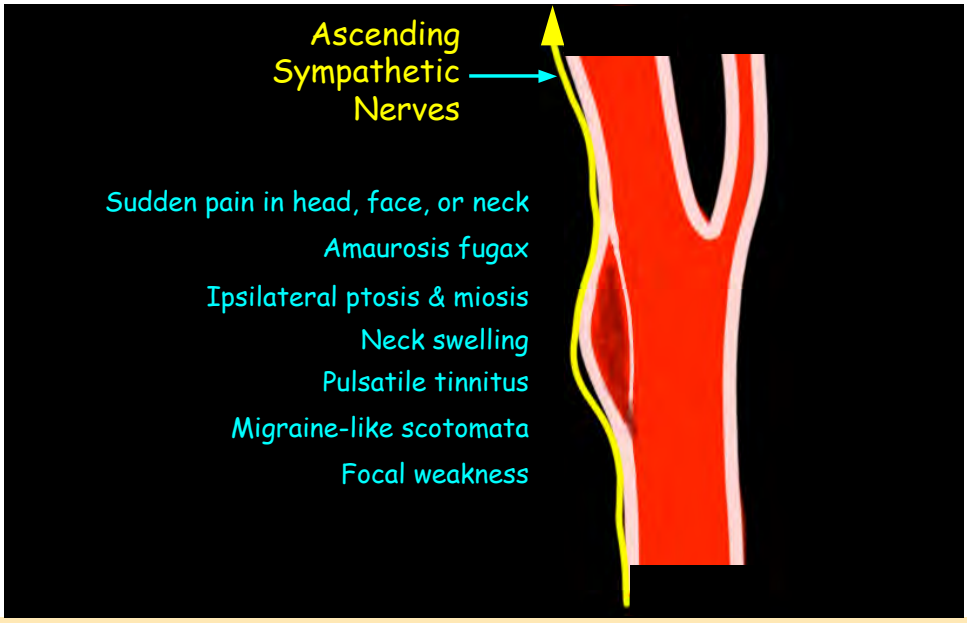


Fig. 311: Carotid artery dissection. *Dissection of the carotid artery produces a distinctive syndrome that includes ipsilateral ptosis (droopy eyelid) and miosis (constricted pupils) from interference with ascending traffic in sympathetic nerves.*

Dissection of the carotid artery manifests with a syndrome that in some ways resembles acute stroke, with sudden pain in the

face or neck, amaurosis fugax (transient, painless loss of vision), and focal weakness. This syndrome also can include neck swelling, pulsatile tinnitus (ringing in the ears), and scotomata (bright perceived flashes) as in migraine.

CHRONIC ORTHOSTATIC INTOLERANCE (COI)

In the clinical practice of adolescent/adult autonomic medicine, probably the most commonly encountered complaint is chronic orthostatic intolerance (COI), a persistent inability to tolerate standing up. This section considers two forms of COI, autonomically mediated syncope (also called neurocardiogenic syncope, vaso-vagal syncope, vasodepressor syncope, neurally mediated hypotension, and fainting) and postural tachycardia syndrome (POTS).

Autonomically Mediated Syncope

Synopsis:
Mainly young adult women or children.
Normal pulse rate during standing.
Associated with several non-specific associated problems (inability to tolerate prolonged standing, heat intolerance, fatigue, chest pain, heart "flip-flops," brain fog, exercise intolerance).
Variable outlook, can improve.
Not life-threatening.

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.

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.)

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.

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

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.

Many patients with frequent episodes of autonomically mediated syncope recognize early symptoms and signs of a fainting reaction coming on and are able to abort the episode before frank loss of consciousness occurs.

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.

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, and headache. POTS more commonly involves symptoms of dysfunction in multiple body systems.

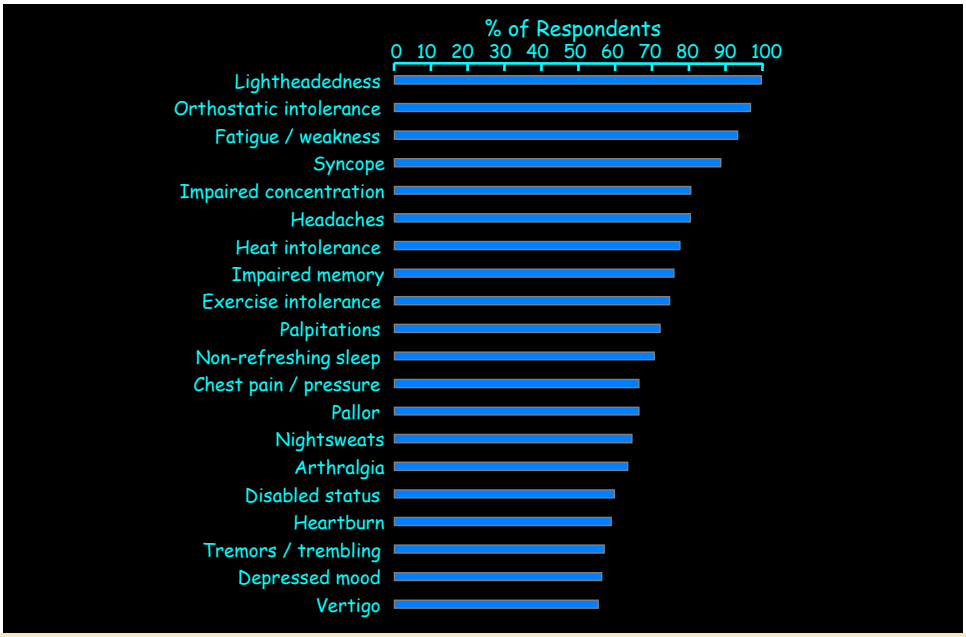


Fig. 312: Symptoms in patients with recurrent syncope. *Patients with frequent episodes of autonomically mediated syncope usually have many other symptoms. The frequencies are based on the author's experience from evaluations of patients referred to the NIH for chronic orthostatic intolerance.*

Tilt table testing can provoke a sudden fall in blood pressure, called neurally mediated hypotension (NMH) or tilt-evoked hypotension (TEH), in patients with autonomically mediated syncope.

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

SYMPATHOADRENAL IMBALANCE

Autonomically mediated syncope is associated with elevated plasma adrenaline levels.

Increased activity of the sympathetic adrenergic system (SAS) is a characteristic feature of autonomically mediated syncope. Unfortunately, provocative tilt table testing as done in most centers rarely includes serial blood sampling for assays of adrenaline levels, and this prominent finding usually is missed, despite clinical signs of SAS hyperactivity such as pallor, sweating, and pupillary dilation.

Autonomically mediated syncope also entails a larger increase in sympathetic adrenergic 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 the plasma adrenaline level than in the simultaneously measured plasma norepinephrine level. This particular pattern of alterations in activities of two components of the autonomic nervous system is the main reason for referring to the condition as autonomically mediated syncope.

Injection of adrenaline into a healthy person does not evoke fainting. This 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 (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.

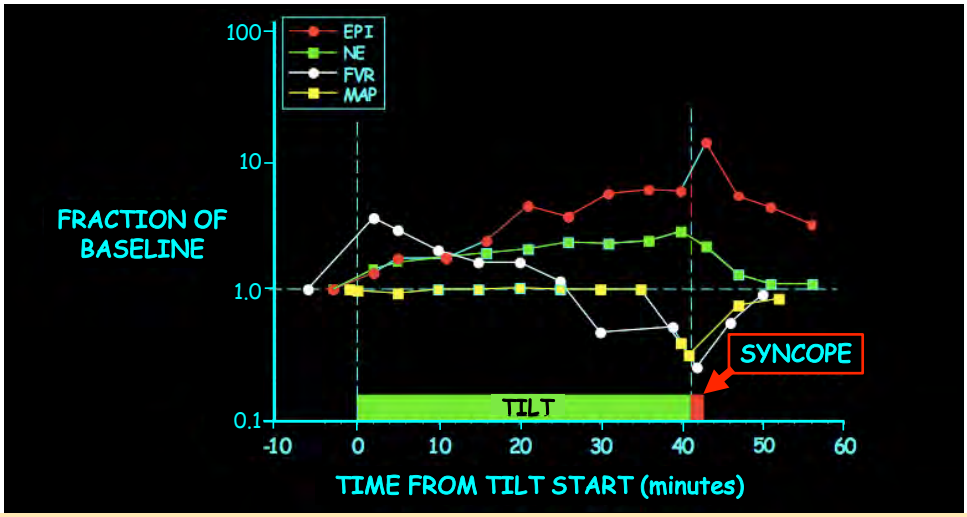


Fig. 313: Tilt-evoked hypotension and syncope. *Note the decrease in forearm vascular resistance (FVR) and mirror image increase in plasma epinephrine (EPI) and greater increase in EPI than norepinephrine (NE)—i.e., "sympathoadrenal imbalance"—before the fall in mean arterial pressure (MAP).*

Since SAI can precede episodes of autonomically mediated syncope, SAI may be a causal factor in fainting. The data shown in Fig. 313 illustrate this phenomenon.

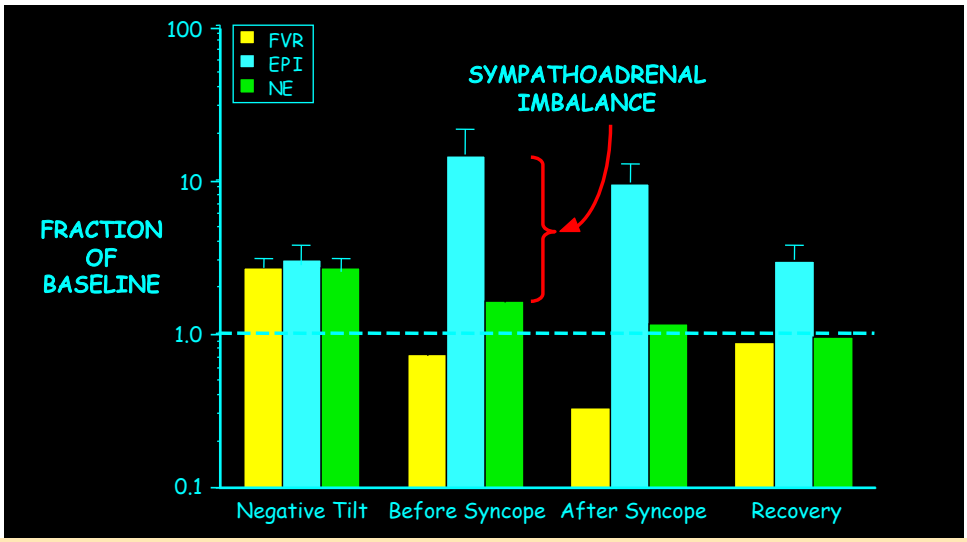


Fig. 314: Sympathoadrenal imbalance (SAI) before tilt-evoked syncope. *Autonomically mediated syncope involves a particular neuroendocrine pattern. Before the acute episode plasma adrenaline (epinephrine, EPI) levels are high, while the sympathetic noradrenergic system as indicated by plasma norepinephrine (NE) levels is less activated or even shuts down. Because of SAI-induced skeletal muscle vasodilation, there is a fall in forearm vascular resistance (FVR).*

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

Increased sweating often 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.

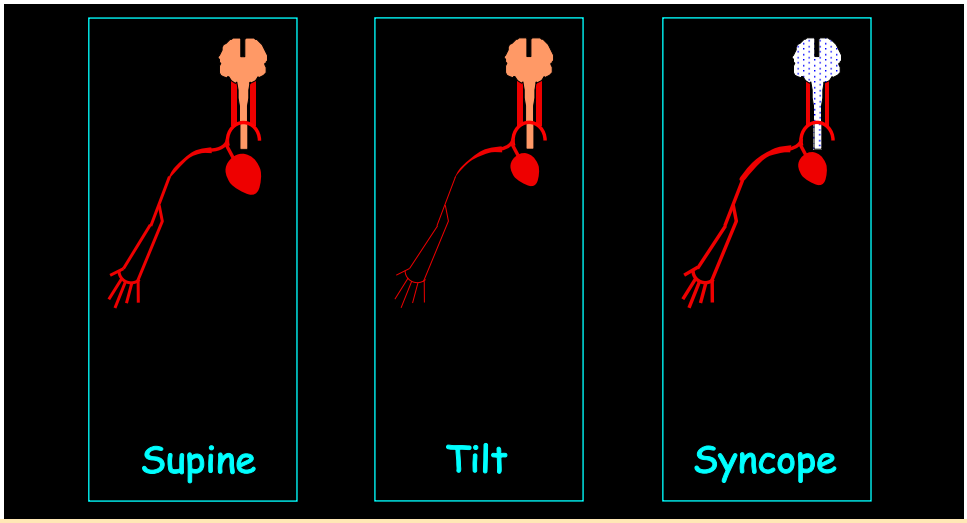


Fig. 315: Concept diagram for tilt-evoked syncope. *Tilting decreases venous return to the heart and cardiac output. This normally is countered by reflexive stimulation of the sympathetic noradrenergic system (SNS), resulting in skeletal muscle vasoconstriction, and delivery of blood to he brain is maintained. In autonomically mediated syncope there is a fall in skeletal muscle vascular resistance. The cardiac output is shunted toward the skeletal muscle—at the expense of blood flow to the brain. It has been suggested that when the situation reaches consciousness there is a distress response, which exacerbates the sympathoadrenal imbalance and precipitates a vicious that rapidly results in a critical fall in blood flow to the brain.*

These signs can distinguish autonomically mediated syncope from somatization, factitious syncope, and malingering.

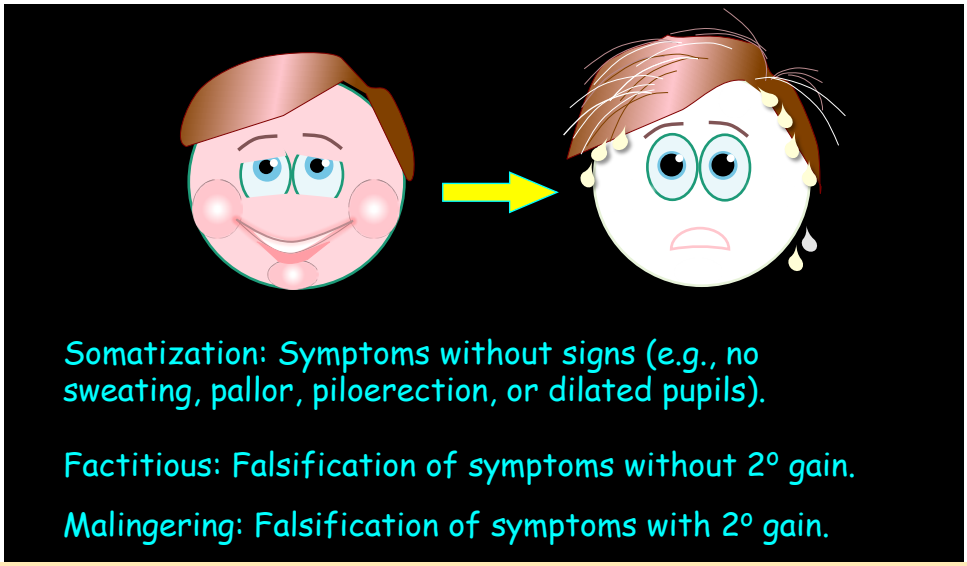


Fig. 316: The picture of autonomically mediated syncope. *Signs of adrenaline excess such as pallor, sweating, piloerection, and mydriasis cannot be explained by somatization, factitious fainting, or malingering.*

FAINTING WHILE LECTURING TO AUTONOMICS EXPERTS

Several years ago, at a combined meeting of the American Autonomic Society and the European Federation of Autonomic Societies in Vienna, I was in the audience when there was a remarkable demonstration of autonomically mediated syncope—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 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 became alert 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."

There was no mention of adrenaline.

FAINTING IN ASTRONAUTS

After prolonged exposure to zero-gravity during spaceflight, returning astronauts all have orthostatic intolerance on landing day. In female astronauts the risk of syncope during head-up tilt table testing on landing day is essentially 100%.

The period of orthostatic intolerance in returning astronauts is quite short, in contrast to the situation in chronic orthostatic intolerance.

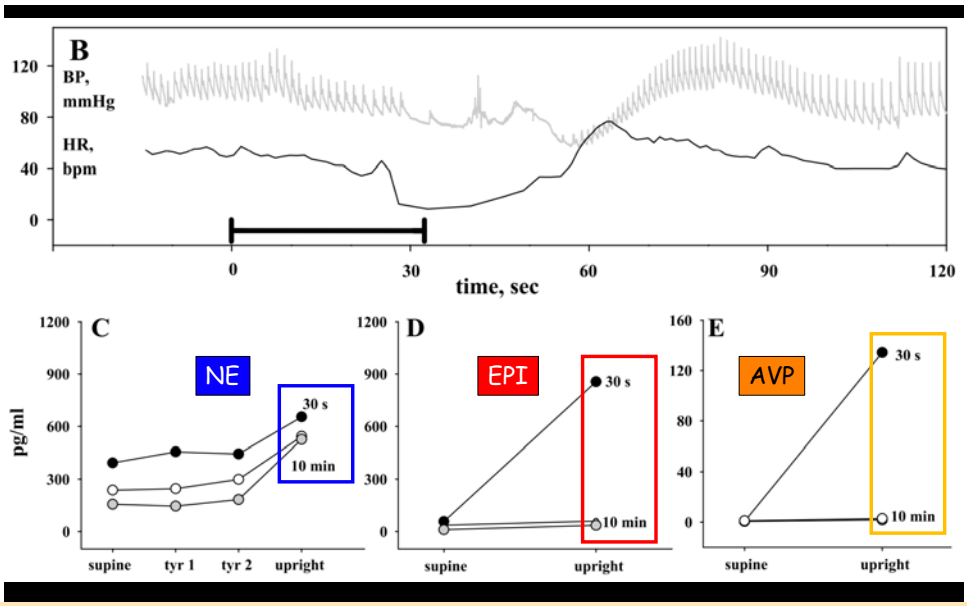


Fig. 317: Sympathoadrenal imbalance (SAI) and tilt-evoked hypotension (TEH) in an astronaut. *Open circles are pre-flight, gray 3 days after landing, and black landing day. On landing day there is rapid TEH associated with SAI, as indicated by a much larger proportionate increment in plasma epinephrine (EPI) than norepinephrine (NE). There is also a marked tilt-evoked increase in arginine vasopressin (AVP) on landing day.*

Vigorous, frequent bouts of exercise during spaceflight and intravenous saline infusion upon return decrease the risk.

Postural Tachycardia Syndrome (POTS)

Postural tachycardia syndrome (POTS) probably is the most common form of chronic orthostatic intolerance (COI).

There are fundament gaps in knowledge about underlying mechanisms of POTS. Some investigators have viewed POTS as synonymous with COI. The condition has features that are

also suggestive of hyperdynamic circulation syndrome or "neurasthenia." Other autonomics experts don't believe POTS involves an autonomic medical problem at all and instead is a manifestation of a psychiatric condition such as panic/anxiety.

Synopsis:
Mainly young adult women.
Too rapid pulse rate during standing.
Non-specific associated problems (chronic fatigue, 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.

In general medical practice, the finding of an excessive increase in heart rate with standing 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 POTS.

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

At least some of the symptoms of POTS are thought to reflect increased effects of the catecholamines norepinephrine or

adrenaline, from overactivity of the sympathetic noradrenergic system (SNS), the sympathetic adrenergic system (SAS), or both. Cardiac norepinephrine spillover is increased in POTS patients even while they are supine.

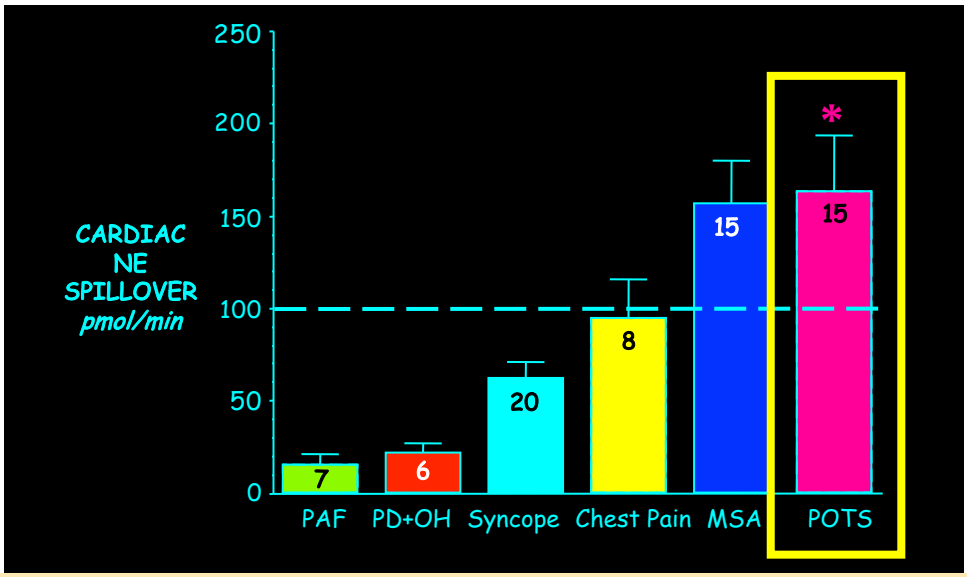


Fig. 318: Cardiac norepinephrine spillover in dysautonomias. *Even when supine, POTS patients have evidence of increased cardiac sympathetic outflow as indicated by cardiac norepinephrine (NE) spillover into the coronary sinus. The numbers in the bars are the numbers of patients.*

THE KEY TO POTS IS THE "S"

The key word in postural tachycardia syndrome is not "tachycardia" but "syndrome."

POTS is a syndrome, not a disease. In most cases the cause is not determined.

A syndrome is a set of symptoms that occur together. Merely having a fast pulse rate while standing is not a syndrome. POTS always involves more than orthostatic tachycardia alone.

POTS patients not only have too rapid a pulse rate when they stand, they also have several other symptoms.

Patients with POTS always have several other symptoms, such as orthostatic intolerance, "brain fog," exercise intolerance, chronic fatigue, a tendency to faint, chest pain, pain in the back of the neck or shoulders ("coat hanger phenomenon"), headache, cool, sweaty extremities, heat intolerance, palpitations, gastrointestinal complaints (nausea, early satiety, slow gastrointestinal transit, bloating, gastroesophageal reflux, abdominal pain), disturbed sleep, panic, anxiety, depression, and generalized disability.

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

PRIMARY VS. SECONDARY CAUSES OF POTS

Trying to identify a specific pathophysiologic mechanism of POTS in a particular patient can be a great challenge to clinicians.

Some sort of schema or algorithm is necessary for a rational approach.

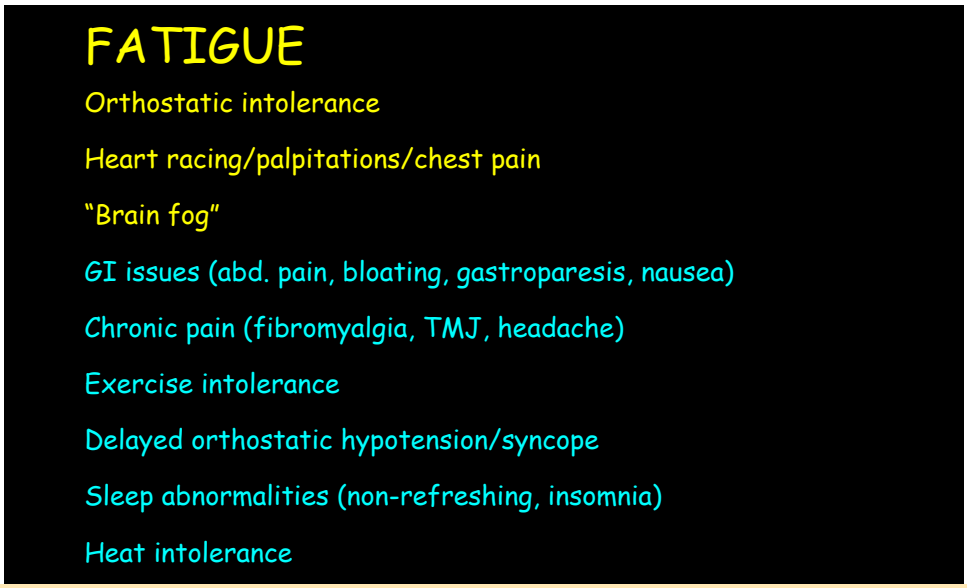


Fig. 319: POTS symptoms. *POTS is a syndrome. It is associated with a variety of symptoms that, when considered individually, are not specific for any particular disease.*

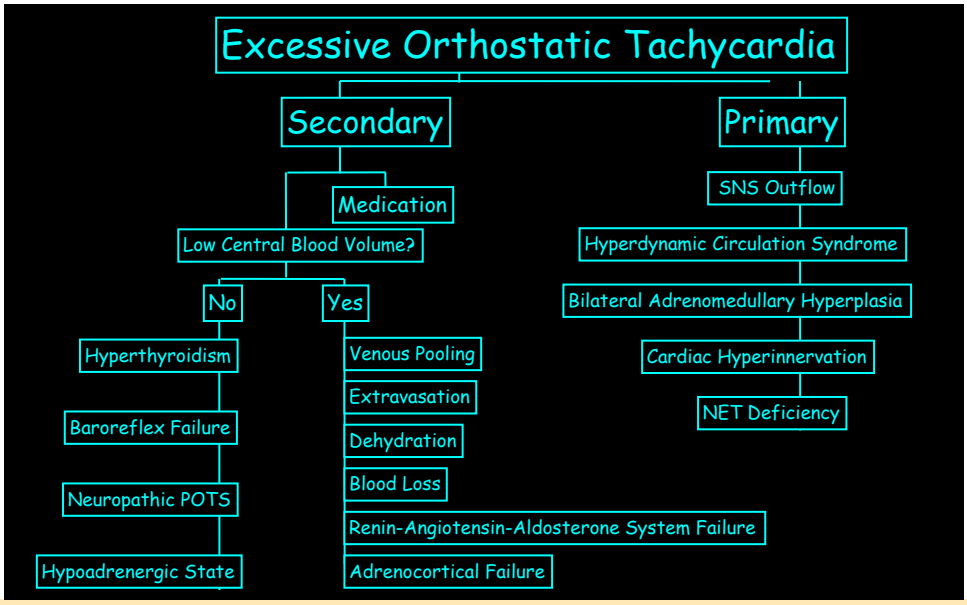


Fig. 320: A pathophysiological schema for POTS. *This algorithm helps systematize the clinical diagnostic approach. Actually carrying out the relevant tests is virtually never done.*

Blood Volume and POTS

Researchers have thought that usually in POTS, sympathetic nerve traffic to the heart is increased as a form of compensatory activation. 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.

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

Low blood volume in turn can result from blood loss, from failure of the bone marrow to produce an adequate number of red blood cells, or from failure of hormone systems such as the renin-angiotensin-aldosterone system.

An “effective” low blood volume can occur, when the blood pools excessively in the veins in the pelvis and abdomen after a person stands. Consistent with the blood pooling idea, inflation of a military anti-shock trousers (MAST) suit reduces substantially the increase in heart rate in response to orthostasis in patients with POTS.

An excessive shift in blood volume distribution might reflect a lack of muscular “tone” in the vein walls. For instance, a problem with the protein structure of blood vessel walls could lead to POTS in Ehlers-Danlos syndrome.

"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 have proposed that excessive orthostatic tachycardia in Grinch syndrome patients is a compensation for low stroke volume. Exercise training is often helpful in such patients.

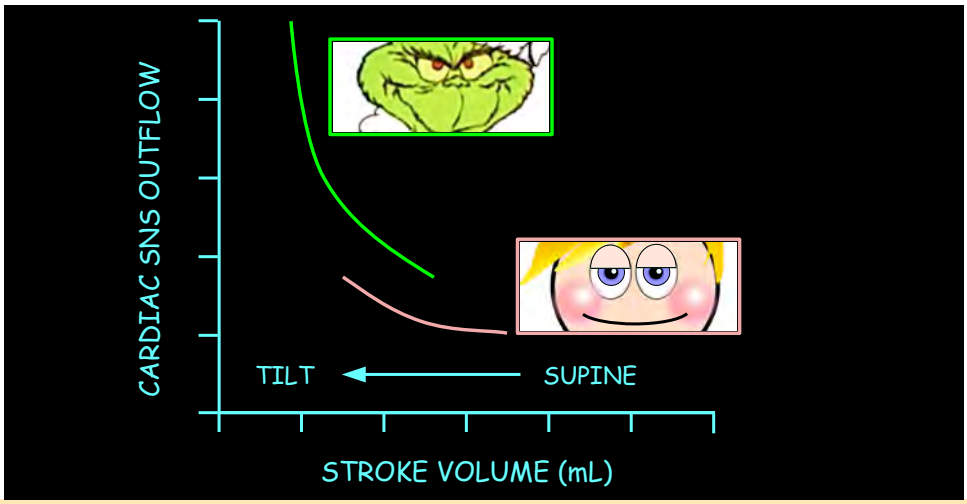


Fig. 321: Grinch syndrome and POTS. *Grinch syndrome is named for the Dr. Seuss character who had a heart "two sizes too small." This concept graph illustrates how a patient with Grinch syndrome might respond to head-up tilt with an excessive increase in cardiac sympathetic outflow.*

We diagnosed Grinch syndrome in a POTS patient—an adolescent with pectus excavatum and a low cardiac stroke index (stroke volume adjusted for body surface area).

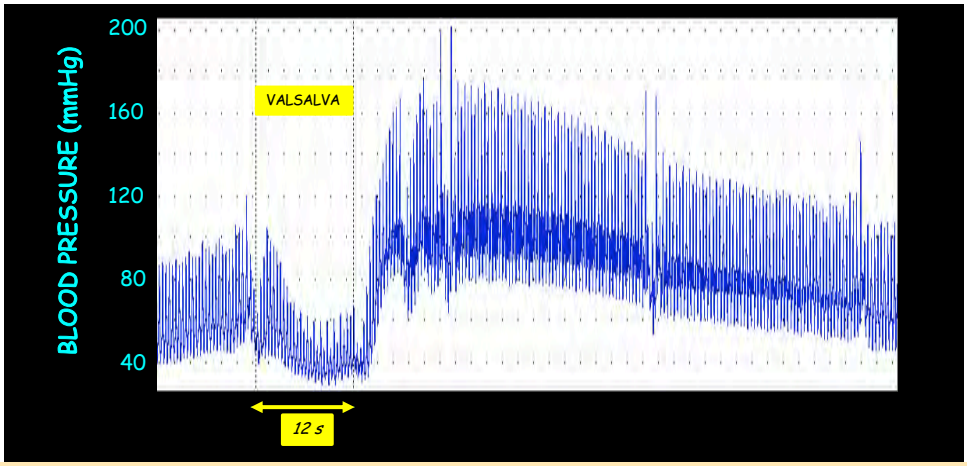


Fig. 322: Excessive blood pressure (BP) overshoot in Grinch syndrome. *This young adult man with severe pectus excavatum had COI and frequent fainting. Grinch syndrome was diagnosed from his low cardiac stroke index and excessive orthostatic tachycardia. Note the excessive BP overshoot in Phase IV of the Valsalva. During tilt table testing the patient developed sympathoadrenal imbalance, forearm vasodilation, sweating, and tilt-evoked hypotension.*

The pectus excavatum may have been severe enough to actually limit the growth of his heart. When he performed the Valsalva maneuver there was a large, prolonged Phase IV overshoot in blood pressure. During provocative tilt table testing he had a progressive increase in skin electrical conductance (a measure of sweating), his plasma adrenaline level increased beyond the proportionate increase in plasma norepinephrine—sympathoadrenal imbalance (SAI)—and his forearm vascular resistance fell. The testing ended soon afterward when he developed tilt-evoked hypotension.

Hyperadrenergic Orthostatic Intolerance

POTS patients often have high plasma levels of norepinephrine (NE) when they are standing up. According to one suggestion, criteria for diagnosing POTS include an upright plasma NE level of 600 pg/mL or more; however, whether increased SNS outflows constitute a primary abnormality or compensatory response usually is unknown in an individual patient.

In "hyperadrenergic orthostatic intolerance" it is thought that there is a problem in the central autonomic network that increases sympathetic noradrenergic system (SNS) or sympathetic adrenergic system (SAS) outflow.

In a related syndrome called the hyperdynamic circulation syndrome the patients have a fast pulse rate independently of posture, labile hypertension, increased heart rate responses to the beta-adrenoceptor agonist isoproterenol, and increased plasma NE and adrenaline levels both at rest and during provocative maneuvers. Beta-adrenoceptor blockers such as propranolol or benzodiazepines such as diazepam improve the symptoms. It is unclear whether patients with hyperdynamic circulation 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 condition initially described in Civil War soldiers. Also called neurocirculatory asthenia, the syndrome consists of a many 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 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 objective signs, which are all non-specific. In neurasthenia injection of adrenaline can evoke these symptoms. Beta-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 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 POTS.

Failure of the arterial baroreflex can produce a hyperadrenergic condition, because the patient cannot buffer the pressor effects of increases in sympathetic noradrenergic and adrenergic system outflows; however, baroreflex function is normal in POTS.

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 NET 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 family has been described in which POTS is inherited because of a mutation of the gene encoding the NET.

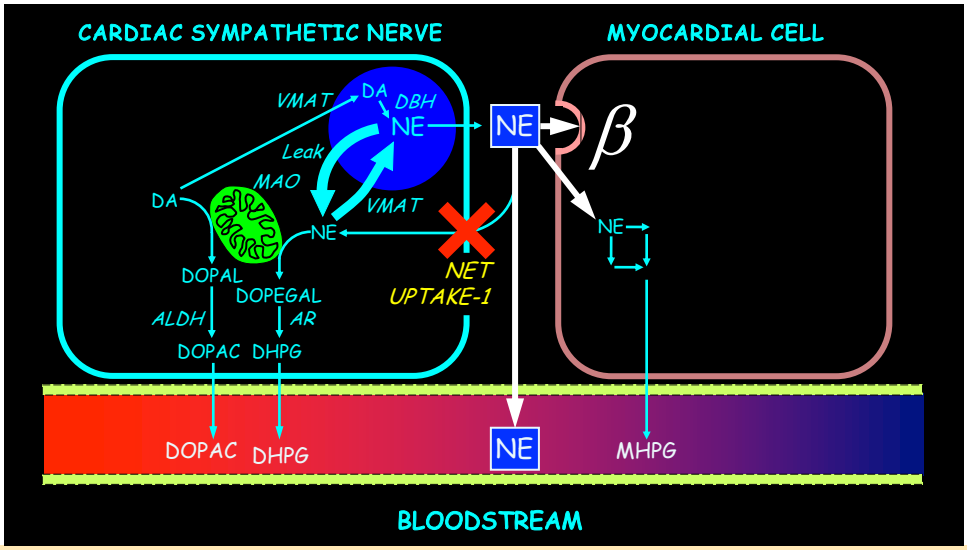


Fig. 323: POTS from NET deficiency. *In NET deficiency, for the same amount of norepinephrine (NE) release there is excessive delivery of NE to beta-adrenoceptors on myocardial cells.*

NET deficiency is a very rare cause of POTS.

Although NET deficiency is an extremely rare cause of POTS, it is important scientifically. 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 in 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.

I've always been puzzled about why decreased NET activity should produces orthostatic intolerance—but I know from personal experience that it does. As part of my own research I once took a dose of 125 mg of desipramine, a drug that temporarily blocks the NET. For hours afterward I had orthostatic intolerance, tachycardia, and brain "fog." According to my team, I also had dysphoria—defined by a sour mood or a state of unease or generalized dissatisfaction with life (but maybe that's me anyway).

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 (SNS) 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 SNS 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.

Gut Wrenching

The median arcuate ligament syndrome (MALS, also called celiac artery compression syndrome), can produce an unusual form of POTS in which abdominal pain, nausea, and vomiting are prominent clinical features. The patients are thin, because meal ingestion evokes pain.

Hearing an abdominal bruit (a whooshing sound due to turbulent blood flow through a narrowed artery) that is worse at end-expiration can be a clue. Doppler-ultrasound testing in this situation shows increased blood velocity through the narrowed artery. Surgical release of the compression can result in rapid improvement.

Mechanisms by which MALS causes POTS are poorly

understood.

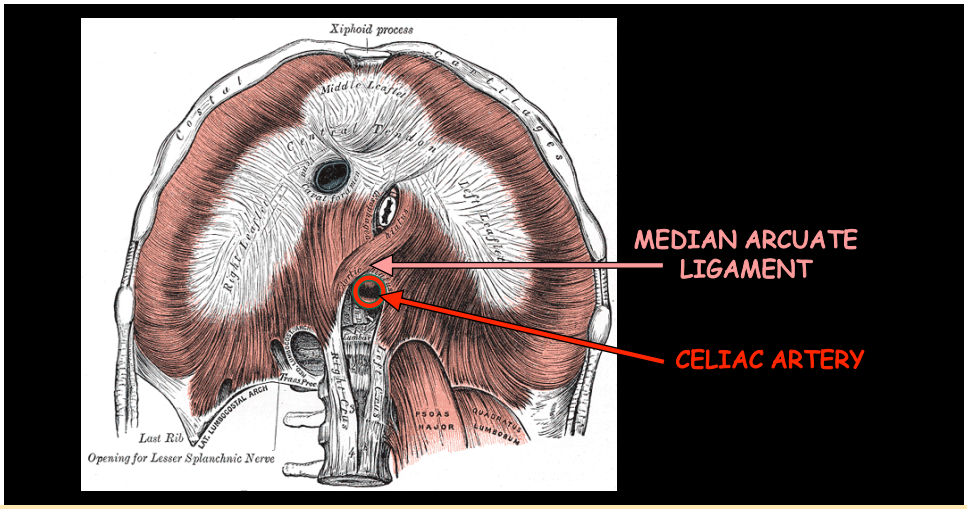


Fig. 324: Median arcuate ligament syndrome (MALS). *MALS results from compression of the celiac artery as it passes through the diaphragm.*

Apples and Pears

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

One possibility is the different body shapes of men and women. At the risk of being stereotypical or chauvinistic, a man's body is shaped like an apple, with broad shoulders, while a woman's is shaped like a pear, with broad hips.

During orthostasis there may be more of a tendency for blood to pool in the abdomen and pelvis of a woman than of a man. If so, then for the same amount of abnormal increase in venous capacitance there would be a more severe decrease in venous

return to the heart in a woman and consequently more reflexive recruitment of sympathetic noradrenergic outflows, resulting in a larger tachycardia response.

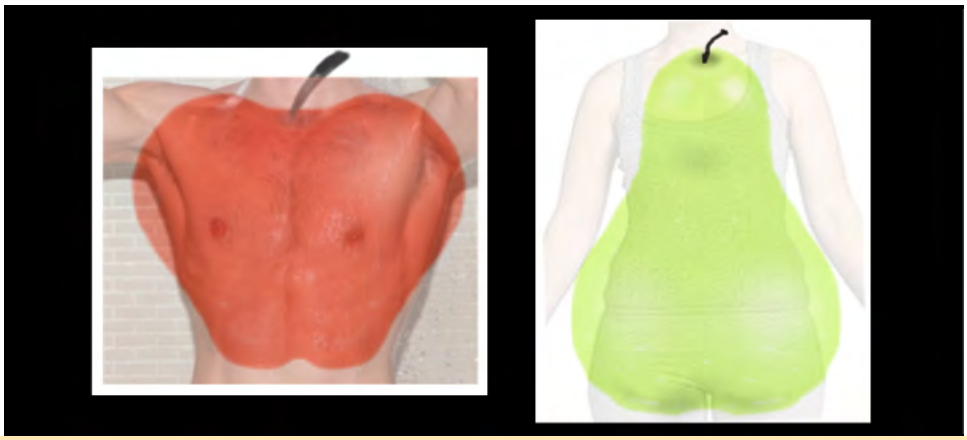


Fig. 325: Male and female body shapes—"apples" and "pears."

During orthostatic stress induced by tilt table testing or lower body negative pressure, women do have more blood pooling in the pelvic region than do men.

Maybe the greater prevalence of orthostatic intolerance in women relates to structural and functional differences between the sexes, 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.

This physiognomic notion, while obviously speculative, is testable.

POTS WITH AUTONOMICALLY MEDIATED SYNCOPE

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

When they do they have the same pattern of sympathoadrenal imbalance (SAI) as found in patients with fainting who do not have POTS. The SAI is usually accompanied by sweating, as indicated by increased skin electrical conductance. There is also substantial orthostatic oscillation of blood pressure. The mechanism of the pressure oscillations is unknown.

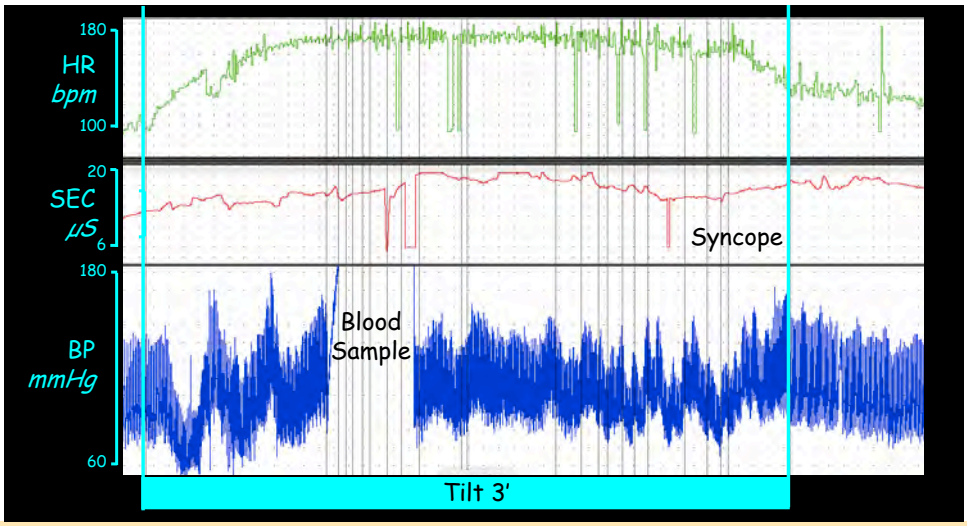


Fig. 326: Syncope in POTS. *In this patient there are rapid increases in heart rate (HR) and sweating (measured by skin electrical conductance, SEC) and oscillating intra-arterial blood pressure (BP) before syncope.*

AUTOIMMUNITY-ASSOCIATED DYSAUTONOMIAS

There are a variety of dysautonomias for which links with autoimmunity have been described. This is a rapidly expanding area in autonomic medicine in adolescents and adults.

It is widely suspected that autoimmunity can cause dysautonomias.

A rather prevalent view among patients and support groups is that dysautonomias such as POTS have an autoimmune basis. Research to test this idea is ongoing. Some clinicians have tried intravenous immunoglobulin (IVIG) to treat patients who have acute or subacute onset of POTS or autonomically mediated syncope.

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 POTS, autonomically mediated syncope, chronic fatigue syndrome, temperomandibular joint disorder, and migraine. One of the most famous patients with

the condition is the professional tennis player, Venus Williams. She has suffered for years with chronic fatigue that accompanies 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.

Fig. 327: Venus Williams. *The professional tennis player had to drop out of the US Open in 2011 due to fatigue related to Sjogren's syndrome.*

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

Mast Cell Activation Syndrome (MCAS)

Mast cells are a type of immune cells that play key roles in acute allergic responses. They express receptors for IgE, the immune globulin involved with anaphylaxis, as well as receptors for a variety of other chemical messengers.

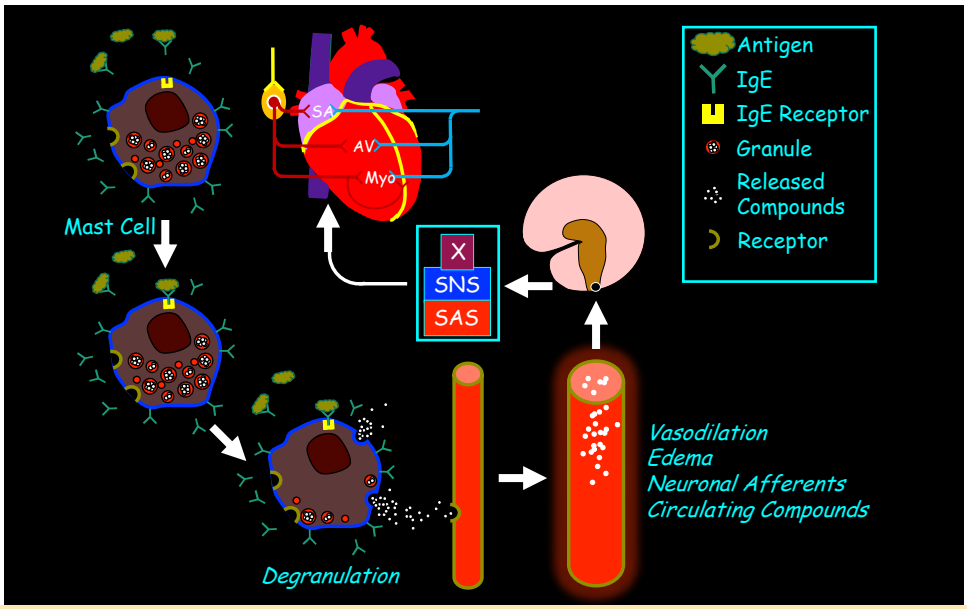


Fig. 328: From MCAS to POTS. *Concept diagram for how mast cell degranulation in mast cell activation syndrome (MCAS) might result in excessive orthostatic tachycardia.*

When activated, mast cells release several compounds, including monoamines such as histamine, serotonin, and dopamine, as well as cytokines such as TNF-α, interleukins, and leukotrienes. Taken together these compounds exert important effects on the cardiovascular, respiratory, and gastrointestinal systems and the skin.

In Mast Cell Activation Syndrome (MCAS), the mast cells release their chemicals inappropriately or excessively. Symptoms of MCAS include flushing, itching, diarrhea, nausea, wheezing, fatigue, “brain fog,” orthostatic intolerance, and fainting reactions.

Mast cells release a protein called tryptase, and MCAS patients have high tryptase levels; however, whether POTS patients as a

group have elevated tryptase levels is unknown.

People with inherited high tryptase levels due to an increased copy number of the *TPSAB1* gene have multisystem complaints such as flushing, itching, nausea, diarrhea, chronic pain, joint hypermobility, orthostatic intolerance, and syncope. How elevated tryptase produces these manifestations remains unknown.

To determine whether a patient with orthostatic intolerance has MCAS, it has been proposed that three criteria should be met: (1) The patient should have symptoms consistent with MCAS, such as repeated episodes of flushing, itching, nasal congestion, coughing, chest tightness, wheezing, abdominal pain, or diarrhea; (2) There should be laboratory evidence of mast cell activation; and (3) there should be improvement of symptoms with the use of medications such as anti-histamines or leukotriene receptor blockers. Cromolyn sodium, which stabilizes mast cells, is also used.

Although patients with Mast Cell Activation Syndrome (MCAS) often have symptoms of POTS, the frequency of MCAS in POTS is unknown.

MCAS, Ehlers-Danlos syndrome, and POTS can occur together. The bases for this triad are poorly understood.

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 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.

Fig. 329: Andy Griffith. *Andy Griffith, who received a Presidential Medal of Freedom in 2005, suffered from Guillain-Barré syndrome.*

Andy Griffith, who played 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 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 system (PNS) failure and activation of the sympathetic noradrenergic system (PNS) and sympathetic adrenergic system (SAS).

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 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)."

Fig. 330: Albert Sabin. *Sabin was the developer of the oral polio vaccine. He may have had the Guillain-Barré syndrome.*

More than 40 years later, in the early 1980s, long after having attained international renown for developing the oral polio vaccine, Sabin was conducting 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 that was manifested at first by weak and wobbly legs. After having studied paralyzing viral diseases for more than a half century, he came down with what could have been a form

of post-viral paralysis.

He was diagnosed with a rare cervical spine disease in which a ligament bordering the spinal canal becomes bony. 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 and then his arms. He developed pneumonia and had an episode of respiratory arrest, which an aide in attendance happened to notice; 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. He slowly regained function of his arms and upper body through rehabilitation therapy at the NIH Clinical Center. 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." 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 obviously wobbly gait. He died of heart failure in 1993 at the age of 86.

The Swine Flu Affair

In January, 1976 an outbreak of H1N1 "swine flu" virus broke out among Army recruits in Fort Dix, N.J. 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 U.S. 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, and about 500 lawsuits against the U.S. Government (corresponding to about $4 billion) were filed related to Guillain-Barré syndrome as a result of the vaccine. A few months later the U.S. Government stopped the swine flu immunization campaign because of the cases of Guillain-Barré syndrome.

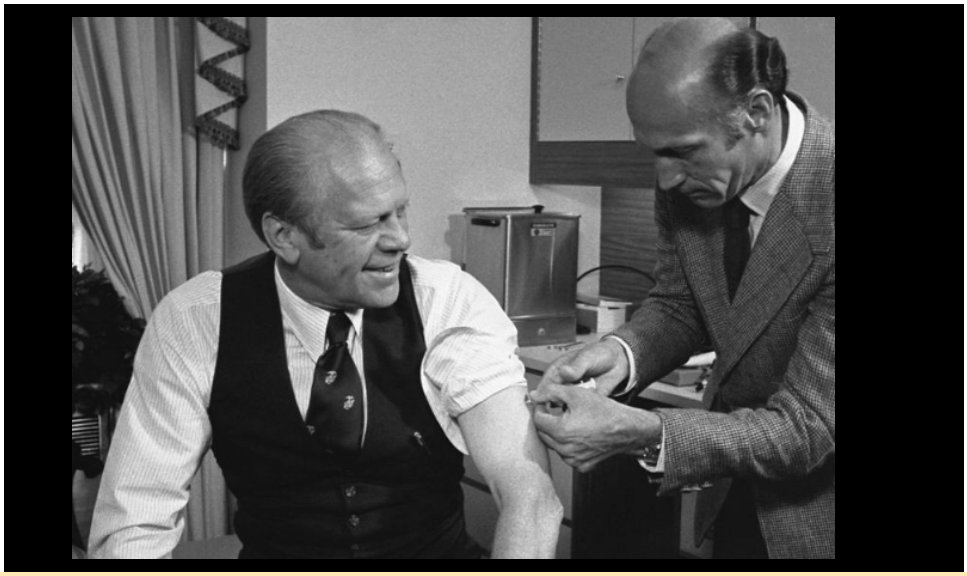


Fig. 331: President Gerald R. Ford receiving the swine flu vaccination.

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

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.

The Old Lady Who Couldn't Spit

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

Her mouth was so dry, she couldn't chew 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 I first saw her, 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 I thought she had pure autonomic failure (PAF), and I predicted that her ^{18}F-dopamine PET scan would show loss of sympathetic innervation of the heart.

Instead, her ^{18}F-dopamine scan was normal.

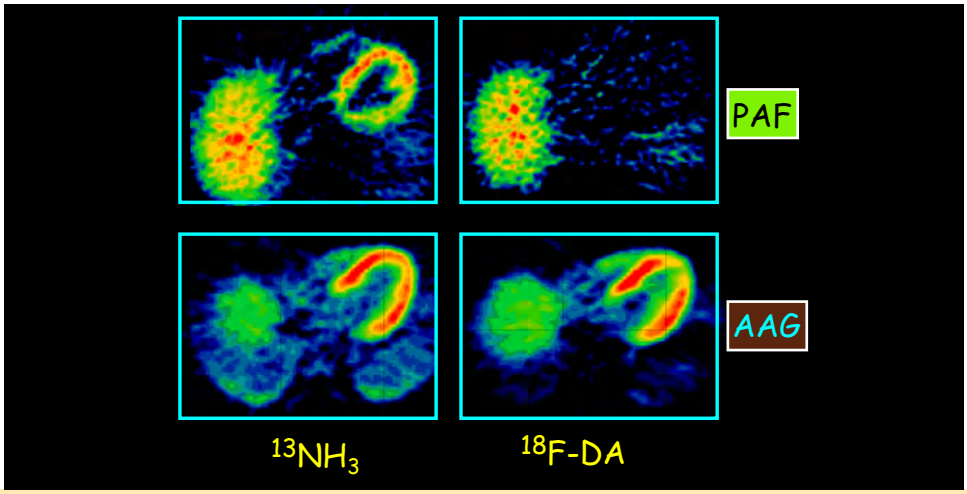


Fig. 332: Cardiac sympathetic neuroimaging in autoimmune autonomic ganglionopathy (AAG). *^{18}F-Dopamine (^{18}F-DA) scanning readily distinguishes AAG from pure autonomic failure (PAF).*

Under the study protocol she received a ganglion blocker, and this produced hardly any effects at all.

At about that time Dr. Steven Vernino (then at the Mayo Clinic) had published a study about autoimmune autonomic neuropathy associated with a circulating antibody to the neuronal nicotinic receptor, which mediates ganglionic neurotransmission. No patient with PAF had had such an antibody; I suspected our patient might and 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).

AAG is a quite a rare form of acquired autonomic failure in which there is decreased activity of all the components of the autonomic nervous system—pandysautonomia.

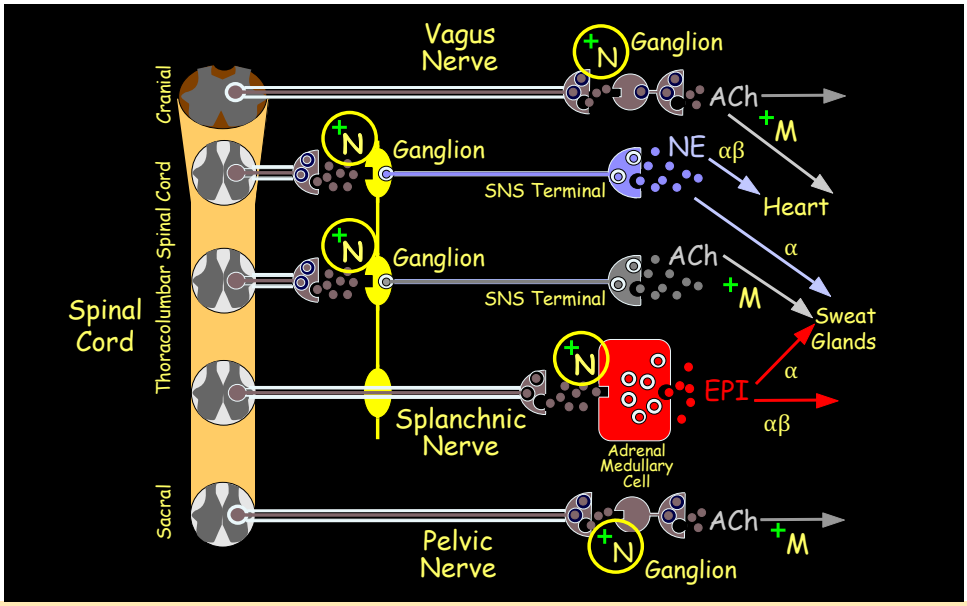


Fig. 333: Basis for pandysautonomia in autoimmune autonomic ganglionopathy (AAG). *Because of the role of the nicotinic cholinergic receptor in ganglionic neurotransmission ($^{+}$N), autoimmunity to the receptor results in a pandysautonomia.*

AAG manifests with symptoms and signs of decreased post-ganglionic neurotransmission. Because of parasympathetic nervous system (PNS) failure, the patient has decreased salivation, lacrimation, gastrointestinal movements, and bladder tone. Because of sympathetic cholinergic system (SCS) failure, the patient has decreased sweating. Because of sympathetic noradrenergic system (SNS) failure, the patient has neurogenic orthostatic hypotension.

Myasthenia gravis also involves autoimmunity to nicotinic receptors, but these mediate neuromuscular transmission and have different components from the nicotinic receptors involved with autonomic ganglionic neurotransmission. The closely related Lambert-Eaton syndrome involves

autoimmunity to calcium channels rather than nicotinic receptors.

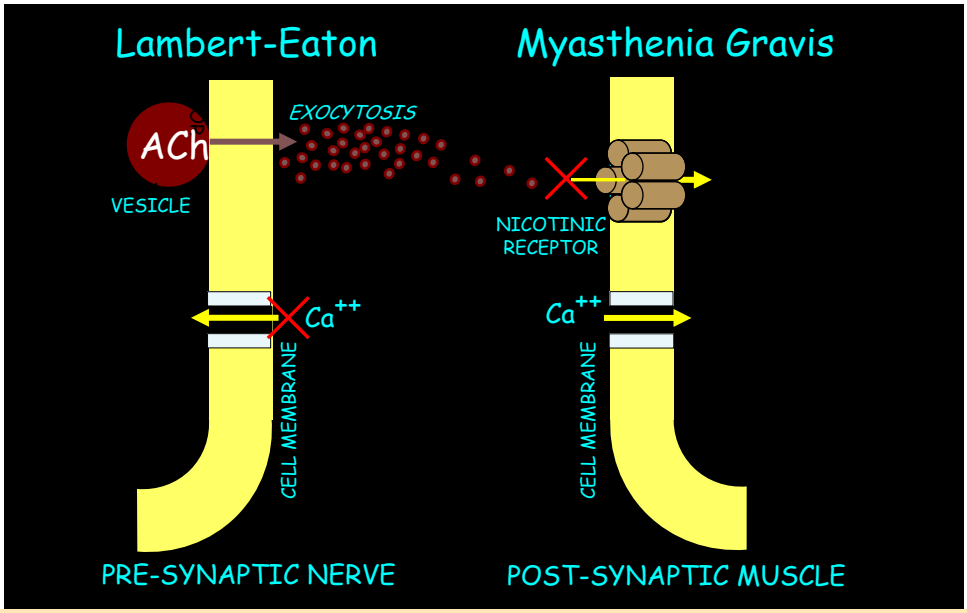


Fig. 334: Lambert-Eaton syndrome and myasthenia gravis. *The autoimmunity in autoimmune autonomic ganglionopathy (AAG) is analogous to that in myasthenia gravis.*

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 norepinephrine stores than do levels of norepinephrine itself. In AAG, plasma

norepinephrine levels are lower than expected for DHPG levels, presumably because of decreased exocytotic release from generally intact post-ganglionic sympathetic nerves.

To treat the patient's chief symptom, dry mouth, we prescribed bethanechol (Urecholine™), which is a muscarinic cholinergic agonist. Bethanechol treatment produced a very gratifying result in our patient—she had a return of her ability to make saliva, alleviating her chief complaint.

Management of AAG usually focuses on anti-autoimmune therapies with plasma exchanges (to remove the circulating antibodies to the neuronal nicotinic receptor), steroids, rituximab (a drug that is toxic to antibody-producing B cells), or mycophenolic acid (Cellcept™). The long-term outlook in AAG is unknown.

Autoimmunity-Associated Autonomic Denervation

Autoimmunity-associated autonomic failure can reflect a post-ganglionic lesion, in contrast with the ganglionic lesion seen in autoimmune autonomic ganglionopathy (AAG).

Autoimmunity-associated autonomic denervation (AAD) seems to manifest first with a pandysautonomia, followed by relatively more rapid recovery of parasympathetic than of sympathetic functions. This sequence suggests that the target of autoimmune attack is unmyelinated post-ganglionic axons, because parasympathetic post-ganglionic axons are short and probably regenerate quickly, whereas sympathetic post-ganglionic axons

are long and probably regenerate slowly and incompletely. Our patient with AAD had a form of rheumatoid arthritis and positive titers for Sjogren's and lupus-related antibodies.

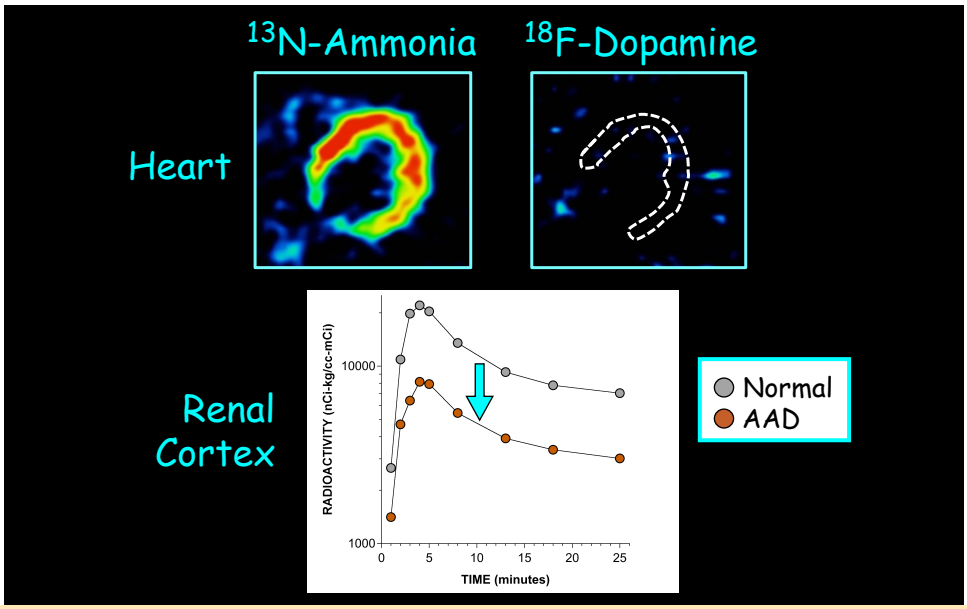


Fig. 335: Cardiac and renal sympathetic neuroimaging in autoimmunity-associated autonomic denervation (AAD). *There is evidence of both cardiac and renal sympathetic denervation.*

From analysis of ^{18}F-dopamine scanning data, AAD involves loss of sympathetic noradrenergic nerves supplying the kidneys as well as the heart. The patient had bilateral Horner's syndrome, implying involvement of sympathetic noradrenergic nerves ascending from the superior cervical ganglion. Extremely low plasma levels of catechols indicated generalized sympathetic noradrenergic deficiency.

The natural history of AAD is unknown.

GERIATRIC DYSAUTONOMIAS

In the elderly, dysautonomia often reflects adverse effects of alterations in activities of components of the autonomic nervous system in the setting of an independent pathologic state. Examples in this book so far include the ironic death of Dr. John Hunter (p. 262); the stereotypical old man with coronary disease who has a lethal heart attack while shoveling snow (Fig. 192); and *takotsubo cardiopathy*, which is most common in post-menopausal women (Fig. 308).

Geriatric dysautonomias also can result from degenerative processes in the central autonomic network or in autonomic nerves supplying body organs. This is the form of dysautonomia that this section emphasizes. Fig. 196 shows the part of the dysautonomias universe that involves geriatric dysautonomias.

Geriatric dysautonomias often involve orthostatic hypotension and deposits of the protein alpha-synuclein.

Many of these conditions are characterized by misfolding and abnormal deposition of proteins, such as alpha-synuclein, amyloid, and tau. Substantial current research on geriatric dysautonomias focuses on the basis for relationships among baroreflex-sympathoneural failure (manifested by neurogenic orthostatic hypotension, nOH), movement disorders, and alpha-synuclein deposits.

AUTONOMIC SYNUCLEINOPATHIES

Neurologists have 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 conditions come under the umbrella of "synucleinopathies," meaning that they all involve abnormal deposits of 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 scientific 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.

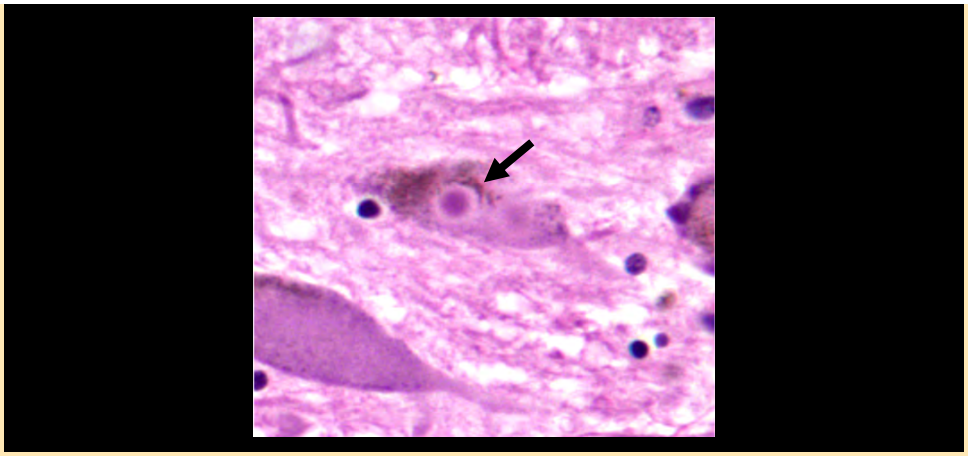


Fig. 336: A Lewy body. *Lewy bodies are inclusion bodies inside neurons that have a particular microscopic appearance. The Lewy body indicated by the arrow is in a neuron in the locus ceruleus (the main source of norepinephrine in the brain) of a patient with pure autonomic failure (PAF).*

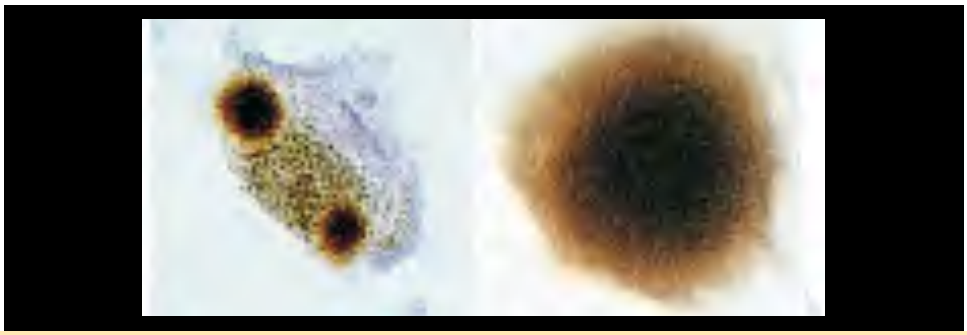


Fig. 337: Alpha-synuclein in Lewy bodies. *The discovery of alpha-synuclein deposition in Lewy bodies led to re-defining Lewy body diseases as synucleinopathies.*

Multiple system atrophy (MSA) is also characterized by alpha-synuclein deposits. In MSA, the deposits are in the cytoplasm of glial cells, which are "helper" cells in the brain that are not neurons. A microscopic feature of MSA is glial cytoplasmic inclusions, or GCIs.

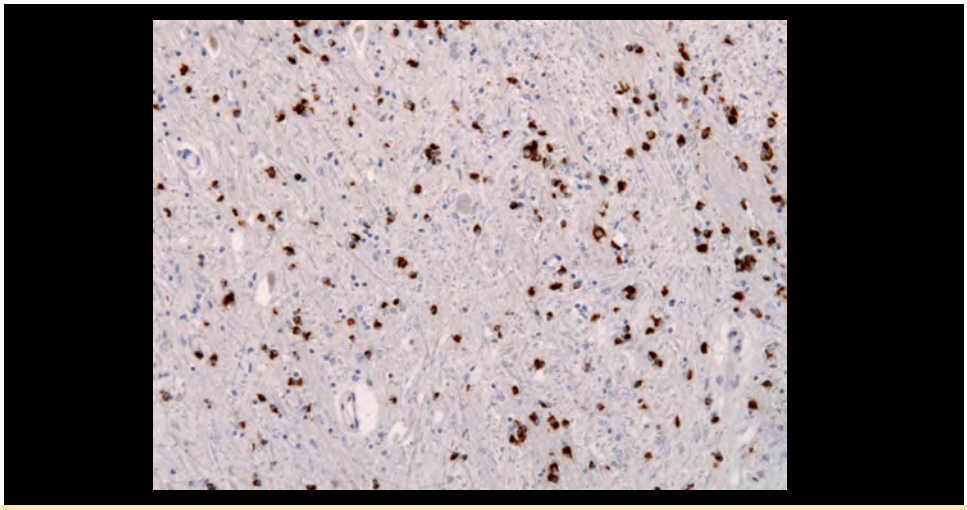


Fig. 338: Glial cytoplasmic inclusions (GCIs) in the brain of a patient with multiple system atrophy (MSA). *GCIs are now considered to be a neuropathologic hallmark of MSA.*

Pure autonomic failure (PAF) also involves Lewy bodies, both in the brainstem (Fig. 336 shows an example) and in sympathetic ganglia. PAF is now considered to be an example of a Lewy body form of neurogenic orthostatic hypotension (nOH).

PAF and MSA, which previously were considered to be "primary chronic autonomic failure" syndromes, are now considered to be in a family of autonomic synucleinopathies.

About 30-40% of patients with Parkinson's disease have orthostatic hypotension (OH), 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 dementia with Lewy bodies (DLB), or

Lewy body dementia. A probably substantial but still unknown proportion of DLB patients have OH (DLB+OH) Most PD patients and at least some PAF patients eventually develop dementia. PAF, PD+OH, and DLB+OH come under the heading of Lewy body forms of neurogenic OH.

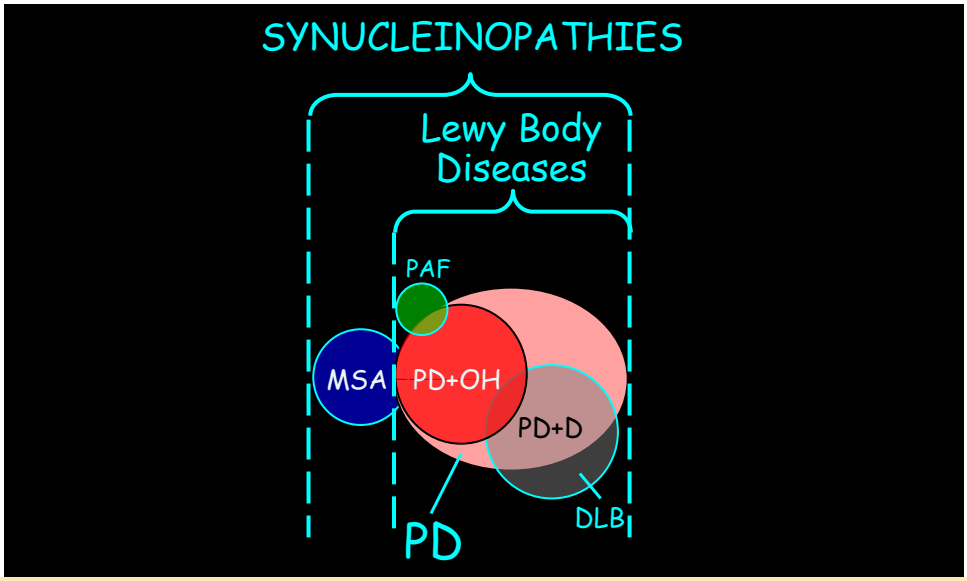


Fig. 339: Autonomic synucleinopathies. *Lewy body forms of autonomic synucleinopathy include pure autonomic failure (PAF), Parkinson disease (PD) with orthostatic hypotension (OH) or dementia (PD+D), and dementia with Lewy bodies (DLB). Multiple system atrophy (MSA) is a non-Lewy body form of autonomic synucleinopathy. These syndromes can overlap.*

Autonomic synucleinopathies share two other core features.

First, patients with autonomic synucleinopathy have "baroreflex-sympathoneural failure." That is, they 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. During orthostasis their plasma norepinephrine (NE) levels increase by less than 60%, whereas in healthy people plasma NE levels approximately double within 5 minutes.

Second, autonomic synucleinopathies all involve catecholamine deficiency, in the brain, periphery, or both. Cerebrospinal fluid (CSF) levels of DOPAC, the main neuronal metabolite of dopamine, and DHPG, the main neuronal metabolite of norepinephrine, are low in PD, MSA, and PAF.

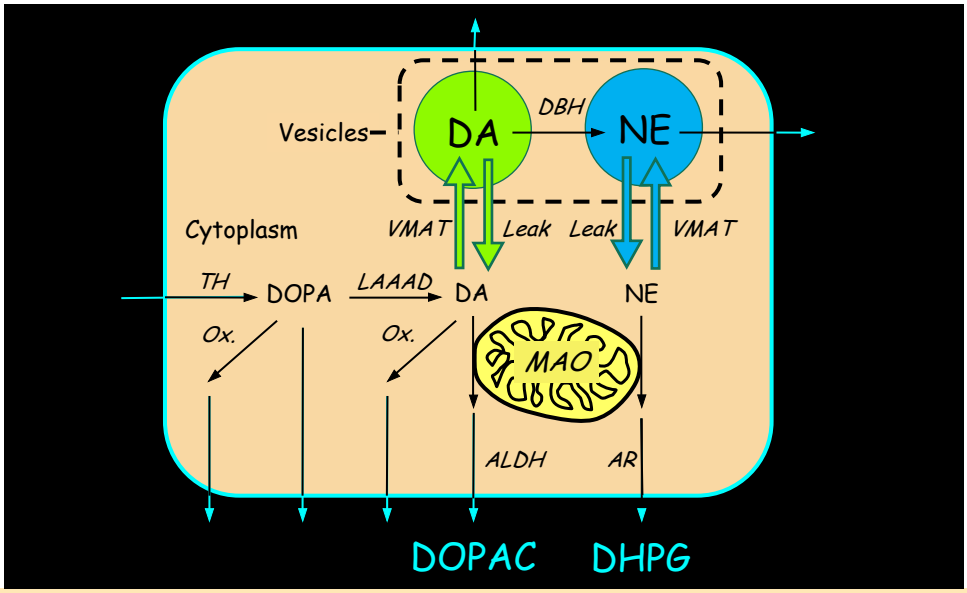


Fig. 340: Determinants of CSF DOPAC & DHPG levels.

In the Lewy body forms of alpha-synucleinopathy, cardiac tissue contents of norepinephrine and dopamine are markedly reduced.

Results of cardiac sympathetic neuroimaging fit with the view that cardiac noradrenergic deficiency is a characteristic feature

of Lewy body forms of autonomic synucleinopathies, in contrast with intact sympathetic noradrenergic innervation in most MSA patients.

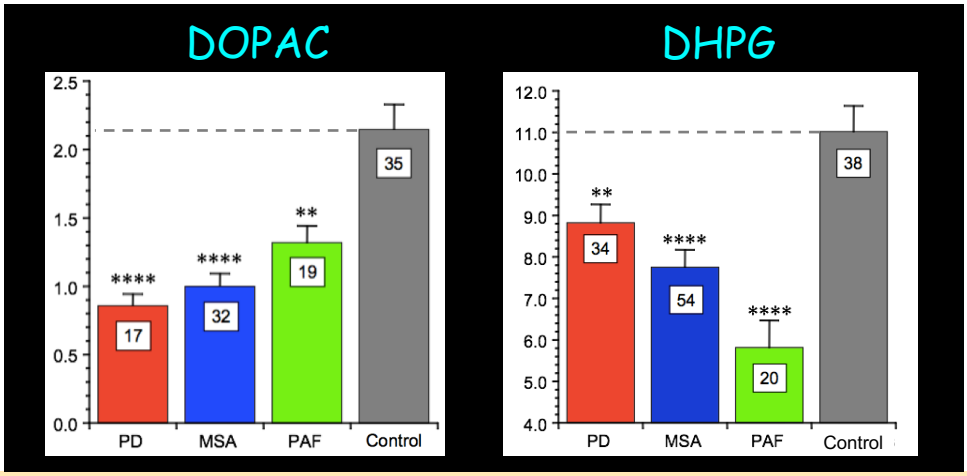


Fig. 341: Decreased CSF DOPAC & DHPG in autonomic synucleinopathies. *(****) p<0.0001 & (**) p<0.01 from control. Boxed numbers are numbers of patients.*

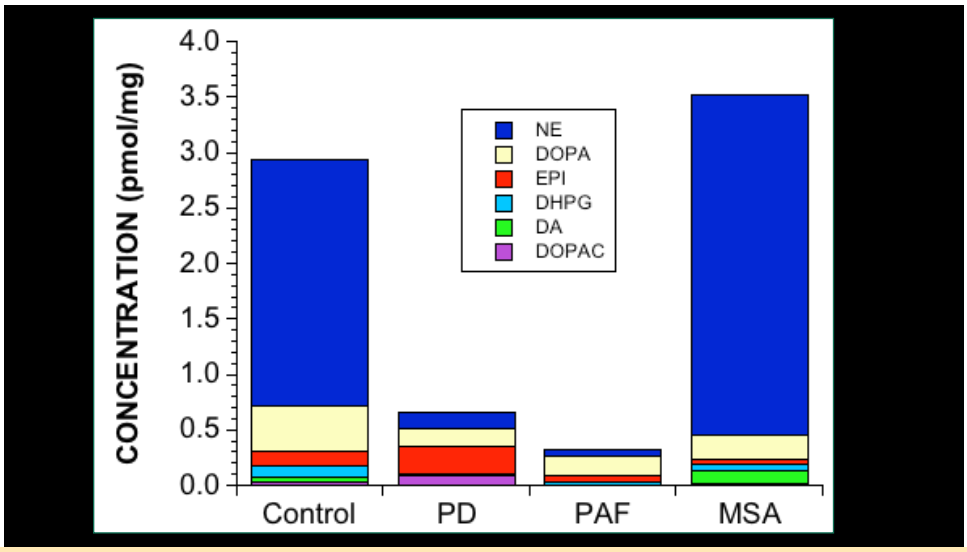


Fig. 342: Cardiac catechols in autonomic synucleinopathies. *The Lewy body forms involve markedly decreased myocardial tissue contents of norepinephrine and dopamine.*

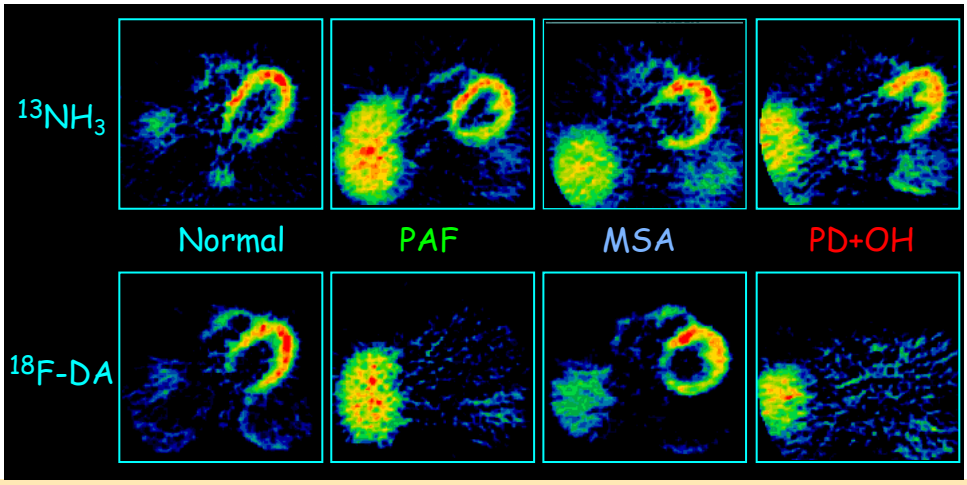


Fig. 343: Cardiac sympathetic neuroimaging in autonomic synucleinopathies. *^{13}N-Ammonia perfusion and ^{18}F-dopamine (^{18}F-DA) sympathoneural PET scans are shown. The PAF and PD+OH patients have evidence of cardiac noradrenergic deficiency. Imaging in the MSA patient is normal.*

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

All PD+OH patients have evidence for cardiac noradrenergic deficiency, whereas most patients with parkinsonian MSA (MSA-P) have intact sympathetic noradrenergic innervation. A minority of MSA patients do have evidence for a loss of cardiac sympathetic nerves; however, the finding of normal cardiac sympathetic innervation excludes PD+OH.

Another valuable clinical laboratory test in the differential diagnosis of PD+OH vs. MSA 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. That is, the UPSIT score is 18 or less out of 40.

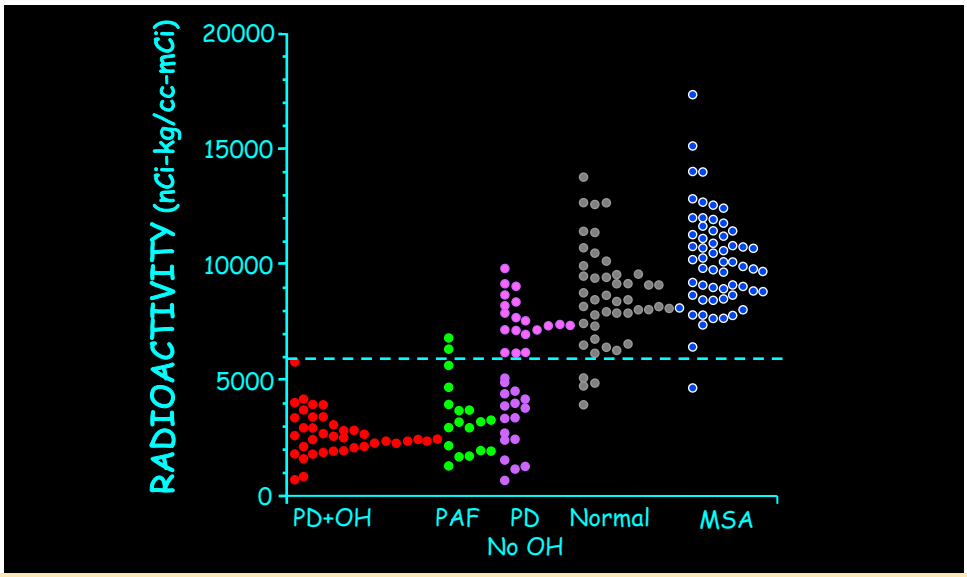


Fig. 344: Cardiac ^{18}F-dopamine-derived radioactivity in autonomic synucleinopathies. *PD+OH patients (red) and PAF patients (green) have neuroimaging evidence of cardiac noradrenergic deficiency.*

In contrast, many MSA-P patients have normal or only slightly to moderately decreased sense of smell. In a patient with parkinsonism and neurogenic orthostatic hypotension, 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 referred for orthostatic hypotension and possible autonomic synucleinopathy, I use a 4-step algorithm.

First, in autonomic synucleinopathies orthostatic hypotension is a persistent, consistent finding. The patient may not always have symptoms of low blood pressure while standing, but the blood pressure always falls.

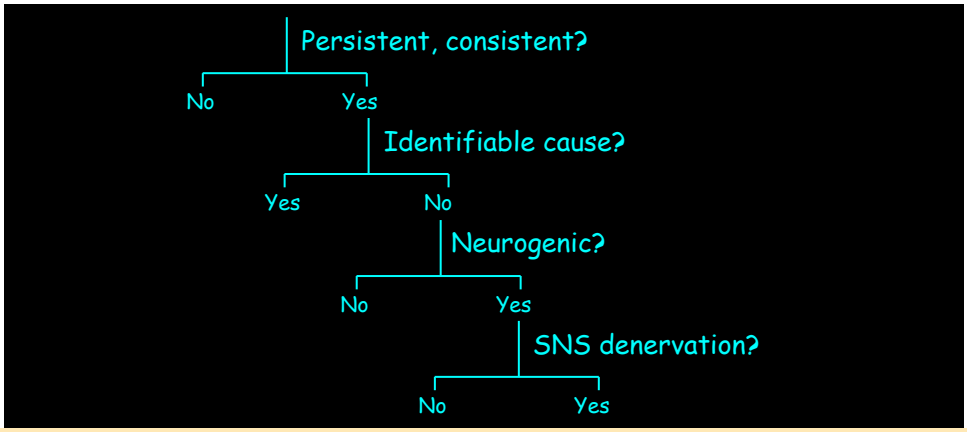


Fig. 345: Four-step approach to the evaluation of orthostatic hypotension (OH).

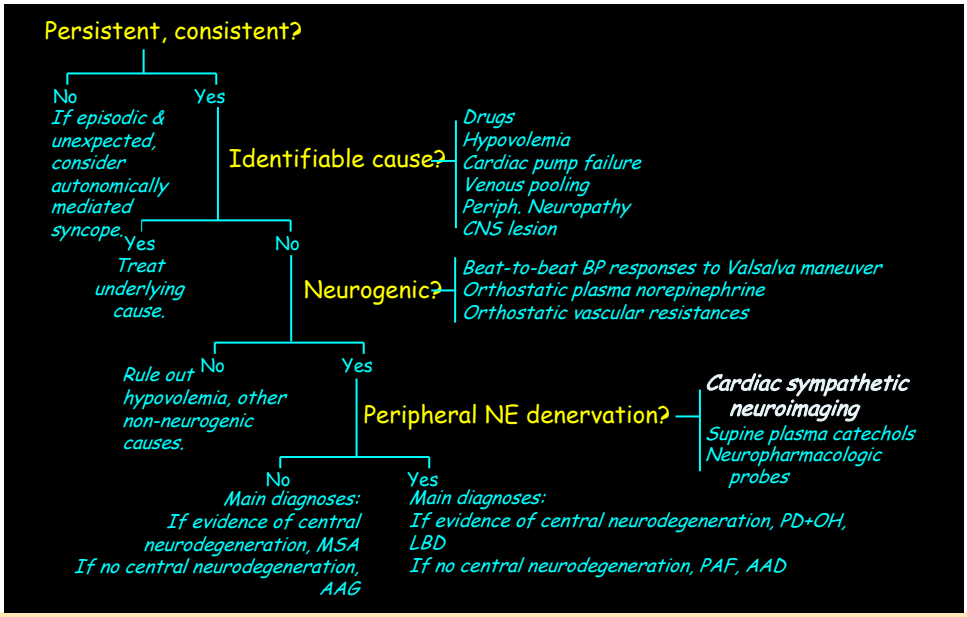


Fig. 346: Detailed algorithmic approach to diagnostic evaluation of neurogenic orthostatic hypotension. *The most sensitive test for peripheral noradrenergic (NE) denervation is cardiac sympathetic neuroimaging.*

Second, secondary causes of orthostatic hypotension 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 is to test for loss of sympathetic noradrenergic nerves. This may be done by conducting cardiac sympathetic neuroimaging, assaying plasma catechols, using neuropharmacological probes, or examining skin biopsies for loss of innervation in pilomotor muscles or in blood vessel walls. Cardiac sympathetic neuroimaging is probably most sensitive.

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 on for many years.
May evolve into Parkinson's disease with orthostatic hypotension (PD+OH) or dementia with Lewy bodies and orthostatic hypotension (DLB+OH).

Pure autonomic failure (PAF, previously called Bradbury-Eggleston syndrome and idiopathic orthostatic hypotension) is the prototype of chronic autonomic failure. PAF is a rare disease that features persistent falls in blood pressure when the

patient stands—orthostatic hypotension (OH)—in the absence of signs of central nervous system disease and in the absence of other known causes of OH. The OH results from sympathetic neurocirculatory failure and therefore is neurogenic (nOH). While chronic and causing disability, PAF not thought to be lethal.

PAF patients report progressively worsening dizziness when standing up, after a large meal, upon exposure to environmental heat, or after exercise. The 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.

Blood pressure responses to the Valsalva maneuver in PAF always show the abnormal pattern that indicates baroreflex-sympathoneural failure.

There is growing evidence that at least some of the noradrenergic deficiency that characterizes PAF reflects functional abnormalities in sympathetic nerves, such as decreased efficiency of vesicular storage of catecholamines, rather that simply a loss of the nerves. This is a matter of active research now.

Because of “denervation supersensitivity” and baroreflex-sympathoneural failure, patients with PAF can have surprisingly large increases in blood pressure in response to adrenoceptor-stimulating drugs.

Plasma norepinephrine (NE) levels often (but not always) are

low in PAF. Because of baroreflex-sympathoneural failure the plasma NE levels fail to increase appropriately when the patient stands. PAF patients usually (but not always) also have low plasma levels of 3,4-dihydroxyphenylglycol (DHPG), which is the main intra-neuronal metabolite of NE.

Virtually all patients with PAF have neuroimaging evidence of cardiac noradrenergic deficiency (Fig. 344).

A recently introduced method to identify Lewy body forms of neurogenic orthostatic hypotension (nOH) in living patients is by immunofluorescence confocal microscopy to measure alpha-synuclein deposition in sympathetic noradrenergic nerves in skin biopsies. This is a matter of active research now.

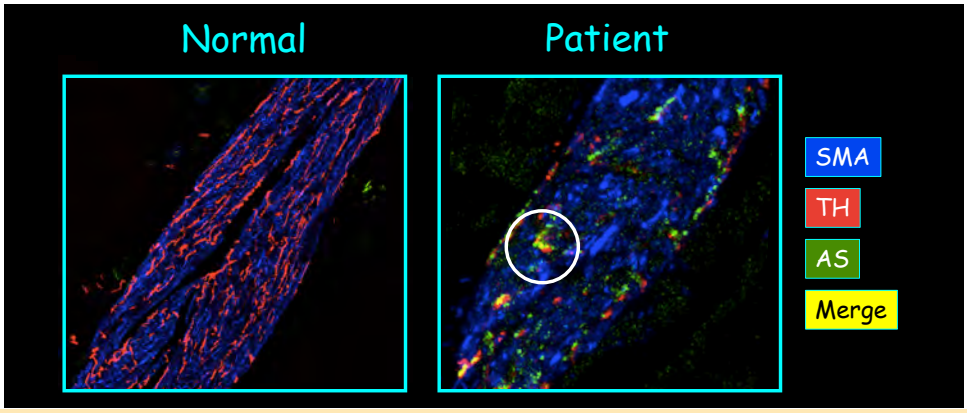


Fig. 347: Alpha-synuclein (AS)-tyrosine hydroxylase (TH) colocalization in arrector pili ***muscle from a patient with PAF that evolved into DLB+OH.*** *Identifying AS-TH colocalization (the yellow highlighted in the circle) has the potential to diagnose a Lewy body form of neurogenic orthostatic hypotension such as PAF in living patients. (Images courtesy of R. Isonaka.)*

At least in some patients, PAF evolves into dementia with Lewy bodies and orthostatic hypotension (DLB+OH), to Parkinson's disease with orthostatic hypotension (PD+OH), or a combination. Fig. 347 shows an example.

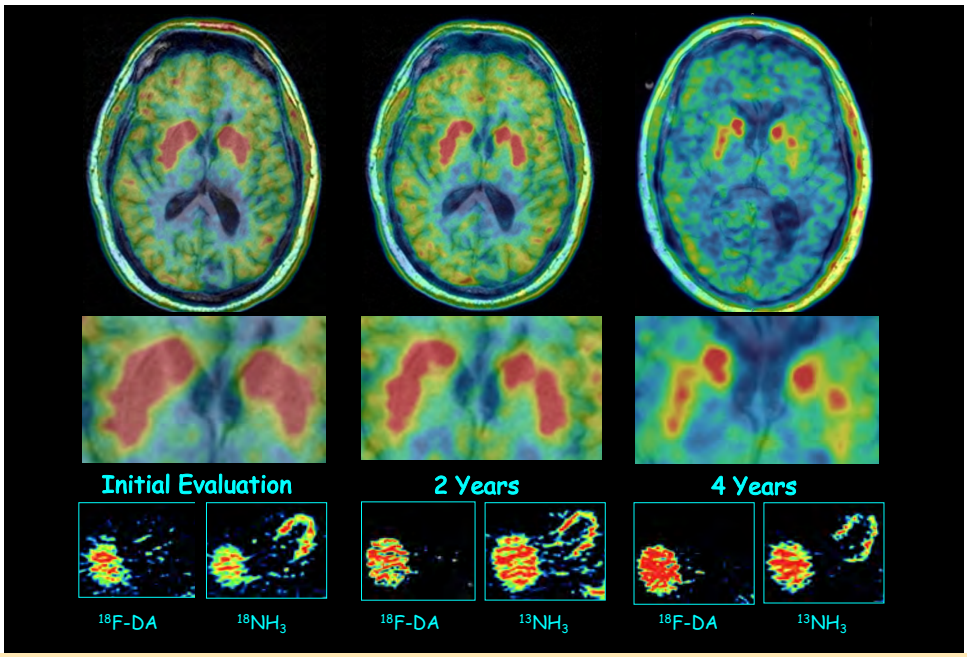


Fig. 348: Evolution of PAF into dementia with Lewy bodies and orthostatic hypotension (DLB+OH). *Striatal ^{18}F-DOPA-derived radioactivity is normal at first but then takes on the abnormal appearance found typically in Parkinson's disease (PD). The patient's PAF evolved into DLB+OH and then PD+OH.*

The frequency with which PAF evolves into a disease with symptomatic central neurodegeneration is a topic of current research.

DEATH IN THE 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.

Another PAF patient was celebrating his birthday with his family at a local restaurant when he excused himself to go the bathroom. He didn't return, and he was found in full cardiac arrest. Although he was resuscitated successfully, he died a few days later. Autopsy showed no important coronary artery disease.

What went wrong in these patients? In neurogenic orthostatic hypotension there is an inability to tighten blood vessels reflexively to counter effects of decreased venous return to the heart. Whatever happens to venous return, that's what happens to the blood pressure. When a person strains at stool, the high pressure in the chest and abdomen decreases venous return to the heart, and this would exacerbate the orthostatic fall in blood pressure. In the confines of a bathroom the patient may not be able to slump to the floor, and if the patient were kept sitting, the blood flow to the brain and heart could become critically low.

A DIVE INTO A NIGHTSTAND

Dream enactment behavior occurs commonly in autonomic synucleinopathies. Dream enactment means the patient acts out his or her dreams and thrashes about in bed. Polysomnography,

a special type of sleep study, shows an absence of the normal loss of limb muscle tone during rapid eye movement (REM) sleep, and 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 dream 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 NIH Clinical Center he dove headfirst into his bed stand. 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 imbalance.

The key gross anatomic change in the brain in PD is a 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—you can see this in Fig. 104.

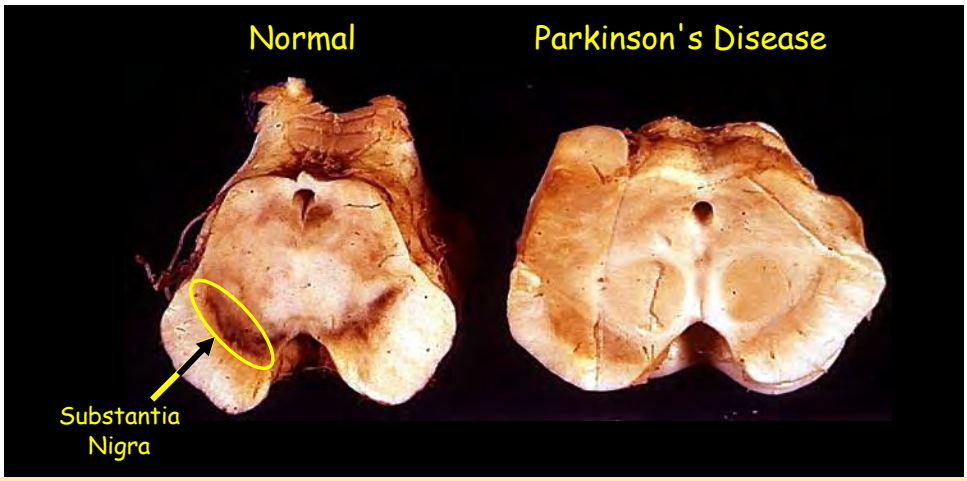


Fig. 349: Nigral depigmentation in Parkinson's disease (PD). *Loss of pigmentation in the substantia nigra is a classic neuropathologic finding in PD.*

THE SAD CLOWN'S EYES

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.

^{18}F-DOPA PET scanning is an excellent way to see if there is a loss 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 of the brain. The eye liner corresponds to the putamen, which 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.

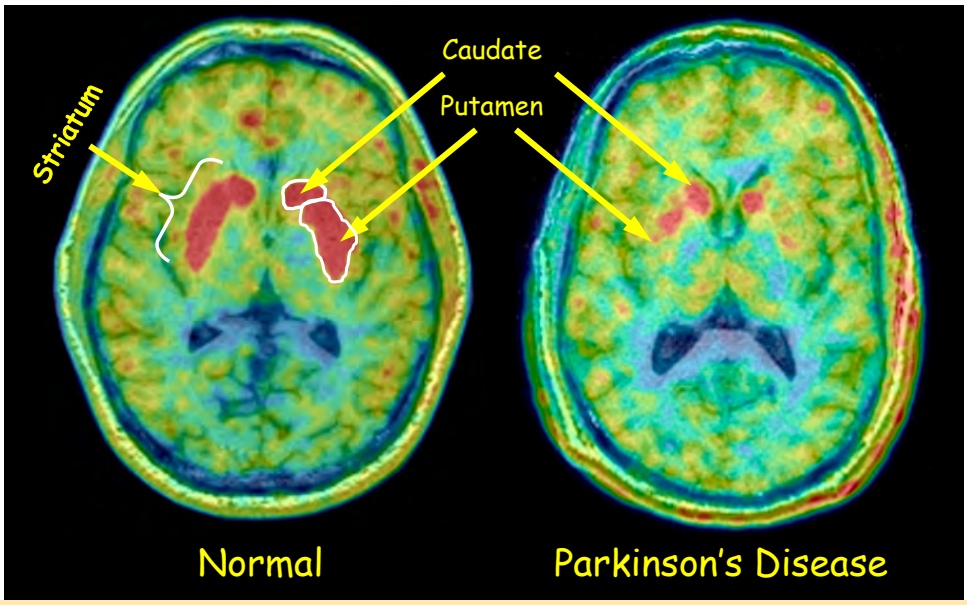


Fig. 350: The "sad clown's eyes." *In PD the "eye liner" of the sad clown's eyes (the putamen) seems washed away.*

CONTRIBUTIONS OF OLEH HORNYKIEWICZ

Profound depletion of DA in the striatum is the classic neurochemical abnormality in PD. This was first described by the Austrian biochemist Oleh Hornykiewicz in 1960. The most severe loss of DA in the brain is in the putamen (there is

equally severe loss in the heart).

PD was the first neurodegenerative disease for which the underlying neurochemical abnormality was identified—severe depletion of the catecholamine dopamine (DA).

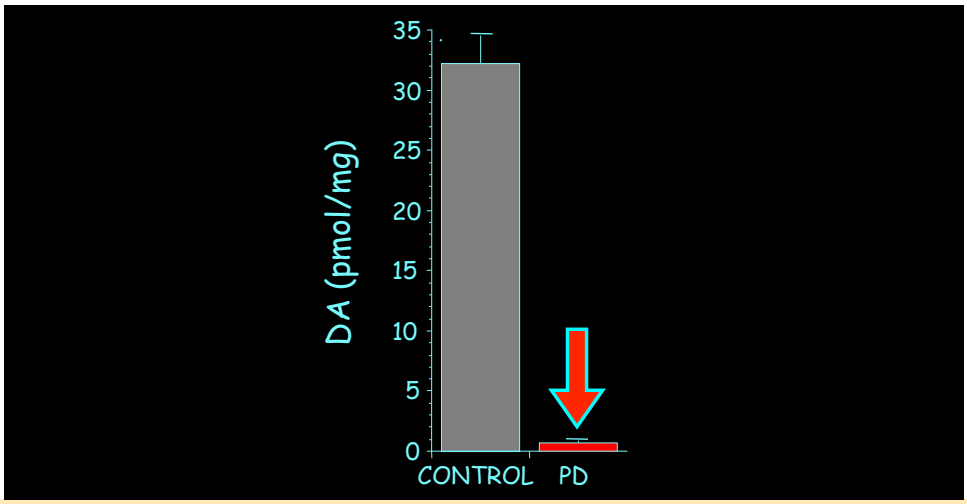


Fig. 351: Putamen dopamine (DA) deficiency in Parkinson disease (PD). *Profound DA depletion in the striatum—especially the putamen—is the neurochemical hallmark of PD.*

All known successful 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.

Hornykiewicz also was the first to attempt levodopa treatment as a means to bypass the DA deficiency in PD.

In 2000, the Nobel Prize in Physiology or Medicine was shared

by Arvid Carlsson, Eric Kandel, and Paul Greengard for "discoveries concerning signal transduction in the nervous system." Hornykiewicz was passed over. In an open letter to the Nobel Foundation more than 250 neuroscientists protested the omission.

Alleviation of dopamine deficiency in PD by levodopa treatment—introduced by Hornykiewicz—was revolutionary in the history of medical neuroscience.

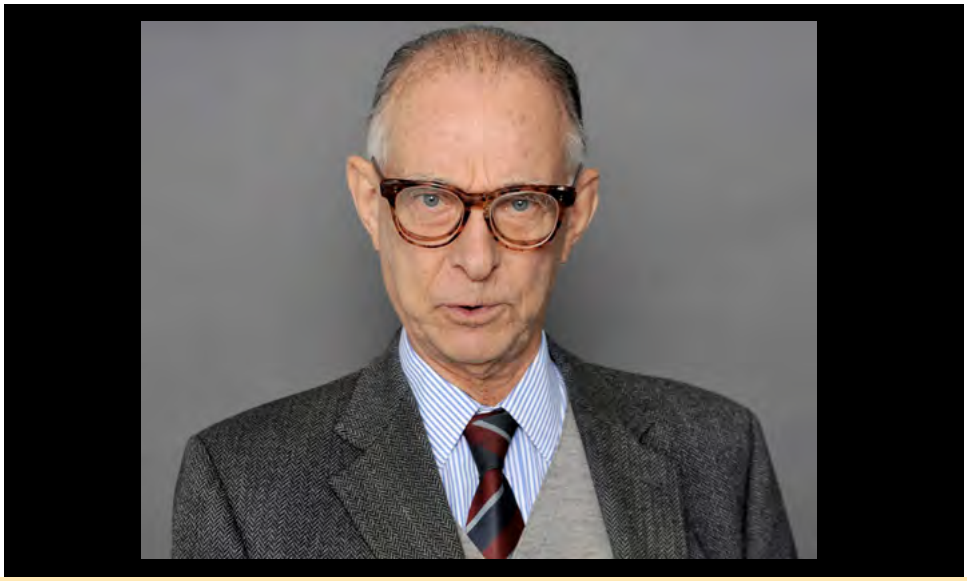


Fig. 352: Oleh Hornykiewicz. *Hornykiewicz discovered the striatal dopamine depletion that causes the movement disorder in PD.*

One of the signatories stated—correctly—"When we review all the discoveries related to chronic neurological disorders made in the last 50 years, none matches the magnitude of the benefit conferred on mankind by the discoveries of Oleh Hornykiewicz."

A DISEASE WITH NO 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 loss of sympathetic noradrenergic nerves and a form of dysautonomia. Sympathetic noradrenergic denervation was the first identified mechanism for a non-motor aspect of PD.

Most patients with Parkinson's disease have evidence for loss of sympathetic nerves in the heart.

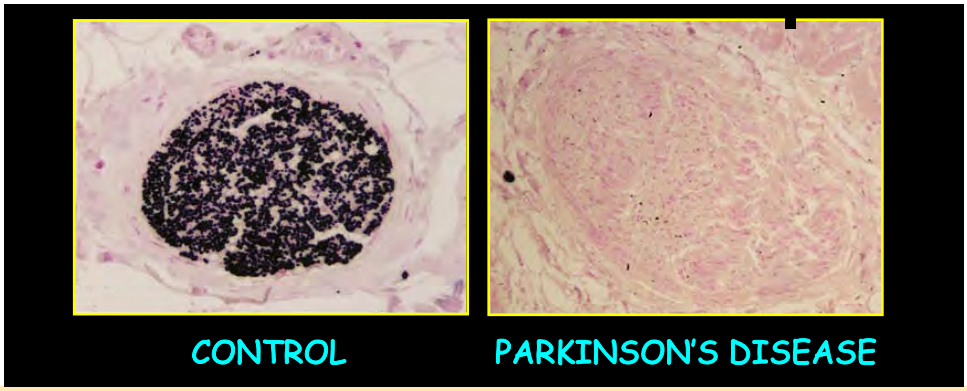


Fig. 353: Cardiac sympathetic denervation in Parkinson's disease (PD). *The finding of markedly decreased immunoreactive tyrosine hydroxylase (black) in epicardial nerve tissue provides pathological confirmation of cardiac sympathetic denervation in PD.*

The amount of immunoreactive tyrosine hydroxylase (THir) in epicardial nerve tissue provides a means to examine post-ganglionic sympathetic noradrenergic innervation of the heart. Epicardial THir is profoundly decreased in PD.

Cardiac sympathetic neuroimaging provided the first evidence for a specific mechanism of a non-motor aspect of PD—loss of sympathetic nerve terminals.

In PD there is just as severe loss of norepinephrine in the left ventricular myocardium as there is loss of dopamine in the putamen.

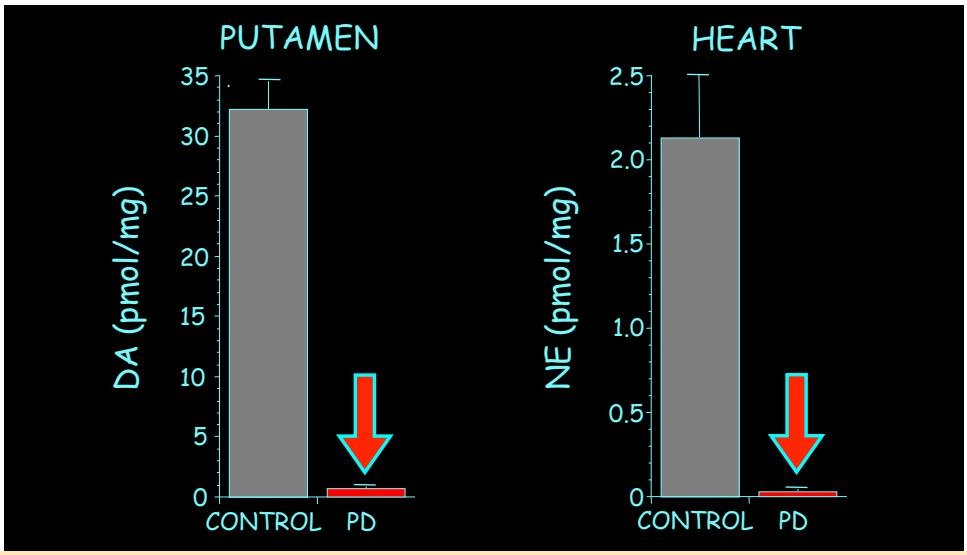


Fig. 354: Drastic putamen dopamine (DA) and cardiac norepinephrine (NE) depletion in PD. *In PD there is just as much loss of NE in the heart as there is loss of DA in the putamen, the brain area with the most DA deficiency.*

Among PD patients who do not have orthostatic hypotension (PD No OH), about 1/2 have loss of sympathetic nerves throughout the left ventricular myocardium at the time of initial evaluation, a substantial minority have partial loss of sympathetic nerves, and a few have normal innervation. The partial loss is in the inferolateral wall of the heart.

The clinical significance of loss of sympathetic nerves in the heart in Parkinson's disease is poorly understood. One would guess that this might cause or contribute to fatigue or to shortness of breath during exercise.

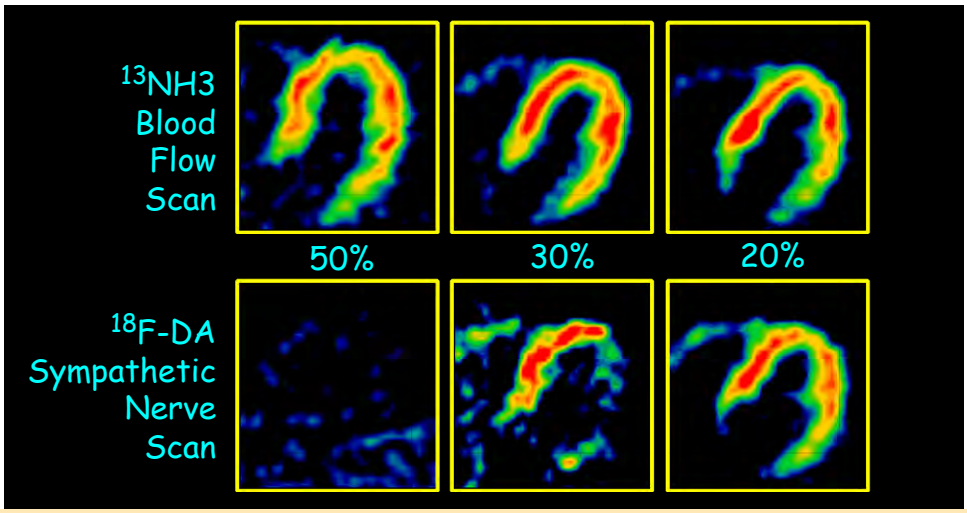


Fig. 355: Cardiac sympathetic neuroimaging in PD without orthostatic hypotension (PD No OH). *About 1/2 of PD No OH patients have diffusely decreased ^{18}F-dopamine- (^{18}F-DA) derived radioactivity in the left ventricular myocardium. Myocardial perfusion by ^{13}N-ammonia ($^{13}NH_3$) scanning is normal.*

In PD When does Cardiac Sympathetic Denervation Develop?

The findings in a case we reported several years ago demonstrate that cardiac sympathetic denervation can precede the movement disorder by several years. This finding fits with Braak's concept about the pathogenetic sequence of synucleinopathy in PD. According to Braak there is early autonomic involvement, followed by alpha-synuclein

deposition in the dorsal motor nucleus of the vagus nerve in the caudal medulla (stage 1), then in the rostral ventrolateral medulla, midline raphe nuclei, and pontine locus ceruleus (stage 2), and only in stage 3 in midbrain substantia nigra.

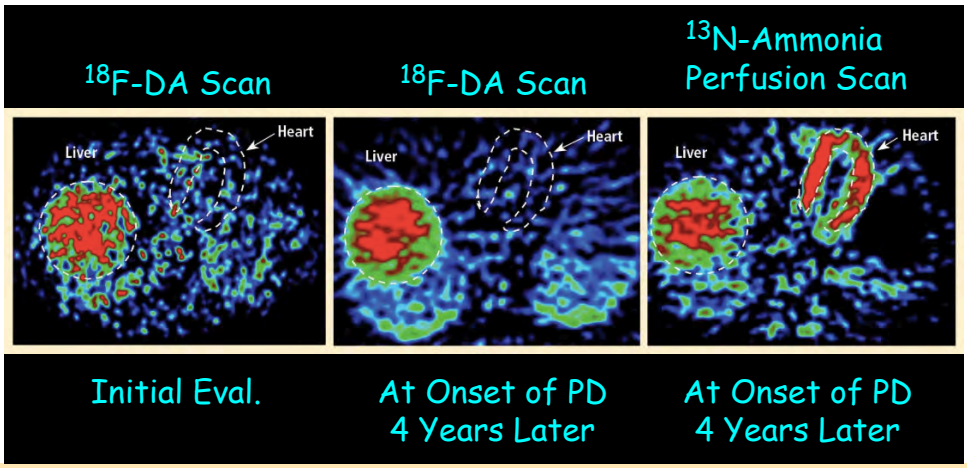


Fig. 356: Cardiac sympathetic lesion preceding the motor onset of Parkinson's disease (PD). *This PD patient had evidence of cardiac sympathetic denervation about 4 years before developing motor signs of PD.*

The patient underwent a workup at the NIH Clinical Center for a possible pheochromocytoma, a tumor that produces and releases catecholamines, because he had variable high blood pressure. As part of the testing the patient had a ^{18}F-dopamine PET scan. The workup was negative, and he was given a diagnosis of "pseudopheochromocytoma."

About 4 years later he returned for testing, this time to be in a study about pseudopheochromocytoma. He reported that over the past few months he had noted the gradual onset of slow movement, limb rigidity, a shuffling gait, and decreased facial expression.

He said he felt and looked like a robot. He was diagnosed with PD by a neurology consultant. Cardiac sympathetic neuroimaging by ^{18}F-dopamine PET scanning showed a loss of sympathetic noradrenergic innervation, as is typical of PD.

In retrospect, the ^{18}F-dopamine PET scan from 4 years previously had shown the same loss of sympathetic innervation throughout the left ventricular myocardium.
This was the first reported case of cardiac sympathetic denervation preceding motor signs of PD.

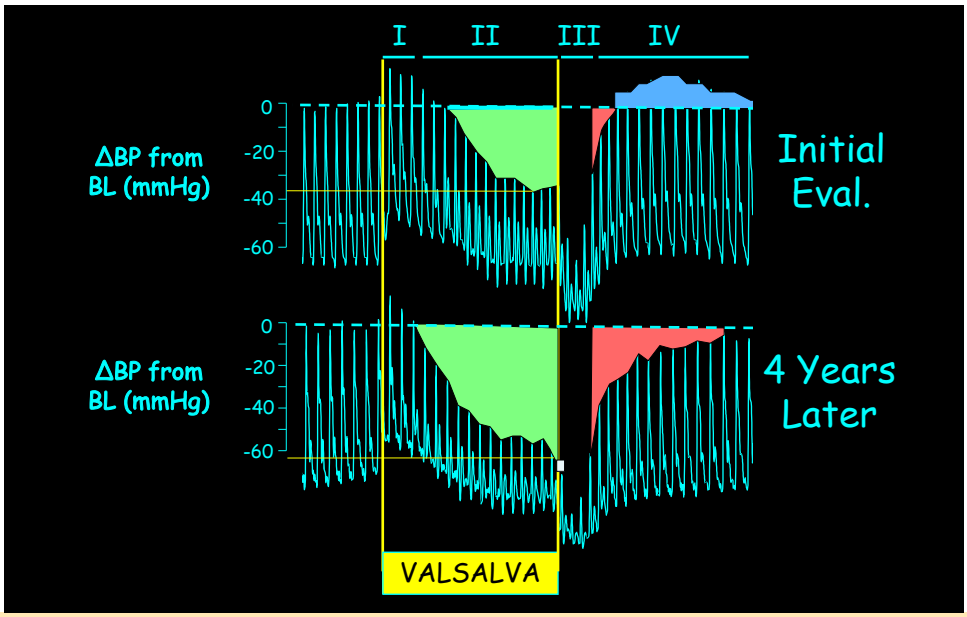


Fig. 357: Valsalva BP before and after motor onset of PD. *Based the calculation of baroreflex areas the patient had a decline in baroreflex-sympathoneural function.*

In the interim the patient also had developed baroreflex-sympathoneural failure. The beat-to-beat blood pressure (BP) response to the Valsalva maneuver now showed a progressive decrease in BP in Phase II and no overshoot of BP in Phase IV.

On the other hand, patients who already have symptomatic PD can have normal or only localized loss of cardiac sympathetic innervation. This doesn't fit with Braak's concept. For instance, several years ago we evaluated a PD patient who did not have orthostatic hypotension and found that she had decreased ^{18}F-dopamine-derived radioactivity in the left ventricular free wall and apex of the heart, but there was normal radioactivity in the septum.

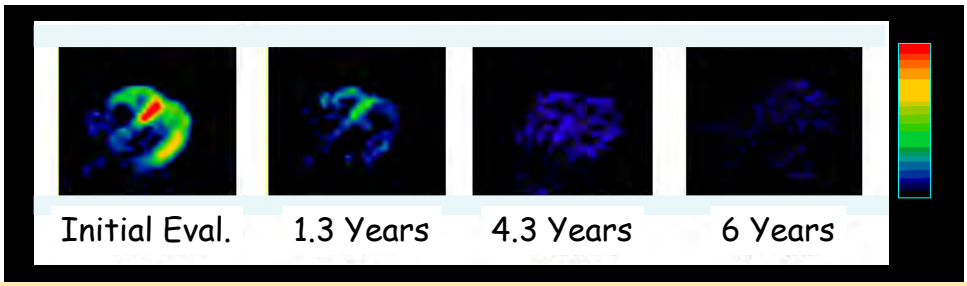


Fig. 358: Progression from partial to diffuse cardiac sympathetic denervation in Parkinson's disease (PD). *This PD patient had partial cardiac denervation when first seen. The denervation progressed rapidly.*

Over the course of just a few years the loss of innervation progressed to completion.

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

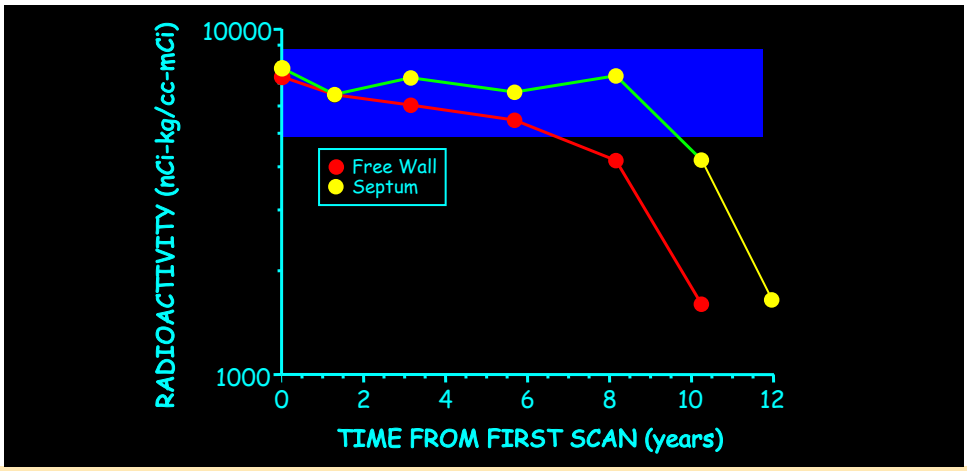


Fig. 359: Progression from normal to diffuse loss of cardiac sympathetic innervation in a Parkinson's disease (PD) patient. *In this patient with PD it took several years for cardiac ^{18}F-dopamine-derived radioactivity to decrease. The loss began in the left ventricular free wall and then progressed rapidly to include the anterobasal septum.*

Across patients with PD there is no relationship between the extent of the putamen dopaminergic lesion, as indicated by the putamen/occipital cortex ratio of ^{18}F-DOPA-derived radioactivity, and the extent of the sympathetic noradrenergic lesion, as indicated by the septal myocardial concentration of ^{18}F-dopamine-derived radioactivity. Instead, the loss of cardiac sympathetic noradrenergic nerves seems to occur independently of the striatal dopaminergic lesion underlying the movement disorder. In some patients the finding of cardiac sympathetic denervation might be a biomarker predicting later development of PD, while in others cardiac sympathetic denervation is a late finding.

It seems that all PD patients eventually lose cardiac sympathetic nerves. It may take several years for this to begin, but once it

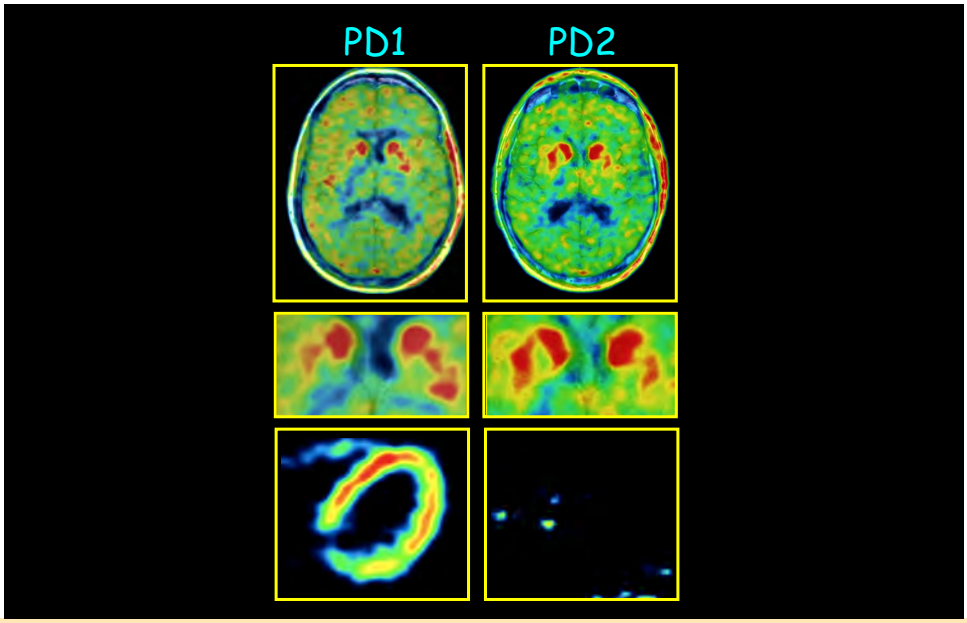


Fig. 360: Independent striatal dopaminergic and cardiac noradrenergic lesions in PD. *In these PD patients with similar abnormalities of striatal ^{18}F-DOPA-derived radioactivity, in patient 1 cardiac noradrenergic innervation by ^{18}F-dopamine scanning is normal, whereas in patient 2 there is a severe sympathetic noradrenergic lesion.*

does, the loss progresses rapidly.

THE "SICK-BUT-NOT-DEAD" PHENOMENON

Until recently it was presumed that the catecholamine deficiency that characterizes PD directly and solely reflects the loss of catecholaminergic neurons. While it is true that there is substantial catecholaminergic denervation in the nigrostriatal dopaminergic and sympathetic noradrenergic systems, the extent of depletion of the neurotransmitters is greater than the extent of the denervation. This seems paradoxical: How can

there be a greater loss of a neurotransmitter than of the nerves that contain the transmitter?

The resolution of this apparent paradox is that the remaining neurons are "sick-but-not-dead." They have functional abnormalities that prevent adequate storage in the vesicles.

Recently the meaning of "sick-but-not-dead" has been fleshed out in detail in the cardiac sympathetic nerves of patients with Lewy body diseases.

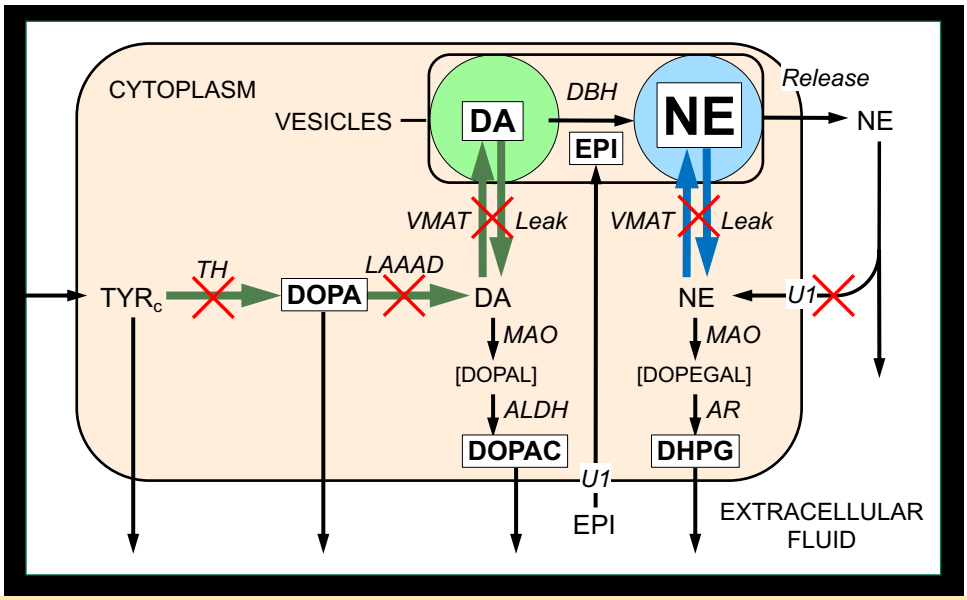


Fig. 361: "Sick-but-not-dead" phenomenon. *Cardiac noradrenergic deficiency in Lewy body diseases results not only from loss of sympathetic nerves but also from multiple functional abnormalities in residual nerves.*

There are three types of functional abnormalities in cardiac sympathetic nerves that contribute to denervation-independent depletion of norepinephrine stores. First, there is decreased

dopamine synthesis via tyrosine hydroxylase (TH) and L-aromatic-amino-acid decarboxylase (LAAAD). Second, there is increased net leakage of catecholamines from the vesicles into the cytoplasm. Third, there is decreased recycling of released norepinephrine because of decreased efficiency of the cell membrane norepinephrine transporter (NET).

The sick-but-not-dead phenomenon has important implications for treatment or prevention. You can't treat neurons that aren't there, but if there were sick-but-not-dead neurons, you might be able to salvage or protect them. The concluding section of this book, on ideas for the future, picks up on this theme.

PD with Orthostatic Hypotension (PD+OH)

Synopsis:
Elderly of either sex and any race
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.

It has been estimated that 90% of PD patients have symptoms or signs of abnormal autonomic functions.

Exactly how these problems, which reflect involvement of different components of the autonomic nervous system, relate to each other is unclear. For instance, in PD the prevalence of constipation and urinary frequency and urgency is about the same regardless of the occurrence of orthostatic hypotension (OH).

OH as defined by an orthostatic decrease of 20 mmHg or more in systolic pressure occurs in 30-40% of patients with PD. 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 orthostatic hypotension 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.

Orthostatic hypotension (OH) in PD is always associated with evidence of sympathetic noradrenergic deficiency. 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. This means that the sympathetic lesion in PD+OH is neurotransmitter-

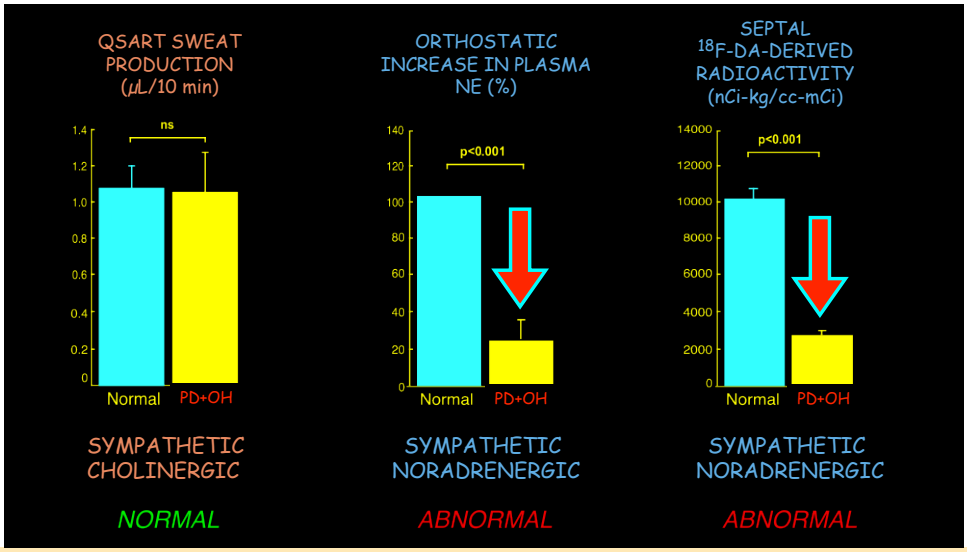


Fig. 362: Neurotransmitter specificity of the sympathetic lesion in Parkinson's disease with orthostatic hypotension (PD+OH). *In PD+OH, sympathetic cholinergic function usually is normal, whereas sympathetic noradrenergic function (measured by the percent increase in plasma norepinephrine (NE) during head-up tilt table testing or by cardiac ^{18}F-dopamine scanning)) is abnormal.*

specific. The results of cardiac sympathetic neuroimaging are so consistent that in a patient with parkinsonism and OH the finding of normal cardiac sympathetic innervation excludes PD+OH.

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

Patients with PD often have constipation and urinary urgency, frequency, and incontinence. These might reflect a form of failure of the parasympathetic nervous system (PNS); whether

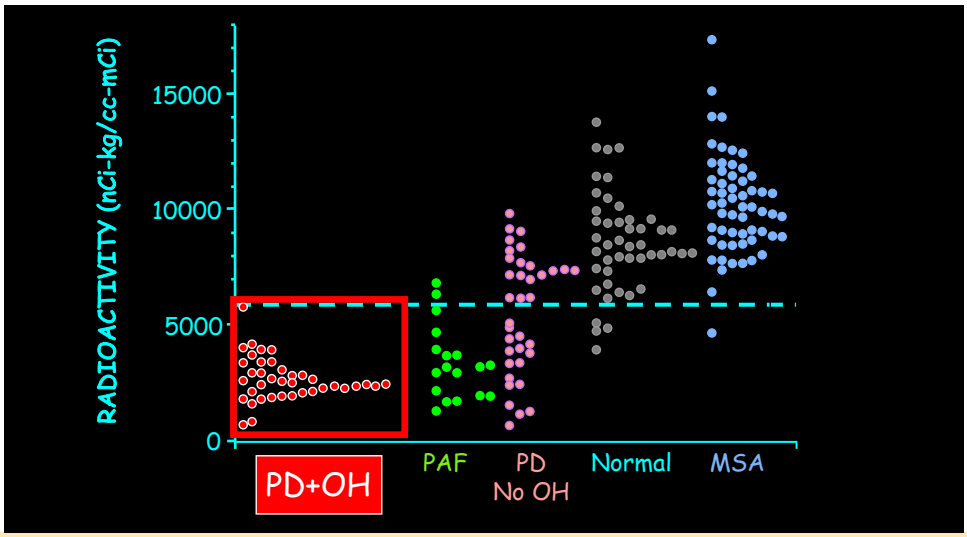


Fig. 363: Cardiac sympathetic neuroimaging in PD+OH. *As shown here by ^{18}F-dopamine PET scanning, all PD+OH patients have evidence of cardiac noradrenergic deficiency.*

this is the case remains unknown. Decreased traffic in the vagus nerve, the nerve of the PNS 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 reflexive regulation of traffic in intact nerves.

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

The Contursi and Iowa Kindreds

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

reported—mutation of the gene encoding the protein, alpha-synuclein. In 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 *SNCA* was found to be causative in this family. This rare form of familial PD is now called PARK1. Exactly why and how this "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.

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-sympathoneural failure and sympathetic noradrenergic deficiency.

Another form of familial PD was reported in a kindred called

the Iowa kindred. Here the causative abnormality is triplication of the normal *SNCA* gene. This form of dominantly inherited PD is now called PARK4. PARK4 patients also have physiological evidence of baroreflex-sympathoneural failure and neuroimaging evidence of cardiac noradrenergic deficiency.

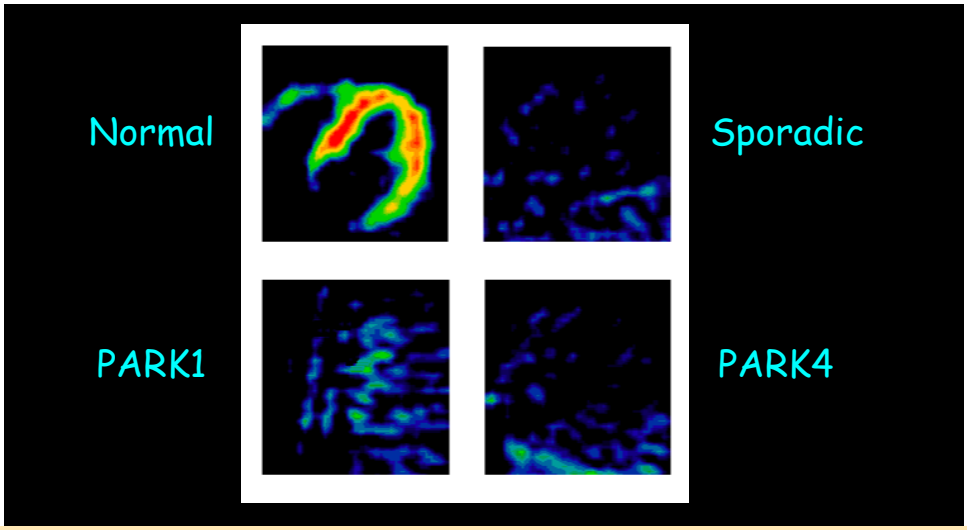


Fig. 364: Cardiac sympathetic lesion in PARK1 and PARK4. *The finding of severely decreased ^{18}F-dopamine-derived radioactivity in PARK1 and PARK4 demonstrates that alpha-synucleinopathy can cause a loss of sympathetic noradrenergic neurons.*

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

Fig. 365: Janet Reno (1938-2016). *Reno, the 78th Attorney General of the United States, developed Parkinson's disease (PD) while in office. She fainted frequently. One may speculate she had PD with orthostatic hypotension.*

PD. About two years later 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 2002 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 a patient with neurogenic orthostatic hypotension (nOH), attending a church service on a hot Sunday morning could be a real autonomic stress test, with fainting evoked by severely decreased blood pressure (BP). First, the patient would likely be standing still for prolonged periods, resulting in blood pooling in the abdomen, pelvis, and legs. Second, nOH is usually worst in the morning. 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, tending to decrease BP. Fifth, if a church breakfast preceded the service, blood could have been shunted toward the gut after the meal (post-prandial hypotension). Sixth, if the worshipper felt distressed during the service, high circulating adrenaline levels could have shunted the cardiac output toward the relaxed skeletal muscle blood vessels and away from the brain.

Janet Reno died of her disease on November 7, 2016, at the age of 78.

Dementia with Lewy Bodies

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

Fig. 366: Celebrities who had dementia with Lewy bodies (DLB). *Estelle Getty, Robin Williams, and Casey Kasem were celebrities who had DLB.*

There are three core features for diagnosing DLB: (1) fluctuating cognition, attention, and alertness; (2) visual hallucinations; and (3) parkinsonism. Two of these core features should be present for a diagnosis of *probable* DLB, and one core feature should be present for a diagnosis of *possible* DLB.

There are also three suggestive features, and if there is one core feature and in addition a suggestive feature, this switches the diagnosis from possible to probable DLB. The three suggestive features are: (1) dream enactment behavior, as in REM behavior disorder; (2) severe sensitivity to neuroleptic drugs (drugs used

for psychoses such as schizophrenia); and (3) deficient dopamine transporter function in the basal ganglia as demonstrated by SPECT or PET imaging.

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 already existing PD.

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, while DLB patients have fluctuating mental status.

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 Lewy body disease, involves cardiac noradrenergic deficiency. Cardiac sympathetic neuroimaging is usually abnormal in DLB, whereas it is usually normal in Alzheimer's disease.

SEEING THINGS? WHO, ME?

I once had a patient who was a retired Professor of physics at a local university. This highly intelligent and educated individual had parkinsonism, orthostatic hypotension, and cognitive impairment. How do you ask such a person if he has visual hallucinations?

I put it this way: "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?" Here is how he answered:

"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 it's 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 IRONIC CASE OF DR. THOMAS GRABOYS

Dr. Thomas Graboys was one of the cardiology "dream team" who evaluated Reggie Lewis after Lewis had collapsed during an NBA playoff game (you can read the story on p. 340 above). Another consultant did a tilt table test and determined that Lewis had merely fainted and could return to playing basketball. Before Lewis ever set foot again on an NBA court, however, he collapsed again—and died. His syncopal episode had not been benign but had been the sign of a serious medical

condition.

Graboys wrote a book, *Life in the Balance*, in which he related that on the morning of his second marriage, *he* had fainted. He called a cardiologist colleague 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. His cardiologist dismissed the problem as mere fainting. Graboys didn't tell his wife about this until later. This proved to be a major, enduring 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's disease with orthostatic hypotension (PD+OH) and dementia with Lewy bodies (DLB).

Fig. 367: Dr. Thomas Graboys (1944-2015). *Graboys was a member of the cardiology "dream team" that examined Reggie Lewis. Graboys died of dementia with Lewy bodies (DLB).*

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 died in January, 2015.

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 Dr. 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 expressed in all body cells, such as mutation of the gene encoding alpha-synuclein, 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? 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. A getaway car is kept in "idle" at the curb outside the bank. 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.

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. Cytosolic dopamine can be rendered toxic by conversion to the catecholaldehyde 3,4-dihydroxyphenylacetaldehyde (DOPAL). A getaway car has a catalytic converter to deal with byproducts of combustion, and dopamine neurons have an enzyme (enzymes literally are catalytic converters) to detoxify DOPAL. If the enzyme (aldehyde dehydrogenase) were inhibited, then eventually there would be "autotoxicity" (that was funny) caused by DOPAL,

and the neurons would die.

With this introduction, in his *Life in the Balance* Graboys wrote as follows 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…"

I can't imagine a more poignant, ironic use of the getaway car analogy.

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 that regulate the autonomic nervous system.

Several unconscious “vegetative” functions fail, such as digestion, urination, speech and swallowing mechanisms, and cardiovascular reflexes.

No one knows what causes MSA. There is no convincing evidence that in the United States the disease is inherited. No environmental toxin is known to cause it.

A currently prevalent but controversial view is that misfolded alpha-synuclein acts like a prion (an abbreviation for “proteinaceous infectious particle”). A prion is a misfolded protein that can cause misfolding of the same protein (templating), in a kind of chain reaction. The prion theory of MSA posits that misfolded alpha-synuclein is transmitted from cell to cell, induces misfolding of alpha-synuclein in target glial cells, and as a result of the glial cell pathophysiology produces central neurodegeneration as is found in MSA. So far the theory has not been tested completely. In particular, there is no evidence for infectious spread of MSA from human to human.

According to another view, MSA reflects a form of autoimmune process where the patient’s immune system attacks and destroys particular brain cells. These concepts are not mutually exclusive, since misfolded alpha-synuclein could arouse an autoimmune response.

Brain tissue from MSA patients shows abnormal accumulations of alpha-synuclein in glial cells (glial cytoplasmic inclusions, or GCIs), which are not neurons. Perhaps the accumulations interfere with the ability of glial cells to produce the nerve growth factor, glial cell line-derived neurotrophic factor (GDNF). Whether GCIs cause or are a result of the disease and

the mechanisms by which alpha-synuclein accumulates in glial cells are unknown.

MSA has different forms that result in different symptoms and signs. In the parkinsonian form of MSA (MSA-P) the patient has symptoms and signs of Parkinson's disease (PD) such as slow initiation of movement, imbalance, muscular rigidity, and stooped posture. Unlike in PD, however, these problems usually do not respond well to treatment with levodopa-carbidopa, the most commonly used drug for PD, 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. The tremor in cerebellar ataxia worsens with intentional movements. The patient has slurred speech and a wide-based, "drunken sailor" type gait.

Some MSA patients have both parkinsonism and cerebellar ataxia. This used to be referred to as a "mixed" form of MSA, but this term has been abandoned. Now some investigators diagnose MSA-P or MSA-C based on the main symptoms at the time of onset of the movement disorder, and others diagnose MSA-C only if there is cerebellar ataxia and no evidence of parkinsonism at any time in the disease course. By either approach, MSA-C is less common than is MSA-P.

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 eponymic term, Shy-Drager syndrome, is no longer used. Previously there also was an autonomic-dominant form of MSA, where the presenting problem was orthostatic intolerance due to OH. This designation is no longer used, although in some patients presenting with neurogenic OH the condition evolves into MSA-P or MSA-C.

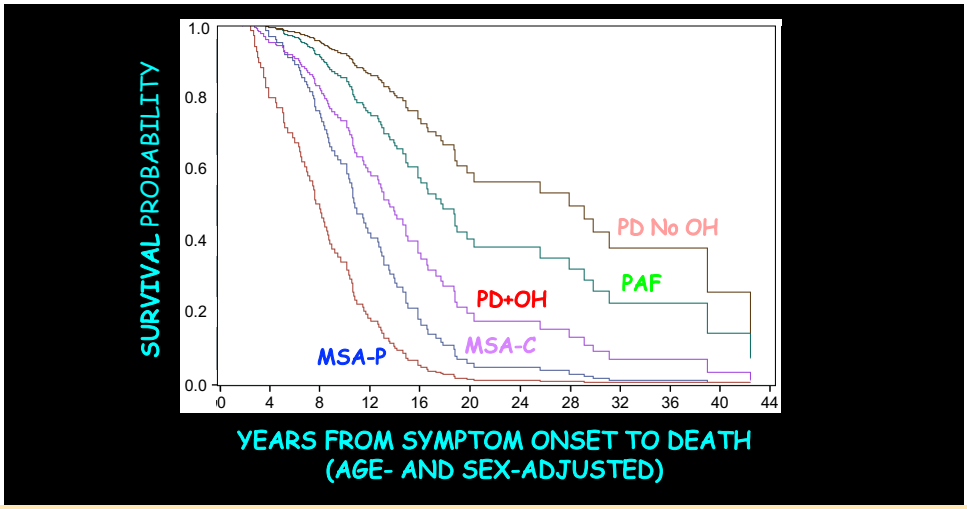


Fig. 368: Survival in synucleinopathies. *Survival is poor in multiple system atrophy (MSA), whether of the parkinsonian (MSA-P) or cerebellar (MSA-C) type.*

MSA is progressive and eventually lethal. The median survival time from the onset of the movement disorder (parkinsonism or cerebellar ataxia) is about a decade.

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.

MSA always involves one or more symptoms or signs of failure of the autonomic nervous system. Decreased parasympathetic nervous system (PNS) activity produces urinary retention and incontinence, constipation, and erectile failure in men. Decreased sympathetic noradrenergic system (SNS) activity 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.

Symptoms and signs of brainstem neurodegeneration 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 "down the wrong pipe." These problems occasionally occur in patients with MSA who do not have orthostatic hypotension or other evidence of SNS failure.

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

Loss of neurons in parts of the central autonomic network probably underlie the autonomic failure in MSA. These areas include the C1 area of adrenaline-producing neurons in the rostral ventrolateral medulla (RVLM), which project to the sympathetic pre-ganglionic neurons in the intermediolateral columns of the spinal cord; and the A1 area of noradrenergic

neurons in the caudal ventrolateral medulla (CVLM), which are part of the baroreflex arc and project to the nuclei of the hypothalamus that regulate vasopressin (AVP) release. Involvement of the micturition center in the pons and Onuf's nucleus in the sacral spinal cord can account for urinary retention; and while loss of neurons in the medullary pre-Bötzinger complex and raphe nuclei might play a role in sleep-related respiratory abnormalities.

Distinguishing the parkinsonian form of MSA (MSA-P) from Parkinson's disease with orthostatic hypotension (PD+OH) can be a difficult clinical diagnostic challenge. In MSA it is thought that the autonomic failure reflects loss of the ability to regulate sympathetic and parasympathetic nerve traffic appropriately, but the post-ganglionic nerves themselves are intact. This appears to be a major difference between MSA and PD+OH, in which OH is associated with a loss of sympathetic noradrenergic nerves, at least in the heart.

Because of the presence of intact sympathetic noradrenergic nerves, patients with MSA have large increases in blood pressure when they receive drugs that release norepinephrine from sympathetic nerves or inhibit the neuronal reuptake of norepinephrine. MSA patients also have large decreases in blood pressure when they receive drugs that reduce norepinephrine release from sympathetic nerves. The finding that ganglion blockade substantially decreases blood pressure in patients with MSA indicates that in MSA the problem is not so much decreased autonomic nerve traffic as failure of the brain to regulate that traffic appropriately.

During supine rest MSA patients have normal plasma levels of

norepinephrine (NE) and other catechols. Typically there is a failure to increase plasma NE levels normally when the patient stand up from lying down, due to baroreflex-sympathoneural failure.

NEUROIMAGING IN MSA

Magnetic resonance imaging (MRI) of the brain can be quite revealing in multiple system atrophy (MSA). As the name implies, there are multiple brain regions affected, especially in the brainstem.

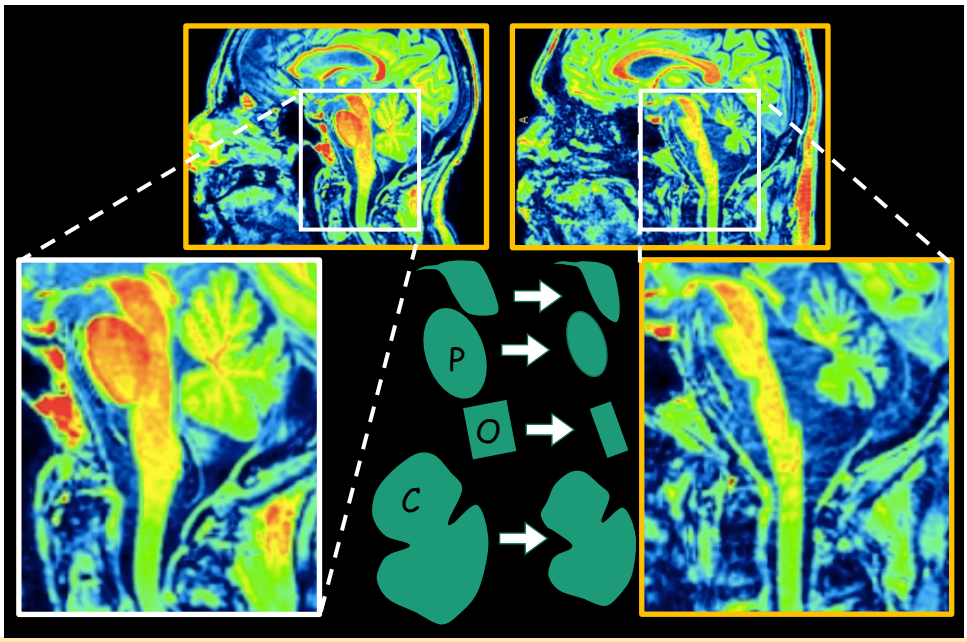


Fig. 369: MRI in MSA-C. *This patient clinically had the cerebellar form of multiple system atrophy (MSA). Magnetic resonance imaging (MRI) showed atrophy of the ventral medulla (the olivary nucleus region, O), pons (P), and cerebellum (C). That is, the patient had olivopontocerebellar atrophy (OPCA). He also had midbrain atrophy (*).*

MRI can identify atrophy of the cerebellum or brainstem as illustrated in Fig 369.

A valuable way to distinguish MSA from pure autonomic failure (PAF) and from Parkinson's disease with orthostatic hypotension (PD+OH) is by cardiac sympathetic neuroimaging. In MSA cardiac sympathetic neuroimaging usually is normal (blue circles in Fig. 363).

In a patient with parkinsonism and OH, the finding of normal results of cardiac sympathetic neuroimaging excludes PD+OH and supports MSA-P.

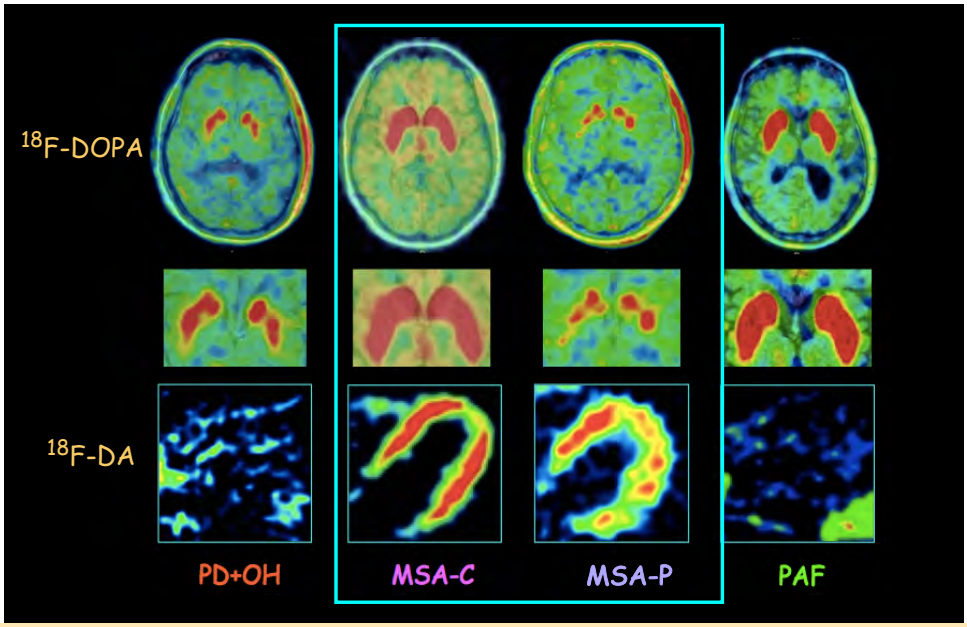


Fig. 370: ^{18}F-DOPA PET scans in MSA-C and MSA-P. *The cerebellar and parkinsonian forms of MSA (MSA-C and MSA-P) usually involve intact cardiac sympathetic innervation by ^{18}F-dopamine (^{18}F-DA) scanning. MSA-P is associated with evidence for loss of putamen dopaminergic innervation.*

In our experience, patients with MSA-P always have abnormal putamen ^{18}F-DOPA-derived radioactivity, whereas patients with MSA-C can have normal radioactivity.

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 cessation of breathing while asleep. Because of urinary retention that can require self-catheterization, there is an increased risk of sepsis from urinary tract infection.

Ma Huang

A patient with MSA first came to medical attention because of a hypertensive crisis after taking *ma huang* tea.

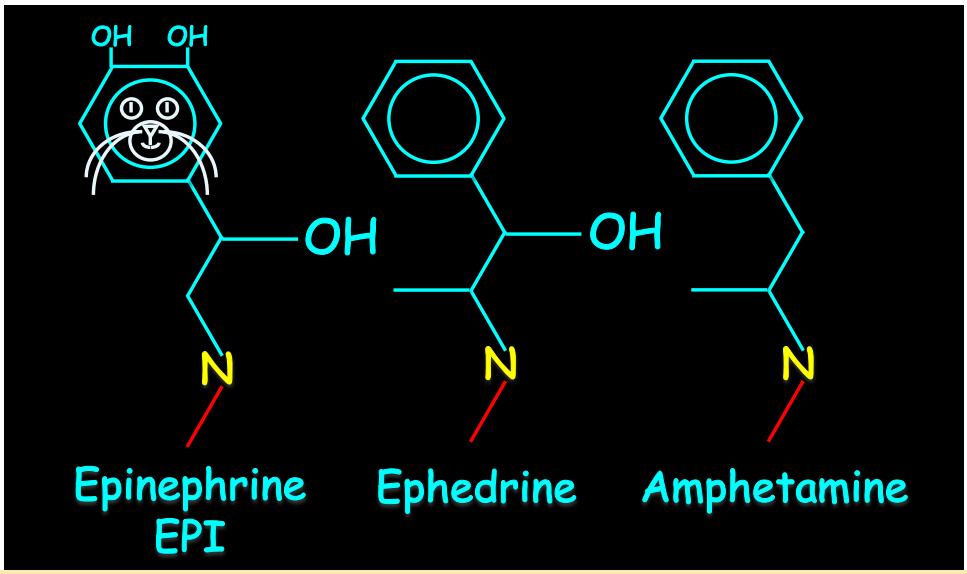


Fig. 371: Ma huang (ephedrine). *Ephedrine resembles epinephrine and amphetamine.*

Ma huang is a Chinese medicinal herb from the shrub *Ephedra sinica.* 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 his fatigue. Instead, he developed a severe headache and went to the emergency room, where he was found have had extremely high blood pressure. Because of the headache and paroxysmal hypertension he initially was diagnosed with a stroke from a subarachnoid hemorrhage, which it turned out he did not have.

What he did have was MSA. Patients with MSA have arterial baroreflex failure; this results in an inability to "buffer" acute changes in blood pressure by compensatory changes in sympathetic noradrenergic system (SNS) outflows. Ephedrine is a classic sympathomimetic amine in the chemical family of amphetamines. Ephedrine augments delivery of norepinephrine to its receptors in the cardiovascular system and therefore increases blood pressure. In the setting of baroreflex-sympathoneural failure, which characterizes MSA, sympathomimetic amines such as the ephedrine in *ma huang* evoke large increases in blood pressure.

In 2004 the US FDA banned the sale of dietary supplements derived from *Ephedra*, including *ma huang* tea.

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 labeled

"Parkinson's-plus," because her condition included parkinsonism but had some features that were not typical for Parkinson's disease (PD).

One of her most prominent symptoms was slurred speech. Eventually her speech became so garbled that she had to use an alphabet board (technically called an augmentative communication board) or a computer to communicate.

Despite this limitation Milly became a highly effective activist and advocate for increased funding of PD research. She was gracious but determined, forthright, and courageous. Her husband, Morton, wrote a book about her that became a best-seller and was the basis for a made-for-TV movie, "Saving Milly."

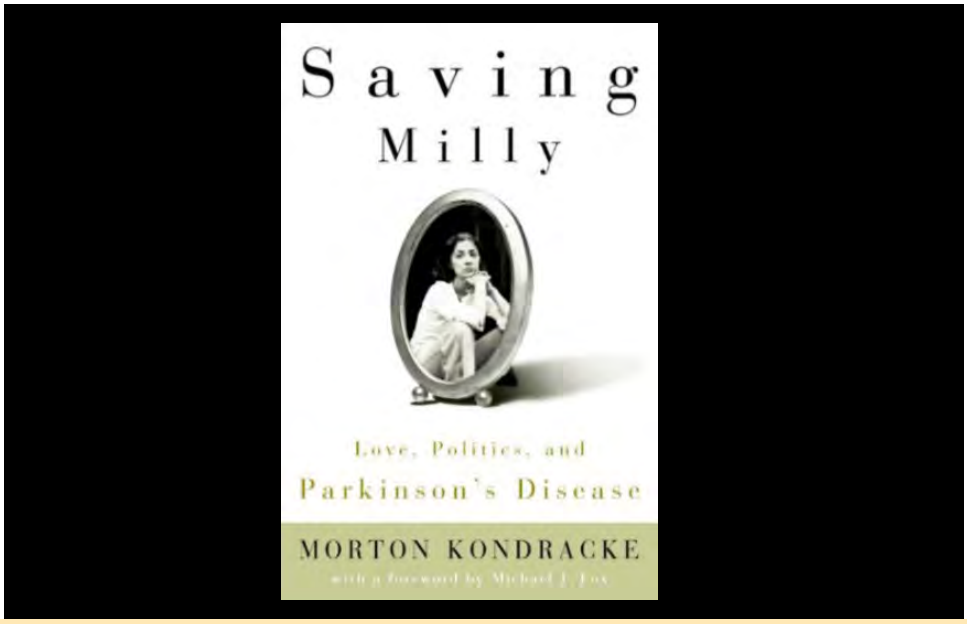


Fig. 372: Milly Kondracke. *Milly Kondracke was thought to have a variant form of Parkinson's disease.*

The book mentions that she had been a research participant in one of my studies at the NIH. Because of her slurred speech, lack of clinical improvement with even intravenous levodopa, and normal cardiac ^{18}F-dopamine-derived radioactivity I suspected she had MSA, which post-mortem neuropathology and neurochemistry confirmed.

Is Onuf Enough?

In the evaluation of a patient with possible MSA the finding of urinary retention is important. Urinary retention is much more common in MSA than in Parkinson's disease with orthostatic hypotension.

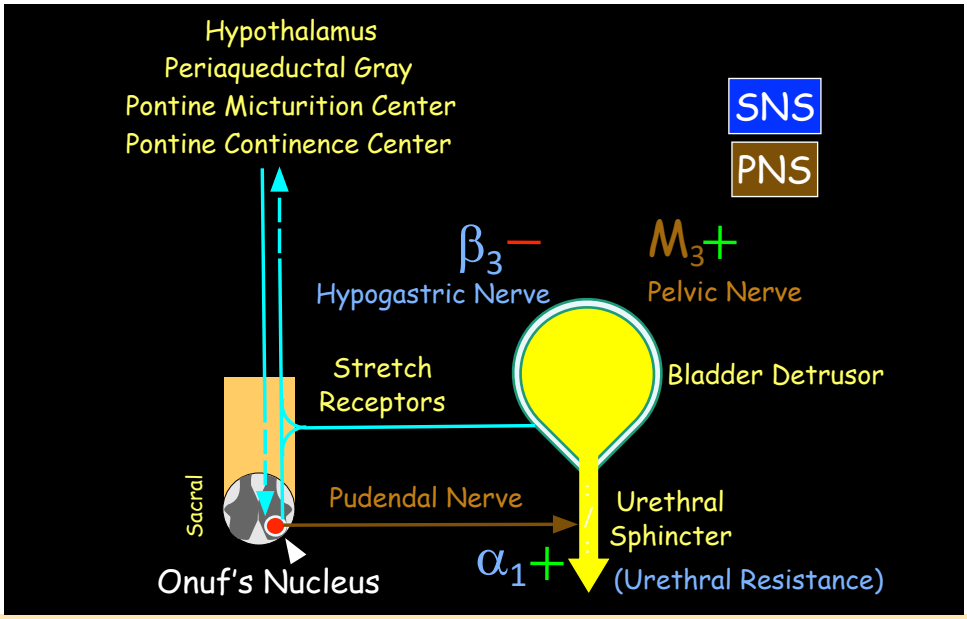


Fig. 373: Onuf's nucleus. *Neuronal degeneration in Onuf's nucleus, coupled with degeneration in brainstem regions in the central autonomic network, can explain urinary retention in MSA.*

One reason is degeneration in a region called Onuf's nucleus, which is in the anterior horn of the sacral spinal cord. Onuf's nucleus receives descending input from the "continence center" or "micturition center" in the pons of the brainstem, and it projects to the urethral sphincter by way of the pudendal nerve. Stretch receptors in the bladder wall send afferent information to the spinal cord, and the signal is transmitted both to the brainstem and to Onuf's nucleus, completing long-distance and local negative feedback loops. It seems likely that abnormalities in both the long-distance and local loops result in the urinary retention found in MSA.

MANAGING DYSAUTONOMIAS

OVERVIEW OF MANAGEMENT

Management of a patient with a dysautonomia involves more than obtaining a correct diagnosis and instituting curative treatment. Even after workups at the most sophisticated and knowledgeable centers, the diagnosis can be uncertain, especially for functional disorders where the pathophysiologic mechanisms typically remain mysterious. Even if there is an agreed upon diagnosis, such as postural tachycardia syndrome (POTS), this does not imply there is an agreed upon idea about the mechanism of the condition, the most appropriate treatment, or the long term outcome.

Expecting cures for dysautonomias is unrealistic in the vast majority of cases. On the other hand, there are many treatments for dysautonomias. This section divides these into education, non-drug treatments, and drug treatments.

We will emphasize the management of neurogenic orthostatic hypotension (nOH) and POTS, because nOH is common in the geriatric age group, and POTS is common in adolescents/young adults.

The most effective treatment of a dysautonomias is education. Non-drug treatments typically are more effective than drug treatments.

NEUROGENIC ORTHOSTATIC HYPOTENSION (nOH)

Education to Treat nOH

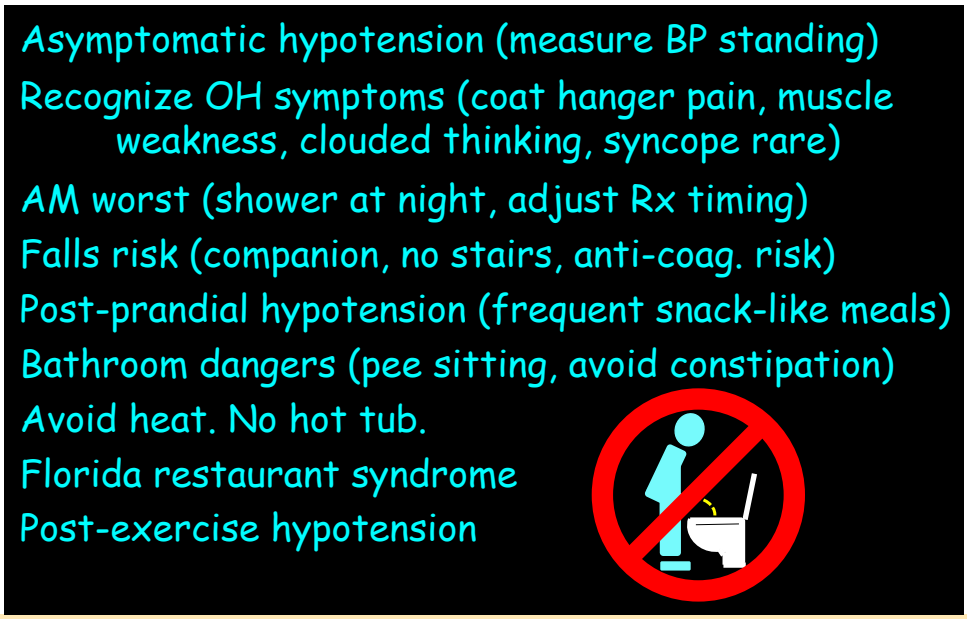


Fig. 374: Management of neurogenic orthostatic hypotension (nOH) by education, part 1.

SYMPTOMS OF OH

Patients with nOH often have no symptoms when their blood pressure is low. This means it is important to have available and use a blood pressure cuff. The key measurement is the blood pressure while standing.

When they do occur, symptoms of nOH can differ markedly across patients. Low blood pressure can manifest as

lightheadedness or faintness but also as “coat hanger” pain, visual changes, muscle weakness, or “brain fog.” Overt loss of consciousness is may not happen because of the warning symptoms.

MORNING HYPOTENSION

In patients with nOH the blood pressure typically is lowest in the morning, upon arising from bed. This may reflect a fall in blood volume overnight as a result of pressure natriuresis. As the day goes on, the blood pressure tends to increase. This means it would be safer for a patient with nOH to take a hot shower in the evening than morning.

The timing of taking pressor medications such as midodrine should also take phenomenon this into account. I usually have patients take 2/3 of the daily dose about an hour before trying to get out of bed in the morning and the remaining 1/3 at lunchtime (to avoid post-prandial hypotension).

FALLS RISKS

Orthostatic hypotension increases the risk of falls. That risk is magnified in patients with central neurodegeneration that manifests with a movement disorder or cognitive dysfunction. Effective management includes reviewing the housing arrangement with respect to climbing stairs. Falls are more dangerous in patients on an anti-coagulant, such as for atrial fibrillation.

POST-PRANDIAL HYPOTENSION

Eating a large meal shunts blood toward the gut as part of the digestive process. In a patient with nOH this shunting could come at the expense of low pressure and decreased delivery of blood to the brain. It is advisable to take frequent, small, snack-like meals.

BATHROOMS ARE DANGEROUS

Patients with nOH should view the bathroom as a dangerous place.

Performance of the Valsalva maneuver decreases blood pressure, and having a bowel movement involves Valsalva maneuvers. It is best to avoid constipation by an appropriate bowel regimen. Constipation is treated non-specifically, with stool softeners, bulk laxatives, milk of magnesia, magnesium citrate, senna, or cascara.

Standing still while urinating can cause blood to pool in the pelvis or abdomen, and in a patient with baroreflex-sympathoneural failure whatever happens to the venous return to the heart is what happens to the blood pressure. Men with nOH should urinate while sitting on the toilet.

HEAT INTOLERANCE

Heat exposure relaxes blood vessels, and because of baroreflex-sympathoneural failure patients with nOH have a decreased

ability to counter heat-induced decreases in blood pressure.

As mentioned previously, the combination of orthostatic, post-prandial, and heat-related hypotension is the dangerous triad I call “Florida Chinese restaurant syndrome” (see the text near Fig. 221).

POST-EXERCISE HYPOTENSION

During exercise, muscle pumping can maintain the blood pressure, even as vasodilator metabolites accumulate. After exercise the blood pressure may fall. Patients with nOH should have this in mind and be ready to lie down quickly after exercising.

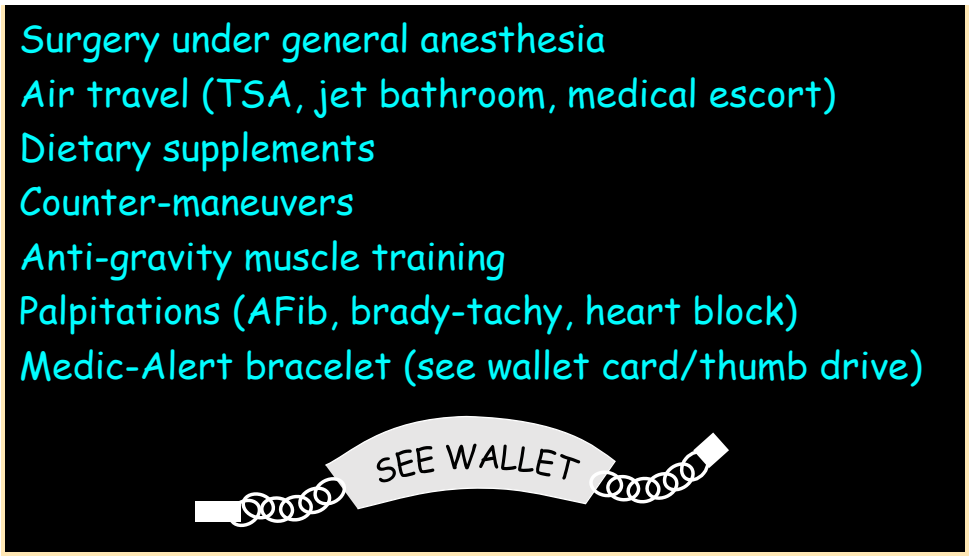


Fig. 375: Management of nOH by education: Part 2.

SURGERY AND GENERAL ANESTHESIA

During surgery under general anesthesia there can be large

swings in blood pressure because of baroreflex-sympathoneural failure in patients with nOH.

AIR TRAVEL

Air travel poses several risks in nOH patients. These include standing relatively motionless on line for TSA security checks. Depending on the severity of nOH, a medical escort may be needed. As noted previously, the bathroom in a jet is an especially dangerous place. I don't know if low cabin pressure (which decreases the amount of oxygen in the air) poses a threat.

DIETARY SUPPLEMENTS & OTC REMEDIES

Dietary supplements and over-the-counter remedies should be reviewed carefully, because they can complicate management of nOH or increase risk. You may recall the anecdote about the MSA patient who had paroxysmal hypertension after drinking *ma huang* tea (p. 559). Yohimbe bark contains a chemical that inhibits alpha-2 adrenoceptors and could also increase blood pressure in the setting of MSA. Over-the-counter decongestants or vasoconstrictor eyedrops might increase blood pressure in a patient with baroreflex-sympathoneural failure.

COUNTER-MANEUVERS

Counter-maneuvers can temporarily maintain blood pressure during upright posture. These include tightening the buttocks, thighs, and calves (recall the "pretzel legs" sign, pg. 322). In an exercise training program, it may be valuable to focus on

maximizing the tone of anti-gravity muscles (e.g., rowing machine, swimming).

CARDIAC ECTOPY

There is an increased likelihood of cardiac ectopy in nOH. Blood pressure may fall excessively when there is a change in heart rhythm, manifesting with palpitations.

Every patient with nOH should have a Medic-Alert or similar bracelet.

Non-Drug Treatment of nOH

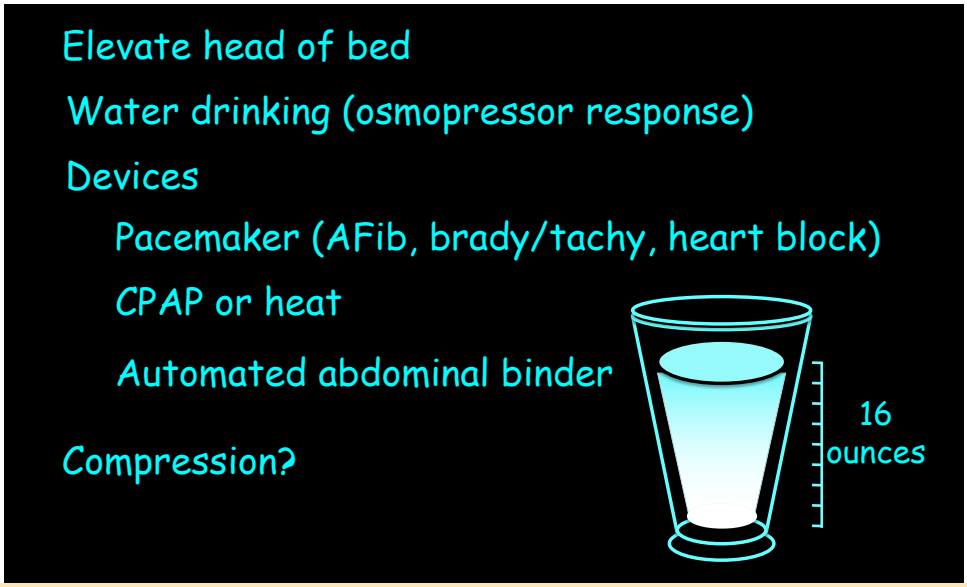


Fig. 376: Non-drug treatments for nOH.

ELEVATION OF THE HEAD OF THE BED

In patients with nOH, elevation of the head of the bed on blocks at night improves the ability to tolerate standing up in the morning.

Fig. 377: Elevation of the head of the bed. *This non-drug treatment can mitigate not only supine hypertension at night but also orthostatic hypotension in the morning.*

WATER DRINKING

A sometimes very effective tactic to increase blood pressure in patients with nOH is to drink 16 ounces of water.

There is an "osmopressor response," in which ingested water without solute acts in the gut or liver to increase sympathetic noradrenergic system outflow. The sensors evoking the

response are still unknown.

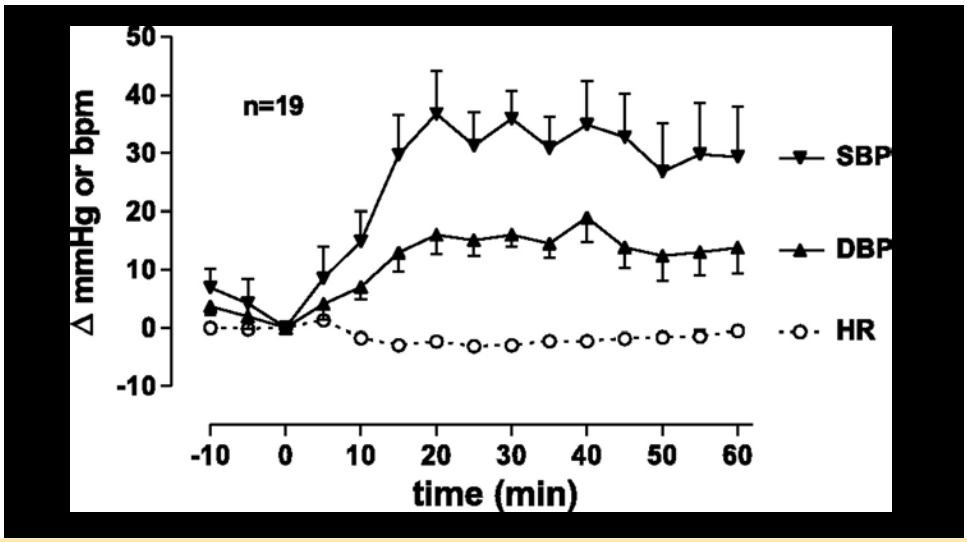


Fig. 378: Water drinking to increase blood pressure. *This graph shows the osmopressor response to ingesting 16 ounces of water.*

HIGH SALT INTAKE

Normally when a person takes in a high salt diet the kidneys increase the amount of salt in the urine, and this limits the increase in blood volume. After a few days of the same salt intake, the rate of sodium excretion equals the rate of intake.

For a high salt diet to increase body fluid volume effectively, drugs that promote retention of sodium by the kidneys, such as fludrocortisone, are usually required.

REHAB MEDICINE

Patients with nOH in the setting of progressive central neurodegeneration 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 the risk of aspiration.

DEVICES

Because of the baroreflex failure attending OH from chronic autonomic failure, decreases in venous return to the heart are translated into decreased blood pressure. When a person stands up, blood tends to pool in the abdomen, pelvis, and legs.

Compression

Inflation of an abdominal binder (which resembles a huge blood pressure cuff) squeezes blood out of the abdomen towards the chest and increases venous return to the heart. An automated abdominal binder is under development to mitigate OH in patients with chronic autonomic failure.

In nOH the problem is less with the veins than with the arteries and arterioles, the blood vessels that carry oxygen-rich blood under high pressure to the organs and limbs. Wearing thigh-high compression stockings is inconvenient and may not be particularly beneficial in the management of nOH.

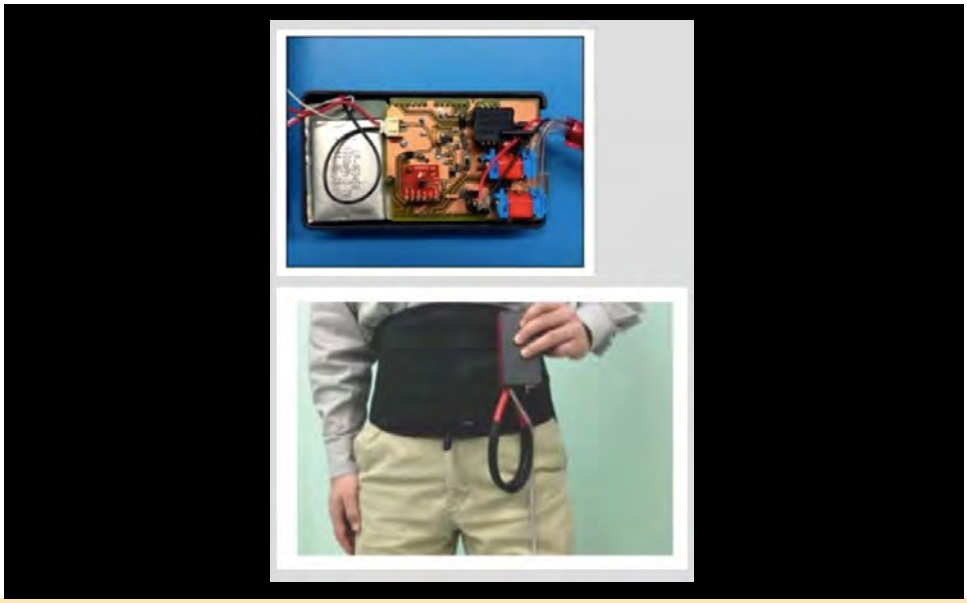


Fig. 379: Automated inflatable abdominal binder. *The underlying concept is that in patients with neurogenic orthostatic hypotension, increasing venous return to the heart increases the systemic blood pressure.*

CPAP + Heat

A substantial proportion of patients with nOH have obstructive sleep apnea and are treated with continuous positive airway pressure (CPAP). By increasing intrathoracic pressure, CPAP may tend to decrease venous return to the heart and therefore decrease blood pressure. CPAP combined with a warming blanket to relax blood vessels might ameliorate nocturnal supine hypertension.

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 long-term blood pressure regulation.

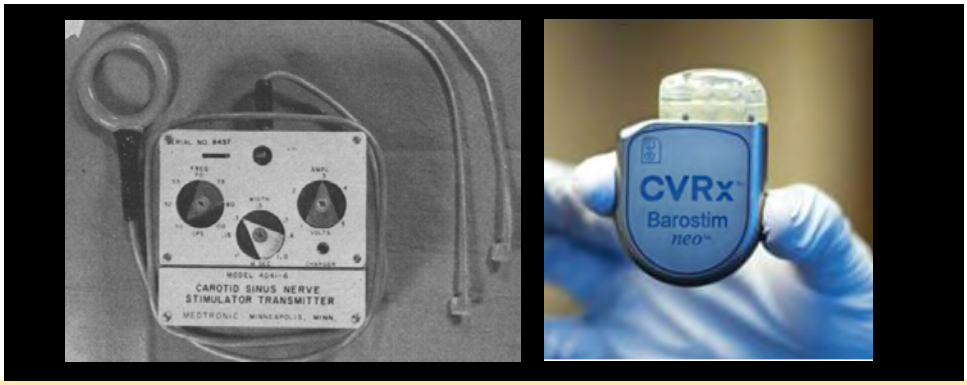


Fig. 380: Carotid baroreceptor stimulation. *Modern implanted carotid sinus stimulators are descendants of "baropacer" devices of the 1960s.*

Early in my career at the NIH, the Cardiology Branch of the National Heart, Lung, and Blood Institute was located on the 7th floor. I was allowed to use a "Baropacer" from the Branch's animal lab for an experiment designed to map out brain pathways mediating the baroreflex, by stimulating the carotid sinus nerves of cats. The experiment was a failure 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 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 (that was funny), including treatment for heart failure, some arrhythmias, and metabolic syndrome, all based on inhibition of sympathetic noradrenergic outflows by stimulating baroreflex afferent traffic.

Similar technology might be developed to treat supine hypertension in patients with nOH.

Drug Treatment of nOH

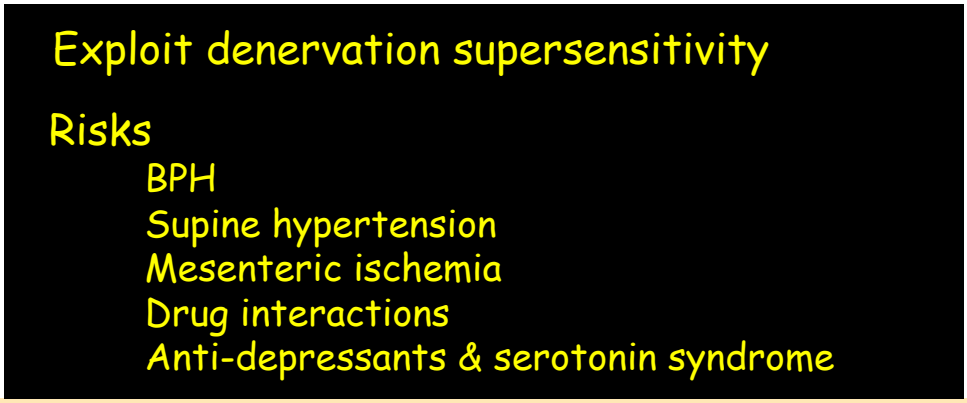


Fig. 381: Considerations in management of nOH by drugs.

FLUDROCORTISONE (FLORINEF™)

Fludrocortisone (Florinef™) is a man-made type of drug called a salt-retaining steroid, or mineralocorticoid. The drug closely resembles the body's main salt-retaining steroid, aldosterone.

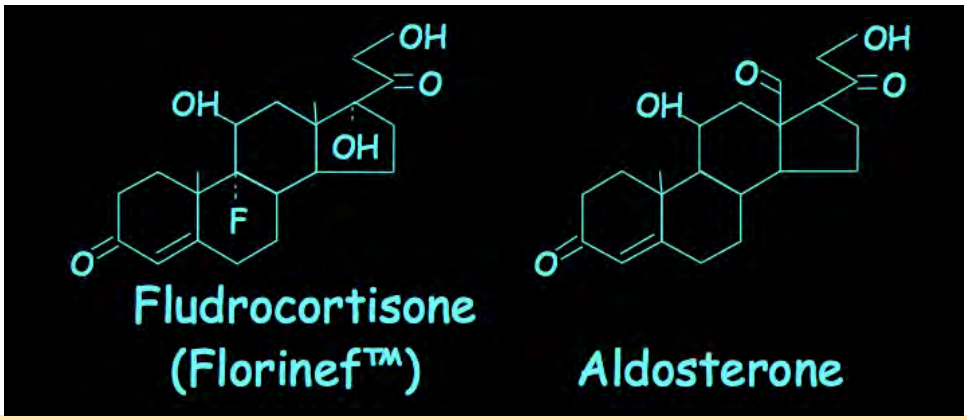


Fig. 382: Fludrocortisone & aldosterone. *Fludrocortisone closes resembles aldosterone, the main salt-retaining steroid of the body.*

In order for Florinef to work the drug must be taken with a high-salt diet. Florinef forces the kidneys to retain sodium in exchange for potassium. Water follows the sodium, and so Florinef is thought to increase the blood volume. The patient gains "fluid weight," and blood pressure increases. Because of the tendency of Florinef to waste potassium, Florinef can cause a fall in the serum potassium level, which if severe can be dangerous. Patients taking Florinef should have periodic checks of their serum potassium level, and if it is low they should take a potassium supplement.

Fludrocortisone (Florinef™) forces the body to retain sodium.

Fludrocortisone treatment increases the blood pressure regardless of the patient's posture. The increased blood pressure when the patient is standing may be large enough that the patient does not have lightheadedness or other symptoms of

orthostatic intolerance.

Since the sodium retention with fludrocortisone comes at the cost of potassium wasting, the treatment can produce low serum potassium levels. As a precaution serum electrolytes should be measured when patients on fludrocortisone are followed.

In order for fludrocortisone to increase blood volume, the patient must be on a high salt diet. A target urinary sodium excretion rate is 200 mEq per day.

MIDODRINE

When a person stands up, the sympathetic noradrenergic system is activated reflexively, the chemical messenger norepinephrine is released from the sympathetic nerves in blood vessel walls, the norepinephrine binds to alpha-adrenoceptors in the blood vessel walls, and the stimulation of the alpha-adrenoceptors causes the blood vessels to constrict (vasoconstriction), increasing the blood pressure. Midodrine (Proamatine™) is a vasoconstrictor that works by stimulating alpha-adrenoceptors in blood vessel walls.

Midodrine works like artificial norepinephrine to increase blood pressure (BP).

In patients with orthostatic hypotension related to a loss of sympathetic noradrenergic nerves, there is little norepinephrine to release. In this situation, the blood vessels become supersensitive (denervation supersensitivity), perhaps by the alpha-adrenoceptors accumulating on the surface of the cells in

blood vessel walls. In patients with "denervation supersensitivity" midodrine can be very effective in raising the blood pressure.

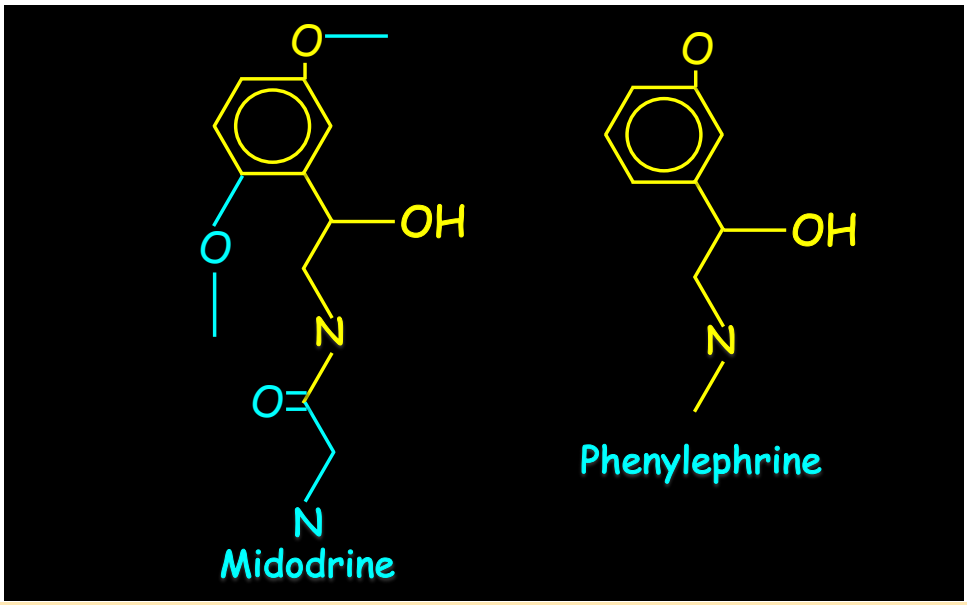


Fig. 383: Midodrine & phenylephrine. *Midodrine, which resembles phenylephrine, works like artificial norepinephrine, increasing blood pressure (BP) by stimulating alpha-adrenoceptors in blood vessel walls.*

In using midodrine to treat elderly men with orthostatic hypotension, the doctor should be aware that stimulation of alpha-adrenoceptors can worsen symptoms of prostate problems. Alpha-1 adrenoceptor blockers are effective in treating benign prostatic hypertrophy (BPH), and alpha-1 adrenoceptors blockers interfere with midodrine's effects.

In patients with sympathetic denervation taking midodrine around the clock may desensitize the alpha-adrenoceptors. It is reasonable to try taking midodrine early in the morning before

getting up and then perhaps at lunchtime to avoid post-prandial hypotension but not to take it later in the day, so that by the next morning the drug has warn off and the alpha-adrenoceptors are maximally responsive.

L-DOPS (NORTHERA™)

L-Dihydroxyphenylserine (L-DOPS, droxidopa, Northera™) is a type of chemical called an amino acid. It is very closely related chemically to L-dihydroxyphenylalanine (Levodopa, L-DOPA), which is an effective drug to treat Parkinson's disease. L-DOPA works by being converted in the brain to the catecholamine dopamine. L-DOPS works by being converted to the closely related catecholamine norepinephrine.

L-DOPS is converted to norepinephrine like L-DOPA is converted to dopamine.

L-DOPS is a neutral amino acid and as such is taken up into all cells via the neutral amino acid transporter. In cells of the gut, liver, kidneys, and other organs that contain abundant L-aromatic-amino-acid decarboxylase (LAAAD), L-DOPS is converted efficiently to norepinephrine (NE). This means that L-DOPS can provide NE even in the absence of sympathetic nerves.

Because L-DOPS is a norepinephrine pro-drug, L-DOPS administration leads indirectly to stimulation of alpha-adrenoceptors in blood vessel walls, causing the vessels to constrict and increasing the blood pressure.

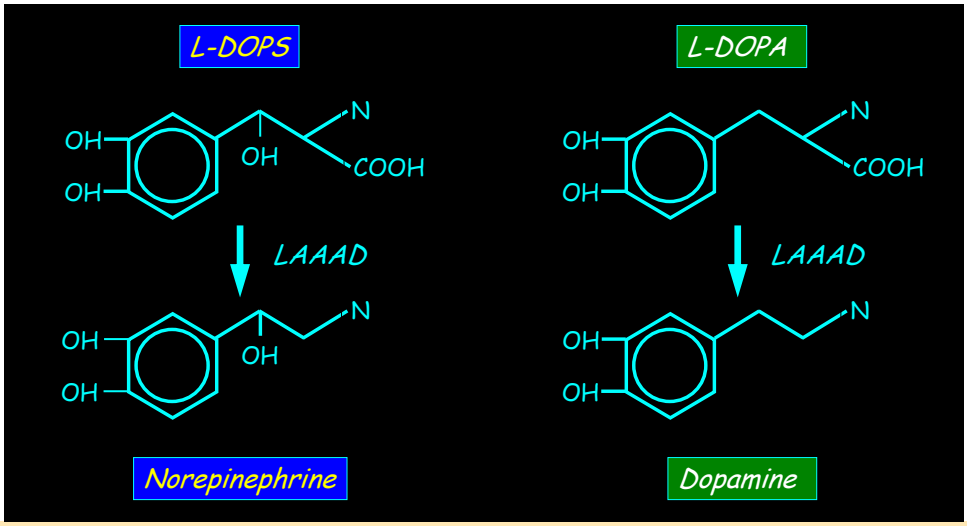


Fig. 384: L-DOPS & L-DOPA. *Just as L-DOPA is converted to dopamine by L-aromatic-amino-acid decarboxylase (LAAAD), so L-DOPS is converted to norepinephrine.*

A potential problem with using L-DOPS to treat orthostatic hypotension in patients with Parkinson's disease is that the patients usually are being treated at the same time with a combination of L-DOPA and carbidopa. The carbidopa interferes with the conversion of L-DOPA to dopamine. Since carbidopa does not enter the brain, the combination results in increased delivery of DOPA to the brain and increased production of dopamine. Carbidopa also interferes with the conversion of L-DOPS to norepinephrine. This might blunt the hoped-for increase in blood pressure by L-DOPS treatment; however, it appears that doses of levodopa/carbidopa used clinically the amount of LAAAD inhibition is too small to prevent the L-DOPS-induced increase in blood pressure.

Amphetamines

Amphetamines are chemicals that resemble the drug dextro-

amphetamine (d-amphetamine). They share a particular chemical structure (alpha-methyl-phenylethylamine), as shown in Fig. 385.

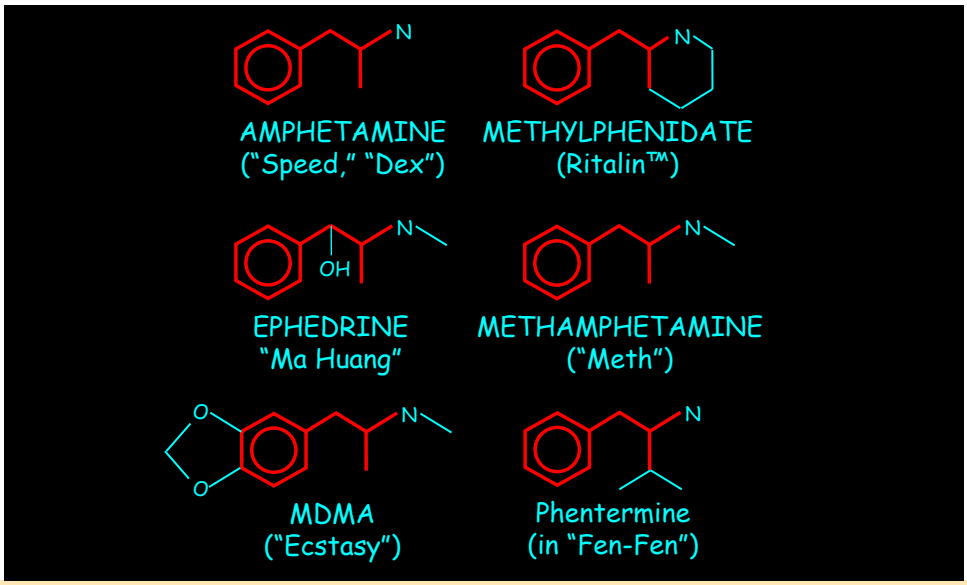


Fig. 385: Some amphetamines. *Amphetamines share an alpha-methyl-phenylethylamine chemical structure (red).*

Amphetamines are indirectly acting sympathomimetic amines. They produce their effects at least partly by increasing delivery of norepinephrine to its receptors, both in the brain and outside the brain.

By way of effects in the brain, amphetamines increase the state of arousal and attention, prevent or reverse fatigue, decrease appetite, and at high doses increase the rate and depth of breathing. They also increase blood pressure, probably by multiple mechanisms in the brain and periphery.

Pseudephedrine (Sudafed™) is structurally a mirror image (stereoisomer) of ephedrine. This difference changes the

properties of the drug and produces much less central nervous system stimulation. By releasing norepinephrine from sympathetic nerve terminals in the mucous membranes of the nasal airways, pseudephedrine tightens blood vessels, making them less leaky and thereby relieving nasal congestion.

In a laboratory pseudephedrine can be converted easily to other amphetamines that are abused drugs. This is why over-the-counter sales of pseudephedrine are now restricted.

Methylphenidate (Ritalin™), another sympathomimetic amine, is used commonly to treat attention deficit-hyperactivity disorder.

Amphetamines work both inside and outside the brain. They increase attention, decrease appetite, interfere with sleep, and often increase the blood pressure.

Phenylpropanolamine (PPE) was used in over-the-counter diet pills until the discovery of serious adverse effects such as severe high blood pressure and stroke. PPE was taken off the non-prescription drug market.

Phentermine prescribed with fenfluramine ("Phen-Fen") was an effective combination to decrease weight, until serious adverse effects of this combination came to light, and this combination is no longer prescribed.

Amphetamines should be used sparingly because of the potential for tolerance and dependence.

SOMATOSTATIN (OCTREOTIDE™)

Somatostatin (Octreotide™) is a hormone that inhibits the release of another hormone, growth hormone, from the pituitary gland at the base of the brain. Somatostatin can tighten blood vessels, especially in the gastrointestinal tract, and raise the blood pressure of patients with orthostatic hypotension. The drug must be injected, and it is expensive.

PYRIDOSTIGMINE (MESTINON™)

Pyridostigmine (Mestinon™) is a drug that works by inhibiting acetylcholinesterase, the enzyme that breaks down acetylcholine. Acetylcholine is the chemical messenger that is responsible for transmission of autonomic nerve impulses in ganglia. By attenuating the breakdown of acetylcholine, pyridostigmine is thought to increase activity of the sympathetic nervous system and improve orthostatic hypotension.

Because pyridostigmine also increases activity of the parasympathetic nervous system, the drug can increase salivation and stimulate gastrointestinal or urinary bladder contractions. There may be psychological changes because of actions of the drug in the brain. By increasing activity of the sympathetic cholinergic system pyridostigmine can increase sweat production.

DESMOPRESSIN (DDAVP™)

Desmopressin (DDAVP™) is a synthetic drug used clinically as

a replacement for the hormone vasopressin (AVP). AVP tightens blood vessels and raises the blood pressure.

Vasopressin is also called anti-diuretic hormone (ADH), because it causes the kidneys to retain water and therefore decreases production of urine. Desmopressin taken nasally is occasionally used to treat orthostatic hypotension.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

SSRIs inhibit a key process that is required for inactivating and recycling the chemical messenger serotonin. The process is reuptake of released serotonin back into the nerve terminals. SSRIs are widely used to treat depression, anxiety, and other psychiatric or emotional problems. Patients with nOH often are treated with SSRIs. This class of drugs exerts relatively little effects on autonomic functions—but see the next section on serotonin syndrome.

Serotonin Syndrome

Drugs that directly or indirectly increase occupation of serotonin receptors can under some circumstances produce a syndrome of confusion, twitching, diarrhea, headache, and evidence of sympathetic activation.

A special word of caution is in order about the treatment of teen-agers with dysautonomia who are depressed: Monoamine reuptake blockers have been statistically associated with an

increased risk of suicide.

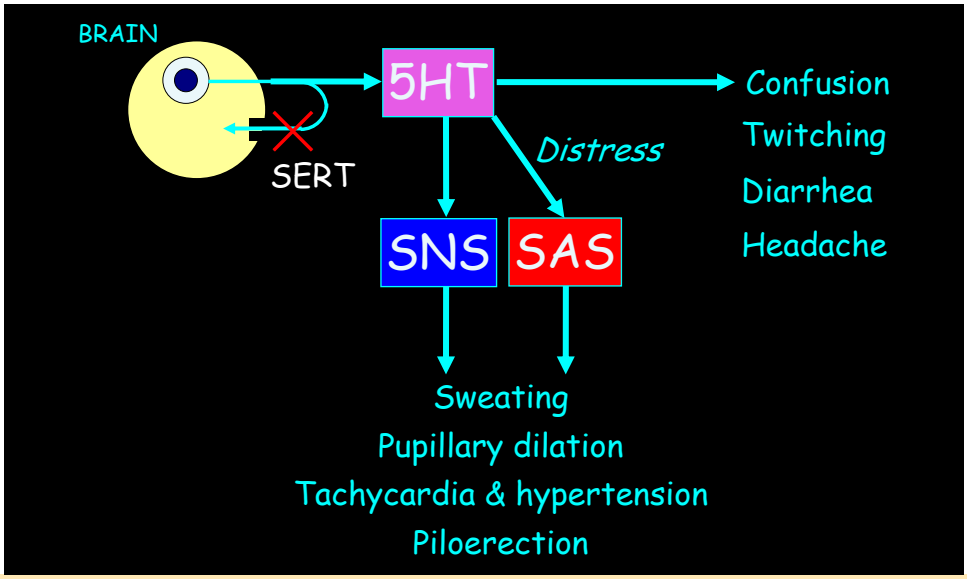


Fig. 386: Concept diagram for clinical manifestations of serotonin syndrome. *Increased delivery of serotonin (5HT) to receptors in the central autonomic network may increase sympathetic noradrenergic system (SNS) and sympathetic adrenergic system outflows.*

ERYTHROPOIETIN (PROCRIT™)

Erythropoietin in the body is released into the bloodstream by the kidneys and acts on the bone marrow to increase the production of red blood cells. Erythropoietin given as a drug (Procrit™) is helpful to treat low red blood cell counts (anemia), such as in kidney failure.

Normochromic, normocytic anemia is a fairly common occurrence in nOH patients, and erythropoietin tends to increase the blood pressure. Procrit may therefore be used to treat low blood pressure in patients who have a low red blood

cell count.

BETHANECHOL (URECHOLINE™)

Bethanechol is a drug that stimulates muscarinic cholinergic receptors. The drug therefore increases production of saliva, increases gut activity, and increases urinary bladder tone. Although bethanechol resembles acetylcholine structurally, bethanechol is not broken down by acetylcholinesterase.

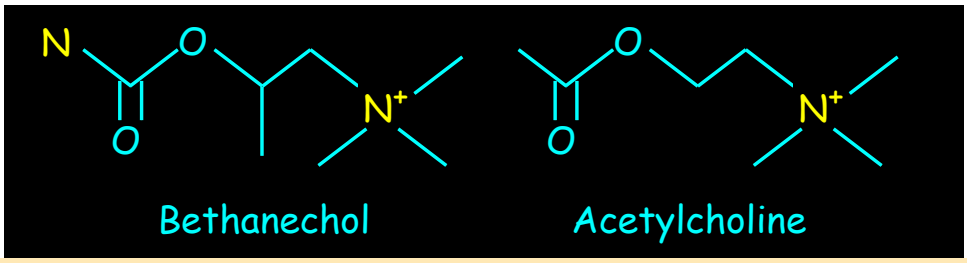


Fig. 387: Bethanechol & acetylcholine. *Bethanechol resembles acetylcholine structurally.*

Bethanechol increases the muscle tone of the bladder, digestive motions of the gut, and salivation. Bethanechol might be tried, to alleviate urinary retention or constipation, which are common findings in MSA.

MANAGEMENT OF COI/POTS

This section is about treatment of chronic orthostatic intolerance (COI), which is being considered together with postural tachycardia syndrome (POTS).

An early step in management of COI/POTS is to search carefully for common, reversible causes, such as diabetes, weight loss, prolonged bed rest, debilitating diseases, and, most importantly, medications.

Treatment of COI/POTS should be tailored to the individual patient.

In devising an individual treatment plan, it may be worthwhile to think about potential pathophysiologic mechanisms, such as low blood volume, increased splanchnic venous compliance, inefficient renal handling of salt and water, a collagen vascular disease (e.g., Ehlers-Danlos syndrome), autoimmunity, physical de-conditioning, or a primary form of hyperactivity of the sympathetic noradrenergic system. In most cases, however, pathophysiologic mechanisms remain unknown, and treatment is largely by trial and error.

Because of the debility caused by POTS, patients can get into a vicious cycle of bed rest, decreased cardiovascular and skeletal muscle tone, worsened exercise intolerance and fatigue, and more bed rest. Enrolling in an individualized exercise conditioning program can be very beneficial.

Patients with COI can feel differently from day to day without any clear reason why. This means that if a treatment is tried it may take a period of time to decide whether the treatment has helped or not.

Because of the syndromic nature of COI it may be worthwhile for the patient and clinician to target for treatment the single most troubling symptom or involved organ system.

Education to Treat COI/POTS

COI and POTS are syndromes. Many manifestations have little to do with orthostatic intolerance or excessive orthostatic tachycardia. Some of these are fatigue, “brain fog,” pain (headache, temperomandibular joint syndrome, complex regional pain syndrome, abdominal pain, fibromyalgia), slow gastrointestinal transit, heat or exercise intolerance, and coat hanger phenomenon. The patient should pay attention to which of these manifestations apply, under what circumstances, and what makes things better or worse.

A substantial proportion of patients with COI have gastrointestinal symptoms and signs leading to a diagnosis of gastroesophageal reflux, slowed gastric emptying, or irritable bowel syndrome. Patients should be aware that taking a high fiber diet might worsen orthostatic intolerance by augmenting shunting of blood to the gut.

Time is a great healer. COI that comes on soon after a viral infection in an otherwise healthy person may “melt away” over many months or years. There is no evidence that COI or POTS

progresses to a neurodegenerative disease.

Non-Drug Treatments for COI/POTS

Non-drug treatments include abdominal compression (e.g., a doubled bicycle leotard or abdominal binder), venous compression hose, high salt intake, a rice-based electrolyte drink (e.g., CeraLyte™), anti-gravity muscle resistance training, swimming, graded exercise training (see the Dysautonomia Information Network website at dinet.org) or even insertion of a pacemaker.

COMPRESSION HOSE/ABDOMINAL BINDER

Fig. 388: Abdominal/pelvic compression. *Compression of the abdomen/pelvis such as by a Spanx™ undergarment may mitigate orthostatic blood pooling. Unedited image from Wikipedia Commons Tobias Maier / CC BY-SA (https://creativecommons.org/licenses/by-sa/3.0)*

Compression hose or other compression garments tend to

decrease the amount of pooling of blood in abdominal and pelvic veins when a person stands. This can decrease leakage of fluid from the veins into the tissues and decrease leg swelling. In patients with veins that fill up or leak excessively during standing, compression garments can improve toleration of prolonged standing. In COI patients a “step-in” abdominal binder may be more efficient than compression stockings, by limiting orthostatic blood pooling in the abdomen and pelvis.

EXERCISE

In patients with COI/POTS, maintaining good muscle tone in the anti-gravity muscles of the buttocks, thighs, and calves maximizes the efficiency of muscle pumping to maintain venous return to the heart during orthostasis. Exercise training improves the ability to increase cardiac output. Moreover, in chronic, debilitating disorders it is important for the patient to regain a sense of at least some control over the situation.

Patients with COI sometimes benefit markedly from an individualized exercise training program. Often, however, the training does not eliminate the sense of fatigue. It might help to have small amounts of exercise daily, even for only 5-10 minutes. The Mayo Clinic offers a residential program that includes supervised exercise training.

After exercise, when muscle pumping ceases the blood can begin to pool rapidly in the legs or abdomen as the rate of sympathetic noradrenergic nerve traffic falls to the resting rate. If the decline in nerve traffic did not balance the decline in production of byproducts of metabolism, then the blood

pressure would fall after exercise. At the same time, loss of body fluid via evaporative sweating during exercise tends to decrease the blood volume. Patients therefore can feel especially unwell after exercise. It is important to stay hydrated and to avoid activities like eating a large meal immediately after exercise.

At the time of an acute episode, isometric counter-maneuvers such as leg crossing and tightening the buttocks can temporarily maintain consciousness.

DIET

Doctors usually recommend a high salt diet for patients with COI. Whether this actually improves clinical manifestations of COI is unclear.

Eating a big meal shunts blood toward the gut. In people with dizziness or lightheadedness when they stand up (orthostatic intolerance), it is usually advisable to take frequent small meals.

Reducing the amounts of sugars or other carbohydrates in meals might help manage symptoms.

Some patients with COI/POTS feel better drinking caffeinated coffee frequently. Others feel jittery or anxious and avoid caffeinated coffee. Still others notice no effect.

TEMPERATURE

Patients with COI/POTS often have an inability to tolerate

extremes of environmental temperature. When exposed to the heat, patients with failure of the sympathetic cholinergic system may not sweat adequately to maintain the core temperature by evaporation of the sweat.

PACEMAKERS AND SINUS NODE ABLATION

Treatments for autonomically mediated syncope are about the same as for POTS.

Whether insertion of a cardiac pacemaker helps patients with autonomically mediated syncope is controversial. Having a pacemaker inserted may not be a cure, because the low pulse rate at the time of fainting might not cause the low blood flow to the brain that results in the loss of consciousness. On the other hand asystole produces loss of consciousness within seconds, and in patients with COI and tilt-evoked prolonged asystole (more than 3 seconds), a pacemaker could be useful.

Patients who have a very fast pulse rate even while supine may be treated by a procedure to destroy the sinus node pacemaker cells in the heart (sinus node ablation). The doctor must be sure that the fast pulse rate results from a problem with the heart and does not result from a compensation by the sympathetic noradrenergic system for another problem, such as low blood volume, because eliminating the compensation could make the patient worse rather than better. Sinus node ablation is not thought to help patients with POTS.

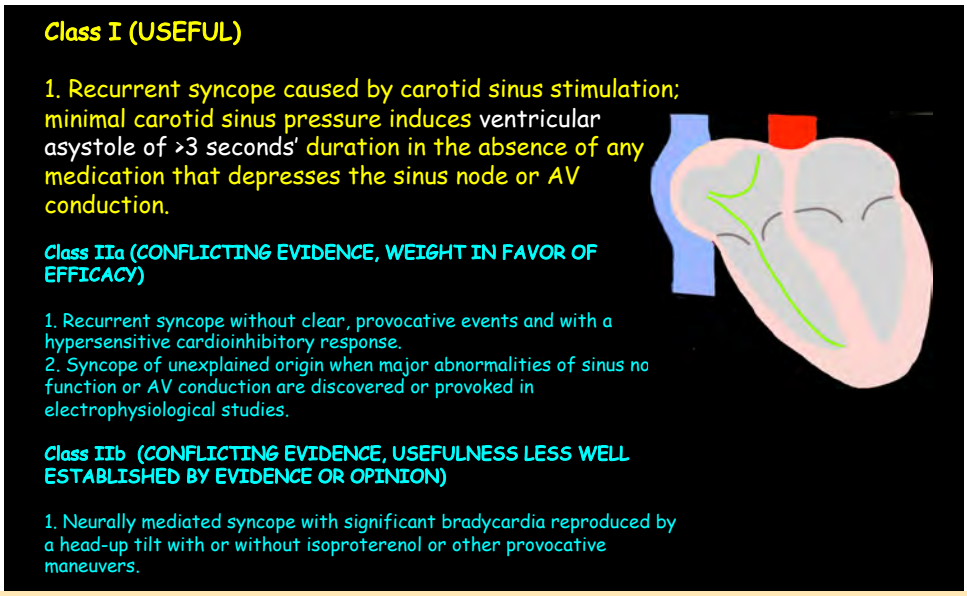


Fig. 389: Cardiac pacemaking for syncope. *According to ACC/AHA Practice Guidelines, cardiac pacemaking is useful for recurrent syncope associated with ventricular asystole lasting >3 seconds that is evoked by carotid sinus stimulation.*

NEUROSURGERY

Some patients with COI/POTS have a type of change in the brainstem called Chiari malformation. This is an anatomic abnormality where part of the brainstem extends below the hole in the skull between the brain and spinal cord. Neurosurgery can correct the malformation, but the orthostatic intolerance does not necessarily disappear. This is a controversial topic, and at a minimum patients should seek a second opinion before agreeing to this procedure.

Drug Treatments for COI/POTS

The following is a listing of drugs that may be used to treat dysautonomias. Treatment with any drug should be undertaken only under the direction of a prescriber well acquainted with autonomic medicine.

Drug	**Goal of Treatment**
Fludrocortisone	Increase blood volume
=(Florinef™)	Increase blood pressure
Midodrine	Tighten blood vessels
(=Proamatine™)	Increase blood pressure
	Prevent fainting
Beta-Blocker	Decrease heart rate
	Decrease blood pressure
	Decrease adrenaline effects
	Prevent fainting
Erythropoietin	Increase blood count
(=Procrit™)	Increase blood pressure
Amphetamines	Tighten blood vessels
	Increase alertness
Selective Serotonin Reuptake Inhibitor	
(=SSRI)	Improve mood, allay anxiety
Alprazolam	Increase sense of calmness
	(=Xanax™)
	Improve sleep
Clonidine	Decrease blood pressure
(=Catapres™)	Improve sleep
Bethanechol	Increase salivation
(=Urecholine™)	Improve gut action
	Improve urination

Pyridostigmine (=Mestinon™)	Increase blood pressure
L-DOPS (=Droxidopa, Northera™)	Tighten blood vessels Increase blood pressure

FLURDROCORTISONE (FLORINEF)

In some patients with COI/POTS, treatment with the salt-retaining steroid fludrocortisone (Florinef™) coupled with a high salt diet can produce improvement; however, in other patients there is no improvement. Perhaps this treatment is effective only in patients who have low blood volume or decreased ability of the kidneys to reabsorb filtered sodium, but there is no relevant research literature. For fludrocortisone to work, the drug should be taken with a high salt diet. A simple sign of drug effect is that the patient gains "fluid weight."

BETA-ADRENOCEPTOR BLOCKERS

Norepinephrine and adrenaline produce their effects by binding to specific receptors, adrenoceptors, on target cells such as heart muscle cells. Beta-blockers interfere with this binding.

There are two types of adrenoceptors, alpha and beta. Adrenaline stimulates both types. Adrenaline tightens blood vessels in most parts of the body, such as the skin, due to stimulation of alpha-adrenoceptors in blood vessel walls. Vasoconstriction of skin blood vessels decreases local blood flow, and the skin becomes pale. This is why pallor can be a sign of high adrenaline levels. In skeletal muscle, however, adrenaline generally relaxes blood vessels, due to stimulation of

beta-2 adrenoceptors. By this action adrenaline tends to shunt blood toward skeletal muscle. This makes sense in terms of the need for abundant blood flow to skeletal muscle in emergency situations. Adrenaline stimulates beta-adrenoceptors in the heart, and this increases the force and the rate of the heartbeat. Because of the effects on the heart, the amount of blood pumped by the heart per minute (cardiac output) increases.

All beta-blockers decrease the rate and force of the heartbeat.

Stimulation of beta-2 adrenoceptors on smooth muscle cells of the airways relaxes the airways. This is a reason that beta-2 adrenoceptor stimulants are used to treat asthma.

Drugs that act at beta-adrenoceptors are often grouped in terms of whether they are “selective” for beta-1 adrenoceptors or are “non-selective,” meaning they block the other types of beta-adrenoceptors as well. There are no approved drugs that block beta-2 adrenoceptors selectively.

In patients with autonomically mediated syncope and high levels of adrenaline in the bloodstream, the adrenaline stimulates beta-2 adrenoceptors on blood vessels in skeletal muscle. This relaxes the blood vessels and decreases the resistance to blood flow. Blood may then be shunted away from the brain and towards the skeletal muscle, contributing to lightheadedness or loss of consciousness. In such patients, non-selective beta-adrenoceptor blockers might be preferable to selective blockers.

In patients with COI/POTS the value of treatment with beta-adrenoceptor blockers will depend on whether the rapid pulse rate when the patient stands up reflects a primary or compensatory response. If the rapid pulse rate were a compensation for another problem, such as low blood volume, then blocking that compensation would not help. If the rapid pulse rate were the result of an excessive rate of sympathetic nerve traffic to the heart, or there were a high intrinsic heart rate, then a beta-adrenoceptor blocker might help.

INTRAVENOUS SALINE INFUSION

Inability to tolerate prolonged standing can result from low blood volume, excessive pooling of blood in the veins of the legs, pelvis, or abdomen during standing, or exit of fluid from the blood vessels into the tissues (extravasation).

In these situations, IV infusion of physiological saline solution can temporarily improve the ability to tolerate standing up.

Saline infusion temporarily increases the blood volume.

IV saline infusion can also be useful for diagnostic purposes.

Some patients with COI/POTS benefit from IV saline infusion given a few times per week by way of a permanent intravenous catheter. The clinician must weigh the potential benefit against the not insubstantial risks, such as of infection and intravascular clotting.

METOCLOPRAMIDE

Metoclopramide is a medication used to alleviate nausea and vomiting and to treat symptoms of gastroparesis and gastroesophageal reflux disease (GERD).

The drug acts as an antagonist at dopamine D2 receptors. As such, it can worsen parkinsonism or evoke tardive dyskinesia. Tardive dyskinesia is a rare but serious complication of dopamine receptor antagonists in which the patient has involuntary movements of the jaw or tongue. Tardive dyskinesia can persist even after the drug is withdrawn.

Metoclopramide also can produce other dyskinesias, possibly via inhibiting D2 receptors on dopaminergic terminals and augmenting dopamine release.

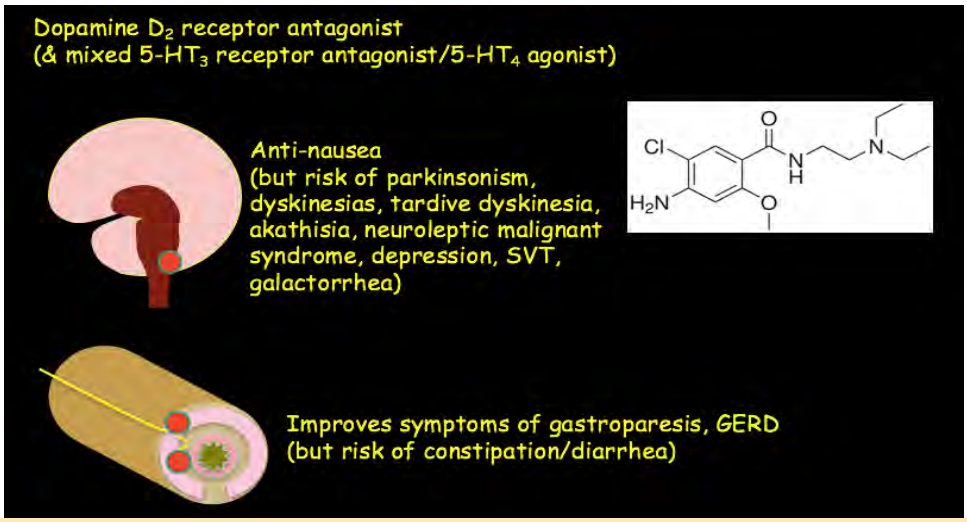


Fig. 390: Metoclopramide. *Here are some uses and side effects of metoclopramide.*

CLONIDINE (CATAPRES™)

Clonidine stimulates alpha-2 adrenoceptors. Stimulation of alpha-2 adrenoceptors in the brain decreases the rate of sympathetic nerve traffic, and stimulation of alpha-2 adrenoceptors on sympathetic nerves decreases the amount of release of the chemical messenger norepinephrine from the nerves. Even though clonidine stimulates a type of alpha-adrenoceptor, the drug normally decreases the blood pressure.

There are several uses of clonidine in the diagnosis and treatment of dysautonomias. In the clonidine suppression test, clonidine is used to separate high blood pressure due to increased sympathetic nervous system activity from high blood pressure due to a tumor that produces catecholamines—pheochromocytoma.

Clonidine works both in the brain and outside the brain. It decreases the blood pressure and often causes drowsiness.

In patients with long-term high blood pressure (hypertension) due to excessive release of norepinephrine from sympathetic nerves (hypernoradrenergic hypertension), clonidine can be very effective in lowering the blood pressure. Clonidine is also effective in treating withdrawal from some addictive drugs. Clonidine may attenuate the large swings in blood pressure that are associated with baroreflex failure.

Clonidine often causes drowsiness and dry mouth. The sedation

may limit its clinical use.

LIVING WITH DYSAUTONOMIAS

This section on living with dysautonomias is directed toward the patient.

Living successfully with a dysautonomia requires understanding about how chronic illness impacts patients, caregivers, and families–at home, at school, and at work. The changes you and your family may face can impose new emotional burdens. Coping with a form of dysautonomia almost certainly necessitates important changes in lifestyle. This section offers some practical guidance.

Finding and Working with a Physician

Because there are many different types of dysautonomias, and because disease mechanisms in dysautonomias often are not well understood in individual patients, your doctor and you will likely spend a lot of time trying to find reversible causes and devising a treatment program. For these reasons the relationship between you and your physician is crucial.

Despite the fact that dysautonomias affect over a million Americans, you will probably find that very few people and surprisingly few doctors have ever heard of dysautonomias. It may be that no doctors in your area specialize in treating autonomic disorders.

Few doctors have heard of dysautonomias.

The medical terminology can be confusing even to doctors. The same basic set of symptoms and signs can be called by a variety of names. For example, symptoms of a long-term inability to tolerate standing up—chronic orthostatic intolerance (COI)—have been labeled as "POTS" (Postural Orthostatic Tachycardia Syndrome, or postural tachycardia syndrome), hyperdynamic circulation syndrome, Mitral Valve Prolapse-Dysautonomia Syndrome, Neurocirculatory Asthenia, Soldier's Heart, and other names in a long list. No wonder many patients feel frustrated and confused!

Finding a physician able to diagnose, treat, and follow patients with dysautonomias will likely take effort on your part.

Unlike diseases or conditions that affect only one part of the body, dysautonomias affect virtually every body organ and system.

Components of the autonomic nervous system play a variety of roles in regulating largely automatic, involuntary, unconscious functions, such as breathing, blood pressure, heart rate, digestion, and urination. Because of the multi-dimensional aspects of dysautonomias it is often difficult to determine which type of physician should manage the condition.

Your care will likely also require extra effort by your doctor. Since the cause of your symptoms may not be well understood, developing an effective treatment plan may take a substantial amount of time.

People with dysautonomias must be both patient and persistent.

Because of large differences among patients, and continuing mystery about mechanisms of dysautonomias, doctors need to learn from their patients about what works and what doesn't.

Your first priority should be to find a physician willing to work with you. Whether that physician is a cardiologist, neurologist, endocrinologist, psychiatrist, internist, or family practitioner is less important than his or her ability to cooperate with you and other physicians on your behalf.

Find a doctor who will work with and learn from you.

The physician will probably focus on treating symptoms. For this reason, much of what is done is through trial and error. Both you and your physician will need to understand that finding a program that works requires time, patience, and open and honest communication. Your relationship and ability to communicate with your doctor will make a big difference in putting together an effective therapy program.

Your symptoms are likely to change over time. Keep your doctor informed about how you are doing and about the changes you notice. For instance, a particular medication might make you feel better in one way but worse in another. Your doctor might be able to change your prescription or start you on another drug that would work the same way but with fewer side effects. If you notice major improvements, you should inform your doctor. It's possible you may not need as much medication

to manage the problem.

Keep your doctor informed.

You should develop a plan with your doctor about symptoms that require immediate attention and those that can wait for a return visit. A brief discussion about this will help give you peace of mind when your symptoms are of concern.

Talking with a physician about multiple symptoms can be a problem, if you've had unpleasant interactions at office visits in the past. You might be concerned about what your doctors might think: "What if they think I'm CRAZY?" Don't let this concern keep you from relaying everything the doctor needs to know. You can't expect your physician to put the puzzle together if you withhold half the pieces. Tell your physician about all your symptoms. Let your doctor decide what is important information.

Create a bullet list of questions to ask. Keep in mind that your doctor has limited time to discuss your condition and treatment. Before visiting your doctor, ask yourself, "If I could improve one symptom, which would it be?" This type of thought process will give you and your physician a better opportunity to work systematically on the symptoms that are causing you the most trouble.

You may want to consider having a family member or friend go with you. Having someone with you may make you feel more comfortable, and a family member or friend can also give your physician details you may not recall.

Keeping a daily journal can also be a useful tool, both for you and your doctor. This allows your doctor an opportunity to see trends or patterns in your symptoms. You might include blood pressure, pulse rate, body weight, and the timing and circumstances of events that trigger symptoms, mood, activity, external temperature, time of day, time of the month, fluid intake—even thoughts at the time of acute events. Talk to your doctor about which information to record. Let your doctor review your journal, since what may seem insignificant to you may be significant to your doctor. It is part of the nature of dysautonomias that symptoms often have peaks and valleys, and patients have good days and bad days.

If your doctor starts you on a new medication, it is important to discuss potential side effects. It is helpful to identify which symptoms are triggered as side effects of drugs and not as a result of your condition.

Day by Day with Dysautonomia

CHRONIC ILLNESS

Dysautonomias usually are chronic. They can continue for long periods or even indefinitely. Many factors affect their courses, including heredity, environment, drug and non-drug treatments, and lifestyle. Living with a chronic illness poses continual challenges, marked by many ups, downs, and unexpected turns.

Living with a dysautonomia poses continual challenges.

ACCEPTING YOUR DISORDER

With an acute illness, you know you will eventually feel normal again. When you have a chronic illness, there is no cure in the traditional sense. You may never return to your "normal" way of life. Adaptation and acceptance therefore become important in maintaining your quality of life.

The first step to accepting your condition is to understand it. Knowing the "details" (e.g., common symptoms) can alleviate uncertainty and help you learn how to manage life with a dysautonomia.

Understand your condition.

MODIFYING YOUR LIFE

In the past you might have been able to work 8 hours and then do chores at home. Now doing so might put you in bed for a week! You may have to learn to pace your activities, take "baby steps."

Making a weekly chart of activities/tasks can help. You might believe that you are not making any progress, yet when you review a list of your activities you might find you are accomplishing a great deal. The list can help you set priorities about tasks that definitely need to be accomplished or can be put off or eliminated. This sort of chart can also help in decisions about how responsibilities can be shared among family members. For example, your spouse might take over the

grocery shopping. Deciding on the right balance between overdoing it and doing too little will take time and a lot of trial and error.

Coping successfully with a chronic illness requires significant lifestyle changes. Modifying your lifestyle to help you maintain as "normal" a life as possible can help you gain a sense of control over your illness, rather than feeling your illness controls you.

Doing things you enjoy can distract you from your illness. Focus on hobbies and activities you can still do and look for new ones to replace those you no longer can pursue. An example would be avoiding noisy shows outdoors in the heat and instead attending quiet shows in the cool indoors.

Take an inventory of your interests. People often forget about things they had an interest in but have not thought about for years.

Know your limitations. Substituting one activity for another may become necessary to maintain your sense of well-being.

DAILY LIFE TACTICS

Here are several basic tips to pace your life.

— Get adequate rest.
— Eat and drink right. Don't fast, and don't pig out.
— Try to keep a regular schedule.

— Get an appropriate amount of exercise, as prescribed by your physician.
— Avoid dehydration.
— Stay on your medication routine.

Mornings can be rough for people with orthostatic hypotension from chronic autonomic failure. Start slowly, use your knowledge, and use your blood pressure cuff.

Studies have shown that patients with neurogenic orthostatic hypotension can have a surprisingly large increase in blood pressure after drinking 2 glasses of water. You may find that drinking water about 15 minutes before getting out of bed in the morning helps you tolerate standing up. If your physician has advised you to increase your intake of fluid and salt, a glass of V8 or tomato juice might be helpful, as these drinks contain large amounts of sodium. Eating a large meal can shunt blood to the gut and decrease the ability to tolerate standing, and exposure to heat can relax blood vessels and decrease the blood pressure. If you attended a large church breakfast in the summer before standing still through a service, you could easily have a severe enough a fall in blood flow to the brain to cause you to faint.

Exercise plays an important role in treating most chronic conditions, including dysautonomias. Staying in shape improves your sense of well-being. The veins in the legs contain one-way valves that allow blood to flow towards your heart without allowing the blood to back up into the legs. Muscle surrounds deep veins in the legs and compresses these veins when you contract your leg muscles. Muscle pumping helps to keep blood moving towards the heart and upper body

when you stand upright. You can do different types of exercise to assist your venous pump. You can learn to tighten your calf, thigh, and buttocks muscles. Ask your physician about whether muscle pumping exercises would be appropriate for you.

Chronic illness, and especially chronic illness from an abnormality in the functioning of parts of the autonomic nervous system, can increase the susceptibility to anxiety, panic, and depression. There is nothing wrong with asking your doctor if you might benefit from medication to help you cope.

Avoid triggers that worsen your condition. Some triggers to keep in mind are:

— Hot environment (e.g., hot shower, sauna, Jacuzzi)
— Dehydration (not getting enough fluids)
— Emotional distress
— Over-stimulation (i.e., amusement parks, concerts, sporting events, video games, loud telephone ringing)
— Large meals
— Skipping meals
— Alcohol
— Skipping medications

DIET

Eating large meals tends to shunt blood toward the gut. This can worsen orthostatic intolerance and make a dysautonomia patient feel sluggish, tired, and worn out. Try eating smaller meals, more often. Check if sugary or starchy foods tend to worsen your symptoms. During eating, you might try elevating your feet to heart level and exercise your legs, to keep the blood

from pooling. Just flexing your feet back and forth might provide a benefit.

For many patients with dysautonomias, a diet high in salt and fluids is necessary. Chicken noodle soup and V8 juice contain large amounts of salt. You should discuss salt intake with your doctor.

ENVIRONMENTAL TEMPERATURE

Patients with a form of dysautonomia often have intolerance of heat or cold. If you have heat intolerance and plan on being outdoors during the summer, dress in cool, light clothes and limit the amount of time you spend in the heat.

You might feel faint taking a hot shower in the morning. Consider taking your shower prior to going to bed at night.

COMPRESSION STOCKINGS/ABDOMINAL COMPRESSION

Compression stockings can help patients who have excessive blood pooling in the lower half of the body when they stand up. If you use compression stockings, it can take some time to take them on and off. You may find it easier to put your stockings on while lying in bed. A small amount of baby powder helps when putting them on. Lying down may also keep you from becoming symptomatic while taking them off.

Compression stockings may be ineffective in preventing a fall in blood pressure standing.

You can buy affordable pantyhose to reduce pooling of blood in veins during standing. Try two pairs, one size smaller than what you would normally wear, and wear both at the same time. Abdominal compression has also been used to help prevent blood pooling when you stand up. Depending on your particular condition, a girdle one size too small can make a difference in how you feel. If wearing girdles or compression stockings isn't your style, try wearing bicycle pants.

MEDIC-ALERT BRACELETS

A patient with a dysautonomia should wear a Medic-Alert bracelet. The back of the bracelet can state "See wallet." Inside your wallet you can have a piece of paper, laminated card, or electronic memory media about your condition, medications you take, allergies and sensitivities to medications, names and phone numbers of physicians, and emergency contact information for spouse or friend. For information on obtaining a Medic-Alert bracelet, visit http://www.medicalert.com.

WORK

Whether or not you keep working is an individual decision affected by a number of factors (e.g., severity of symptoms, type of work, financial situation).

It is likely your ability to work will be affected in some way by your illness.

It may be that you can no longer work full days, or you may no longer be able to travel as part of your job. If your job requires

you to be on your feet all day, this may not be possible any more.

You might have to struggle with what to tell your employer. Do you maintain your privacy, or let your employer know, so special accommodations can be arranged? This is a personal decision with no universal right or wrong answer. It may help to make a list of the pros and cons of disclosing your condition. Many things are going to affect your decision, including your specific work environment and job duties.

Work can involve episodes of emotional distress even in healthy people, so it's no surprise that it can worsen symptoms in someone with a dysautonomia.

You're probably going to have to make changes at work. This might mean setting more limits. It can be scary and frustrating to have to "slow down" at work. You might be afraid of what will happen and what people will think of you. You have to remember that if you don't slow down, you may be jeopardizing your health, which in the long run will result in being able to do even less. If you are contemplating taking time off from work, be sure to investigate all your options regarding possible assistance. You might be able to telework.

There may come a time when you have to discontinue working altogether. The decision to leave the work world, whether temporarily or permanently, can be accompanied by a whole host of emotions, including anxiety, depression, guilt, or relief. To minimize anxiety associated with leaving work, structure your day (e.g., read books, listen to music, take a course over the internet, talk with friends), and try to learn something new.

Make a list of your positive traits, to remind you that you are of value even if you're not working. Social networking with others in your situation can alleviate the sense of loneliness.

TRAVEL

Driving is one of the most important aspects of our independence and often a necessity of everyday life. Discuss driving with your doctor. Your doctor can help to determine if your condition puts you at risk. If you are not able to continue driving, you will have to find ways others can help with your travel needs. Besides family, friends, and neighbors, your community may have programs. Your local Chamber of Commerce or United Way can give you information about public transportation and other programs.

Wearing sunglasses when you travel can reduce stimulus overload. You may notice that your symptoms don't seem as intense when you travel in the evening than in the daytime, or vice versa. Wearing earplugs can also help reduce the impact.

Depending on your specific condition, wearing a girdle, compression stockings, or bicycle pants while traveling may be helpful. Have you ever noticed a change in your skin color when you stand upright? Rapid changes in the color of the skin are the result of blood. Compression garments may help you to keep blood in the upper part of the body when you are standing on line.

For many patients with dysautonomias, air travel can be a nightmare. It is best to discuss this with your physician. If your

physician tells you it is all right for you to fly, discuss the following to see if they make sense for you:

— Drink extra fluids for at least a couple of days before departure.
— Eat a diet high in salt (V-8 juice, chips, pretzels, beef jerky, pickles).
— Avoid stressful, stimulating situations the day before or of departure. For instance, avoid going to the mall for last-minute shopping.
— Wear compression stockings and an abdominal compression garment.
— Wear earplugs or eyeshades.
— Ask your doctor about a medication to calm you and enable you to sleep during the flight.
— Fly with someone who knows your disorder.
— Request bulkhead seating, so you can elevate your feet to heart level during the flight.
— Request a wheelchair at your destination.
— Try to arrange a day of rest after your flight.

WHEN TO ASK FOR HELP

It is not easy to find the right balance between independence and seeking help. At different points, you may need practical, financial, emotional, or physical help.

> We all need help from others, whether we're healthy or not.

People often feel guilty asking for help from family and friends.

Think about how things would be if the shoe were on the other foot. If your spouse or best friend had a chronic illness that required your assistance, would you resent a plea for help?

Explaining exactly how someone can help can provide a sense of relief to the helper, who may not know what to do. Don't assume that others can read your mind. You need to be clear in relating how you feel and what you need. You can make a list of the areas where you do and do not need assistance. Your friends, family, and caregivers need to do the same. You yourself may not be sure what you want.

SOCIAL ACTIVITIES

Staying involved in family and social activities as much as possible can help you cope with your illness. If you notice that these activities make your symptoms worse, then limit the time you spend on them. For example, if a family picnic were an all day function, you might plan on staying for only an hour or two.

You do not experience your illness in a vacuum. Those close to you are also impacted. They won't experience the same physical effects you do, but they may experience other struggles (e.g., emotional, financial). This is a time of heightened stress and anxiety for the entire family.

Try to arrange a quiet time to sit down and talk with your family about issues related to your health. Explain clearly, and speak directly. Ask if they understand what you're trying to say, and clarify what is not clear. Listen to what they have to

say. Try to express yourself in a non-threatening manner. Statements like, “Why do you always avoid me?” will probably make your loved ones feel attacked and cause them to become defensive. Instead, try to phrase your statement in neutral terms, such as, “Help me understand what you are going through. I feel like you don’t want to be around me anymore and that hurts me. I miss being around you.” Remember that no one will be put off by your expressing how you feel.

Your loved ones should also be allowed to express their feelings. They may be experiencing some of the same emotions you are, including anxiety and guilt. Feelings of anger and other negative emotions are also likely and are normal. You and your family members can expect to feel hurt at times. Try to remember that these negative emotions are reactions to the situation and not to you yourself.

ATTITUDE IS A BATTLE

It is natural to have negative thoughts when your world seems to be crashing. People with chronic medical conditions are susceptible to experience emotional distress, fear, depression, anger, frustration, anxiety, or other negative emotions.

Blaming or attacking your physician, family, friends, or even God won’t improve your health. Having a positive attitude might make things easier on your family, friends, and neighbors.

This sounds rather platitudinous. What practically can be done? Talking to others with the same condition can help. There is

nothing wrong with discussing your anger, frustration, concerns, and fears. A health psychologist may help you acquire coping strategies. Some psychologists emphasize the importance of a "family session," where all members of the family can relate the effects that the illness has had on them. Keep in mind that the entire family is affected by your illness.

The key to happiness is appropriate expectations.

Take time to recognize your abilities and what you can do. For example, you may need help with grocery shopping but not with putting the groceries away. It may take time to discover what you can still do despite your limitations. Make small goals. Your goal today might be to walk from the bedroom to the kitchen. Next month it might be to clean the kitchen.

Referral to an Autonomics Specialist

Physicians in several fields of medicine see dysautonomia patients, but unfortunately there are too few specialists in autonomic medicine.

Testing in a specialized autonomic function laboratory can help identify what form of autonomic problem you have and speed development of an effective therapy program

Consider specialized testing.

You should not feel reluctant to talk to your physician about going to another facility for testing. You will likely find that

your physician will actually encourage you to do so, because the visit may provide valuable and otherwise unobtainable information that your doctor can use to help you.

There are relatively few autonomic function experts and testing laboratories.

An educated general practitioner can take care of most of the management of dysautonomia patients. For a list of physicians and facilities in your area, try visiting the websites of the American Autonomic Society, at www.americanautonomicsociety.org; Dysautonomia International, at www.dysautonomiainternational.org; or the Dysautonomia Project, at thedysautonomiaproject.org.

RESEARCH FACILITIES – SHOULD I PARTICIPATE IN A STUDY?

There are a limited number of academic medical centers in the United States that conduct research on the autonomic nervous system. Some are at Vanderbilt in Tennessee, the Mayo Clinic in Minnesota, the Harvard system in Massachusetts, NYU in New York, the University of Texas in Dallas, and at the National Institutes of Health (the NIH) in Bethesda, Maryland.

Different centers study different types of dysautonomias. Patients are recruited to participate in research studies (also known as “protocols,” because the studies are designed, defended, approved, monitored, and reported according to pre-determined, detailed, written criteria). Each protocol has

specific requirements, both for inclusion and exclusion. For a list of ongoing studies funded by the NIH you can contact the NIH's Clinical Trials web site at www.clinicaltrials.gov.

Some benefits of participating in research are:

— You are seen by people who specialize in this area of medicine. What may be unusual for your local physician may be routine for the investigators conducting the research.

— You have the opportunity to learn more about what may be causing your symptoms. The testing could reveal important information about your condition that may not be available to your personal doctor.

— The medical institution may cover the costs of the research testing, which otherwise would be expensive if available at all.

— Even if you don't benefit personally from your participation, you may help researchers understand the illness better, making it possible for them to devise better treatments.

It is important that you investigate the study thoroughly and review the consent information prior to participation. If you decide to participate in a study, keep in mind some of the possible limitations of the research:

— You may be required to stop taking your medications, for the doctors to see how you function without them.

— You may have to pay for travel.

— Some tests can be painful, uncomfortable, or not directly related to your problem.

— You may have to spend several days in the hospital.

— You may need pre-certification from your insurance company.

— You will have to meet the criteria for participation in the study. Not everyone qualifies, and research patients may not be recruited once a quota is filled.

— Most important, you should understand that the usual primary focus of a research study is not to help a single patient but to learn more about the condition in general.

Research studies may not provide for your long-term care or follow-up.

You will likely be returning to the care of your personal physician after participating in the research. Nevertheless, the researcher and the study results may help you and your doctor gain more knowledge about your condition and help devise an effective therapy program.

Physicians conducting research should not take the place of your local physician.

The research might give you immediate results, but alternatively it might take several months or even years before the research is completed and the results fully analyzed. You

should have a clear understanding of what type of feedback to expect.

Keep educated about your condition. Passing along new information will help both you and your doctor. You will find that most physicians appreciate information provided them, especially if from a reliable source. Resource tools available today allow you a tremendous opportunity to stay abreast of new discoveries. You can find updates from a variety of sources (see the listing later in this section), patient conferences, books, and newsletters. The National Library of Medicine's websites offer you easy access to medical search engines that can also help keep you informed of new research discoveries.

Caregiving and Support

Caregiving is taking care of and feeling responsible for another person, loved one, or family member. Family caregiving is extremely important for coping with and successfully managing dysautonomias.

FAMILY CAREGIVING

A family caregiver is someone who has primary responsibility for the well-being of another family member experiencing chronic limitations as the result of illness or injury. Caregiving has many facets, and each situation is different. The spectrum of caregiving responsibilities and capabilities may entail emotional, physical, social, practical, financial, logistical, and psychological care and support.

It is difficult to identify caregivers, because they don't feel that they are caregivers. Much of what caregivers do is out of love, respect, and being "family." The emotional and practical wear and tear on caregivers is real and needs to be understood. Caregiving doesn't come with a set of instructions, and after months or years caregiving can feel like a rut or trap. Without understanding the responsibilities of family caregiving many succumb to anger, resentment, confusion, and even physical ailments.

First and foremost is the need to recognize the role of being a caregiver. Not recognizing the caregiver role inherently prevents one from getting the understanding, help, support, and resources caregivers need.

Family caregiving is hard.

WHY IS CAREGIVING SO HARD?

— Family caregiving involves routine and repetitive day-to-day psychological and social issues, economics, and perhaps physical care needs, and ongoing balancing act of work, household, and other activities.

— Family caregiving is not intuitive. Your maternal/paternal instincts and childrearing experience are not substitute training for family caregiving.

— There are numerous role reversals, such as kids caring for parents.

— People tend to wait for a crisis rather than plan strategically.

— Family caregivers can feel transparent, with everyone focused on the care receiver and not appreciating the caregiver's efforts. Family caregivers can feel lonely, like they are in this by themselves and that no one understands what they are going through.

People don't know what they don't know. Without instructions, planning, and clear understanding of the caregiver role, ongoing problems get harder to solve. Expectation management is a key ingredient in being a successful caregiver.

Caregiving for a dysautonomia patient is special.

Why is caregiving for someone with a dysautonomia different?

— People with a form of dysautonomia often don't look sick. Family, doctors, friends, schoolmates, and relatives have a hard time believing in the reality of the illness. Suspicions of malingering, psychosomatic illness, and "being lazy" are aroused frequently.

— Dysautonomias typically are chronic illnesses. A chronic illness or disability such as congestive heart failure or stroke in an elderly person may mean 5-7 years of caregiving. When the onset is at birth or during adolescence, we may be talking about almost an entire lifetime. The younger the individual when illness strikes, the greater the scope of impact, including school, social life, relationships, future goals, responsibilities, work, and the entire family structure.

Kids don't think of themselves as caregivers, and they may be frightened and confused by the feelings they have. Most doctors and teachers do not think about children in this sort of role. If your children have this role, they need special support and a trusted outsider to talk to as well as Mom or Dad.

SPOUSAL CAREGIVING BY MEN

For reasons that remain poorly understood, most patients with functional dysautonomias such as POTS are women. Spousal caregiving by men can be difficult. Seeing a wife or partner suffering and feeling inadequate to relieve the suffering can create a sense of emotional impotency. Physical sexual and other shared pleasures may be limited or lost, leaving the husband feeling lonely and unappreciated.

Lost opportunities for promotion, business travel, or increased responsibility add to the burden. The potential alteration or dissolution of plans, dreams, and expectations of life imposed upon by chronic illness must be faced. The loss of an anticipated future must be grieved. The process of grieving goes through stages from denial to acceptance and may last for years. The partners may be at different stages on the road to acceptance.

Unresolved issues from the past with family or with spouse may become overwhelming. The role of spousal caregiver may not always be possible. Some will leave. Often, however, one may find courage, strength, and renewed love in long-term commitment to stay in the relationship.

INTIMACY

Intimacy, which is important in a normal relationship, is greatly impacted and strained by the limitations of dysautonomias.

Intimacy is a major issue in caring for a spouse with a dysautonomia.

You can love someone and never be intimate or sexual with him or her.

You can have sex and never have intimacy with, or love for, the other person. You can love someone and have great intimacy without having physical sex. Whatever works for you is fine. The subject of intimacy is at the core of many of the issues couples face; it is inescapable for those dealing with chronic illness.

With dysautonomia you may look fine but feel awful. When you feel lousy, you don't feel sexy. That’s a strain on any marriage or relationship.

YOU ARE NOT ALONE

Whatever your beliefs, or whether you have a formal religion, having a sense of spirituality, an awareness of a guiding creative force, or a sense of transcendence can be a comfort and a coping mechanism. Use this as it fits for you.

It is likely that for a relationship to work in the setting of a dysautonomia will require outside professional help. If you are

a family caregiver, recognize you are not alone. Others have worked through similar life-changing events. You must recognize your problems and actively seek your own help. No one else is automatically coming to solve them for you.

Organizations with family caregiver support create an opportunity for defining roles, outlining responsibilities, sharing information, and gaining better understanding. Just as important as knowing what doctor to go to and what medication to try is to recognize the major burden of family caregiving with the knowledge that you are not alone. Understanding this is not only helpful to those with chronic caregiving responsibilities but also to spouses, children, other family members, friends, and the community.

SUPPORT GROUPS

Support groups are an invaluable tool to help deal with the challenges of dysautonomias. There can never be enough of sharing thoughts, helping one another, learning, and listening.

One of the best sources of help is a support group. A support group is a regularly scheduled, informal gathering of people whose lives are affected directly by a chronic illness or by the caregiver role. Members benefit from the peer acceptance and recognition of their common concerns and are grateful for the wisdom, insight, and humor of people in the same situation.

Learning coping techniques from others in a support group is extremely valuable. Patients with chronic illness need reliable guidance—understandable, clear, compassionate, and practical.

Including the caregiver, significant other, or family members is especially important. Participants in support groups learn quickly from one another. Professional facilitators help accomplish even more.

Support groups are also a safe place to be heard and to listen and to understand symptoms and treatments. Support groups offer understanding on how to "reinvent yourself," how to work with your healthcare team, how to communicate better with family and caregivers, and how to acquire effective strategies for daily living.

Today, physicians, social workers, rehabilitation specialists, neuropsychologists, and others refer patients to recognized support groups. Below is a listing of some dysautonomia support groups and their web addresses.

- Dysautonomia International (dysautonomiainternational.org)
- The MSA Coalition (multiplesystematrophy.org)
- The Dysautonomia Foundation, Inc. (familialdysautonomia.org)
- The Dysautonomia Project (thedysautonomiaproject.org)
- Dysautonomia Information Network (dinet.org)
- National Dysautonomia Research Foundation (ndrf.org)
- Syncope Trust and Reflex Anoxic Seizures organization (stars.org.uk)
- Dysautonomia Youth Network of America (dynakids.org)
- National Society for MVP and Dysautonomia (mvprolapse.com)
- Dysautonomics (adiwebsite.org)
- Fight Dysautonomia.org (fightdysautonomia.org)

- American Dysautonomia Institute (dysautonomics.com)

Taking the initiative to begin a support group and following through is a major commitment but with many rewards. It doesn't take special training, but it does take effort, dedication, and some ingenuity. You may also find it to be very rewarding.

IDEAS FOR THE FUTURE

HOW DOES HOMEOSTASIS HAPPEN?

Homeostasis is a founding principle of integrative physiology. In systems biology, however, homeostasis is almost invisible. In integrative physiology homeostasis is a key *goal* that drives body processes. In systems biology homeostasis is a *result* that emerges from continual adjustments in the operations of complex networks.

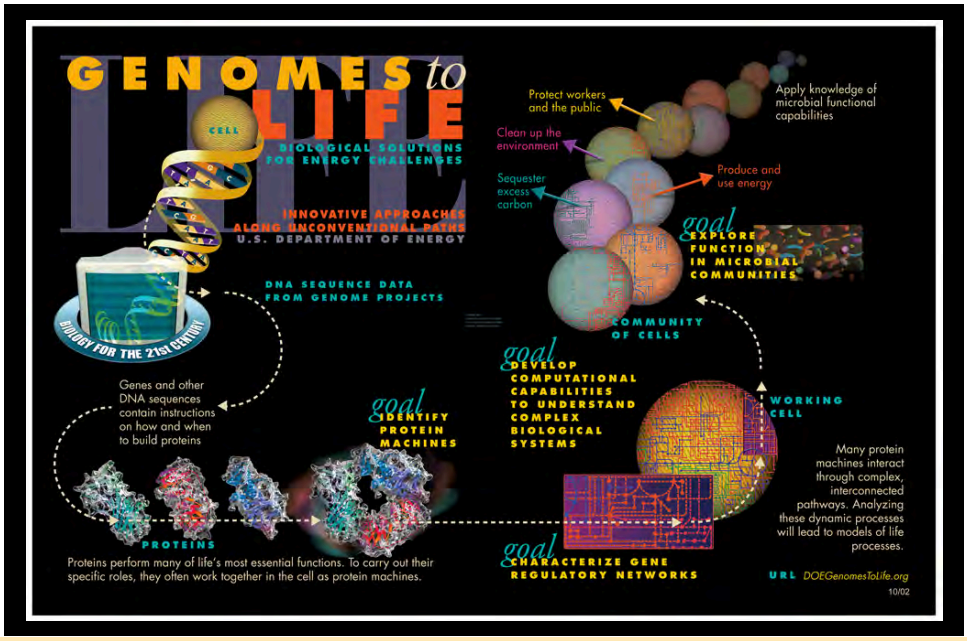


Fig. 391: Systems biologic diagrams. *Systems biology focuses on networks in complex webs, across various levels from genes to cells to organisms to society.*

The integrative physiologist emphasizes homeostasis of "regulated variables" (e.g., core temperature, blood oxygen, blood pressure) via comparator "homeostats" (e.g., the "thermostat," "glucostat," and "barostat") and "regulators" that determine algorithms for responding. The systems biologist

views such an emphasis as teleological and unparsimonious, because regulated variables and homeostats are unobservable constructs, and regulators, being defined circularly in terms of the presumed regulated variables, have no scientific meaning.

The integrative physiologist views systems biological explanations as inadequate, because they cannot account for phenomena we humans believe exist, even if we cannot observe them directly, such as intuitions, emotions, motivational states, and the conscious mind.

In integrative physiology, "function" refers to goals or purposes. Systems biology is data driven. It explains biological phenomena in terms of "omics"–i.e., genomics, gene expression, epigenomics, proteomics, and metabolomics–it depicts the data in computer models of complex cascades or networks, and it makes predictions from the models. In systems biology, "function" refers to mechanisms, not goals.

Both of these approaches are scientific. How can they be reconciled?

As discussed previously, according to Mayr's concept of teleonomic activities, goal-directed behaviors or processes depend on the operation of a *program*. The program contains not only the blueprint of the goal but also the instructions about how to use the blueprint. This of course is an entrée to genetics. Resolution of the dialectic between integrative physiology and systems biology may come from avoiding teleological purposiveness, transcending pure mechanism, and incorporating adaptiveness in evolution. This is what is meant by "Darwinian medicine."

Even within evolutionary medicine there is an intellectual hurdle. Genetics provides the most recent frames of movies that have been playing throughout evolutionary time. We only have the current frames. It is very difficult if not impossible to understand what the ecological niches were at the time that natural selection actually was operating on genetic variation. And there are thousands of such movies.

Another resolution comes from recognition that the integrative physiological and systems biological perspectives reflect two minds—minds that each of us possesses and can't escape. Daniel Kahneman (Nobel Prize, 2002) has conceptualized two systems of thinking—System 1 and System 2. System 1 thinking is fast and intuitive, uses little energy, and enables multitasking but incorporates preconceptions and biases and therefore is prone to erroneous decision making. System 2 thinking is slow, analytical, unbiased, and more likely to lead to correct decision making but is slower, uses more energy, and obviates multitasking.

Teleological thinking seems to be a form of System 1 thinking. The autonomic adjustments that maintain homeostasis of temperature, glucose, and blood pressure, etc., can be understood easily by System 1 thinking: the body contains a thermostat for regulating core temperature, a glucostat for regulating blood glucose, a barostat for regulating blood pressure, and so forth.

By System 2 thinking, not only does the body's thermostat not have a purpose, there is no thermostat at all. The thermostat is unnecessary for describing the complex and dynamic mechanisms determining core temperature. The same applies

for glucose, blood pressure, and all other internal variables.

Our brains use both Systems. By System 1 thinking, we instinctively seek out purposes in our experiences. We ask—and can't avoid asking—"why" questions. The integrative physiologist tests whether induced concepts stand up to scientific testing by observation and experimentation. By System 2 thinking we don't seek out purposes or ask "why" questions. The systems biologist doesn't induce concepts so much as apply technologies to describe network facts. Computational models representing those facts are then developed that yield testable predictions.

Rapprochement of integrative physiology with systems biology will come when we recognize that each of us has a System 1-thinking, intuitive, feeling mind that seeks out purposes and asks "why" questions and a System 2-thinking, rational, unfeeling mind that doesn't. We flip-flop from one to the other.

What Good are Homeostats?

If homeostats are unnecessary and overly simple, what good are they?

First, having metaphorical regulators representing complex central neural networks and conceptualizing purposes for controlling regulated variables enable definitions of otherwise difficult ideas. An example is stress. In stress, a homeostat senses a discrepancy between afferent information about the regulated variable and the set point for arousing a response. Stress is then a condition, and the error signal is the measure of

the extent of stress. The integrated error signal could correspond to a kind of “memory” that would more be more efficient than the instantaneous error signal in returning the regulated variable to the set point value.

Second, the homeostat theory lends itself straightforwardly to computer models for phenomena such as homeostatic resetting (allostasis), compensatory activation of alternative effectors, effector sharing, allostatic load, and induction of pathophysiological positive feedback loops.

Third is the capability to induce experimental therapeutic concepts that observation or experiment can test. Examples are gastric bypass surgery to treat metabolic syndrome, vagal stimulation to treat inflammatory disorders, and beta-adrenoceptor blockade to treat heart failure.

Fourth, based on homeostatic thinking one can gain insights into pathophysiologic mechanisms underlying clinical syndromes. Recall the case of the patient with sleep apnea who intentionally modified his CPAP device to breathe in CO_2 and developed dangerously severe hypertension (Fig. 160). Homeostatic thinking led to the discovery that labile hypertension can be a late sequela of neck irradiation (Fig. 294) and that familial dysautonomia entails afferent baroreflex failure (Fig. 270). Hyperglycemia in the setting of gastrointestinal bleeding, hyperthermia and hypokalemia following cardiac arrest, and hyponatremia in heart failure can be explained by effector sharing. Increased sympathetic noradrenergic system (SNS) outflows in hypothyroidism, hypopituitarism, and adrenocortical failure can be explained by compensatory activation of alternative effectors.

Fifth, thinking in terms of homeostatic is valuable for teaching about clinical physiology and pathophysiology. For instance, one can grasp the four phases of the blood pressure and heart rate responses to the Valsalva maneuver and the abnormalities encountered in sympathetic neurocirculatory failure by having in mind the baroreflex arc and the garden hose analogy (Fig. 231).

THE CHANGING FACE OF DISEASE

The systems that maintain the stability of the inner world eventually degenerate, and as their efficiencies decline the likelihood of deleterious, self-reinforcing positive feedback loops increases, threatening organismic stability and survival. Moreover, the medications and treatments clinicians prescribe interact with their patients' internal systems. Multiple, simultaneous degenerations, combined with multiple effects of drugs and remedies and myriad interactions among the degenerations and the treatments constitute the bulk of modern medical practice. Autonomic medicine offers a schema and vocabulary for approaching the imposing complexity of managing patients.

The Human Genome Project and its descendants have produced a huge fund of information about the normal and diseased human genome. This information is not static but is expanding rapidly, due to identification of single nucleotide polymorphisms, splicing variants, whole gene or nucleotide sequence repetitions, variations in genes encoding transcription factors and promoters, multiple simultaneous genotypic

changes, genetic imprinting, mosaicism, and stress and other epigenetic effects on chromosomes. We also are now seeing the introduction of computerized applications to analyze that information.

Even as genetic information-gathering has expanded, however, the very nature of disease has changed.

The era of "strep throat medicine" has come to an end. The era of chronic, complex disorders of regulation has begun.

These involve derangements of multiple body processes, drug treatments, and interactions among the derangements and the drugs, posing enormous personal and societal burdens. The notion that diseases have simple, single causes that can be cured with a "magic bullet" like penicillin does not apply to dysautonomias or to a large number of other disorders of regulation of the "inner world" inside the body.

For developmental diseases of specific, isolated body processes, genotypic or gene expression data might suffice to identify the pathophysiologic pathways from etiology to clinical phenotype in intra-uterine or postnatal development. Much less clear is how genetic changes already present at birth interact with individual life experiences to lead to multi-system degenerative disorders decades later.

Homeostatic Medicine

Norbert Wiener introduced the term, "biocybernetics," as a correlate of his cybernetic theory of control systems. He distinguished two forms of biocybernetics, medical biocybernetics and neurocybernetics. He conceptualized that in medical biocybernetics, "homeostasis is the main consideration," whereas neurocybernetics centers on "the pathways of actions via sense-organs, neurons and effectors." He did not think there was a sharp distinction between the two fields.

Medical biocybernetics might be taken as tantamount to a form of medical robotics, as in the NIH Common Fund's program, Stimulating Peripheral Activity to Relieve Conditions (SPARC). What I have in mind is somewhat more global, addressing genetic, environmental, and autotoxic factors that continually challenge homeostasis.

"Homeostatic medicine" seems closest to what I have in mind. The apparent steady states of the inner world depend on complex coordination by the brain. The brain dominates in regulation of the inner world, to maintain apparent constancy despite continual changes. In higher organisms the brain dominates in regulation of the body's inner world, via a hierarchy of centers.

Homeostatic medicine emphasizes disorders of the multiple interacting systems that regulate the "inner world" of the body.

Homeostatic medicine uses integrative physiological concepts to explain diseases in terms of interactions among genetic makeup, life experiences, drug treatments, and time, with the goal of developing strategies to treat, prevent, or palliate multi-system disorders.

Dysautonomias may be a perfect example of how applying concepts of homeostatic medicine can advance medical science and patient care.

Mind-Body Disorders

Dysautonomias are mind-body disorders.

This is a difficult subject for both doctors and patients. The problem is the old notion that the body and mind are separate and distinct in a person, and so diseases must be either physical or mental. If the disorder were physical, it would be "real," something imposed on the individual, while if it were mental, and "in your head," it would not be real, but something created in and by the individual.

Fig. 392: Mind-body duality and illness. *The mind-body dualism approach isn't helpful in dealing with dysautonomias.*

Distinctions between the "body" and the "mind" are unhelpful in trying to understand dysautonomias.

These notions date from the teachings of the Renaissance philosopher, Descartes. In my opinion, by now they are outdated and unhelpful in trying to understand disorders of the autonomic nervous system.

Here is why. In this book you have learned about the "inner world" and the "outer world." The mind deals with both worlds, simultaneously, continuously, and dynamically in life. Conversely, both worlds affect the mind, and each individual filters and colors perceptions of the inner and outer world. For instance, there is no such thing as a person exercising without "central command," to tense and relax specific muscles. At the same time, and as part of the same process, the brain automatically directs changes in blood flow to the muscles. The exercising muscle and changes in blood flow lead to information—feedback—to the brain about how things are going both outside and inside the body.

The autonomic nervous system operates at the border of the mind and body.

The brain both uses and depends on the autonomic nervous system for the internal adjustments that accompany every motion a person performs and every emotion a person feels.

You already know this, if you think about it. When you jog, for instance, the blood flow to the skin and muscle increases, the heart pumps more blood, you sweat, and you move more air. These are automatic features of the experience of exercising. Can you imagine exercising and not noticing these things?

It's also true that virtually every emotion a person feels includes changes in the same body functions. For instance, when you are enraged, the blood flow to the skin and muscle increases, the heart pumps more blood, you sweat, your nostrils flare, and you move more air.

From the point of view of the bodily changes, it would matter little whether these changes resulted from the physical experience of exercise or the mental experience of rage. Both situations involve alterations in the activity of components of the autonomic nervous system. Both situations involve changes in the inner and outer worlds. And if your autonomic nervous system were to malfunction, your reactions to either situation would not be regulated correctly; in either situation you could feel sick, look sick, and be sick!

A "systems" approach helps to understand dysautonomias. According to the systems approach, the mind simultaneously directs changes in the somatic nervous system and the autonomic nervous system, based on perceptions about what is going on in the inner world and the outer world.

Note that the autonomic nervous system affects both the inner world and outer worlds. For instance, if a person looked pale, because the blood had drained from the face, and were sweaty, trembling, and mumbling incoherently, other people would likely react to these signs of distress and ask, "Are you OK?" And it is well known that strong emotions, probably via adrenaline release, can energize an individual. Recall that one of the entries under weightlifting in the Guinness Book of Records referred to a 123-pound mother who summoned the strength to lift the front end of a car after a jack had collapsed

and the car had fallen on her child.

Analogously, the somatic nervous system can affect the inner world via the autonomic nervous system. For instance, you can voluntarily increase your blood pressure any time you want, by clenching a tight fist, or dunking your hand in ice cold water.

How would a systems approach help to understand a dysautonomia? A malfunction at almost any part of the system could lead to alterations in activities of components of the autonomic nervous system. For instance, if there were no feedback to the brain about the state of the blood pressure (part of the inner world), then there would be an inability to keep the blood pressure within bounds, by changing the activity of the sympathetic noradrenergic system. If there were no feedback about the extent of physical exercise, there would also be an inability to adjust the blood pressure and blood flows appropriately. Of course, if there were a failure of the autonomic nervous system itself, this would also interfere with regulation of the inner world, but there would also be difficulty in dealing with the outer world, manifested by problems like exercise intolerance or an inability to tolerate standing for a prolonged period (orthostatic intolerance). Finally, if the person had a psychiatric disorder such as panic/anxiety, then the inappropriate emotional experience of fear would be linked to both autonomic nervous system and somatic nervous system changes.

A clinician’s ability to treat a dysautonomia successfully also benefits from a systems approach. Treatments at any of several steps might help, but the best place in the system to insert a treatment would be the step closest to where the cause is—if

there were only one.

Dyshomeostasis

You have learned that when a monitored variable is regulated by a negative feedback loop, the monitored variable reaches a stable steady-state level; and that disruption of a negative feedback loop always increases the variability of the level of the monitored variable. Decreased efficiency of regulation of monitored variables of the body's inner therefore threatens homeostasis.

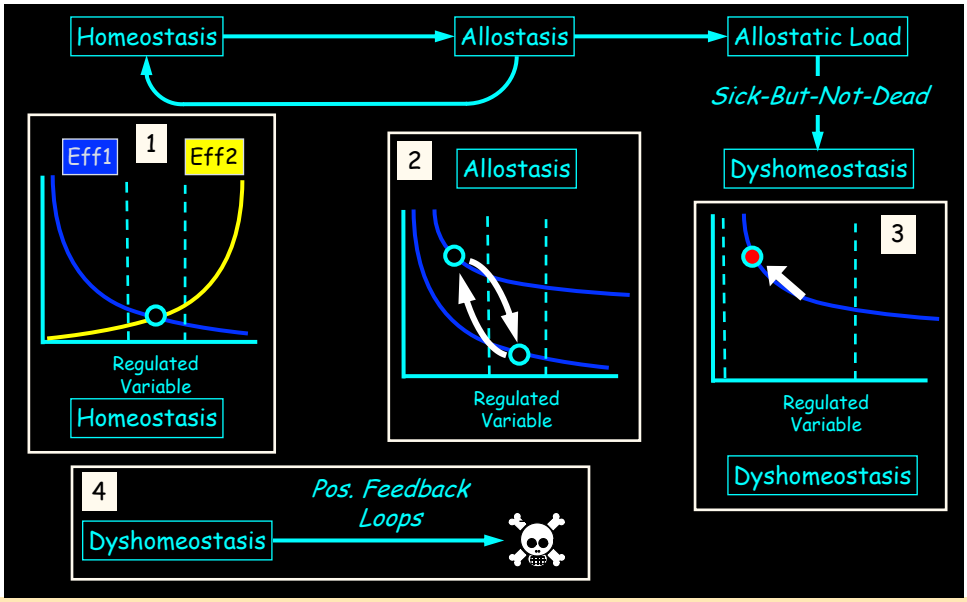


Fig. 393: Steps in degenerative diseases. *The steps are homeostasis, allostasis, dyshomeostasis, and death.*

A goal of homeostatic medicine is to devise means to detect early or even prevent catastrophic positive feedback loops. Here are some scenarios in which transition from a negative

feedback to positive feedback situation is harmful.

— A footballer practicing in full uniform in the heat releases adrenaline, which constricts skin blood vessels and augments heat production in the body, producing heat exhaustion.

— Heart failure stimulates the sympathetic nervous system and the renin-angiotensin-aldosterone system, which increases fluid retention and growth of heart muscle, worsening the heart failure.

— Chest pain from coronary ischemia due to coronary artery disease evokes distress, stimulating the SNS and SAS, increasing the work of the heart and worsening the ischemia.

— Orthostatic hypotension from failure of the SNS causes lightheadedness, a fall, fracture of a hip, and prolonged bed rest in traction, worsening the orthostatic hypotension when the patient tries to get up.

— Loss of dopamine terminals in the nigrostriatal system in the brain increases pathway traffic to the remaining terminals, accelerating dopamine turnover and thereby production of toxic by-products of dopamine metabolism, increasing the rate of loss of dopamine terminals, eventually manifesting clinically as Parkinson’s disease.

— A viral illness causes dehydration, orthostatic intolerance, and compensatory activation of the SNS, resulting in postural tachycardia syndrome (POTS). Because of ongoing fatigue, the patient spends more time in bed, the muscles atrophy, and the

blood volume declines, resulting in worsening of orthostatic intolerance and exaggeration of POTS symptoms.

The timing and rapidity of system failure from positive feedback loops depend on dynamic interactions between usage experience of the system and built-in manufacturing and design characteristics. In the body, the occurrence, timing, and rapidity of progression of degenerative diseases depend on interactions between environmental exposures and genetic predispositions. The concepts of allostasis and allostatic load provide a framework for linking stress, distress, and acute and chronic dysautonomias.

WHY DO CATECHOLAMINE NEURONS GET SICK?

Randolph M. Nesse and George C. Williams, in their book, *Why We Get Sick,* ask, "If senescence so devastates our fitness, why hasn't natural selection eliminated it?" Williams provided an answer in 1957 in his pleiotropic theory, according to which genes causing senescence have early benefits. In lay terms, "senescence is the price we pay for vigor in youth."

In young reproducers, advantages afforded by catecholamine systems, such as fight-or-flight behaviors, metabolic and temperature regulation, initiative, vigilance, resilience, registration of distressing events in long-term memory, and anti-fatigue may come at a cost: eventual accumulation of allostatic load in catecholaminergic neurons that may precipitate positive feedback loops and kill those neurons.

Catecholamine Autotoxicity

Catecholamine neurons are rare in the nervous system, and why they are vulnerable in Parkinson's disease, pure autonomic failure, and related disorders has been mysterious. One explanation is that catecholamine neurons are susceptible *because* they are catecholamine neurons.

"Autotoxicity" refers to inherent cytotoxicity of catecholamine metabolites in the cells in which they are produced. The essence of the catecholamine autotoxicity theory is that catecholamines can be turned into suicide chemicals that will kill the neuron if they are allowed to oxidize and if the toxic oxidation products aren't detoxified efficiently. Even before the neurons die, they are sick.

THE GETAWAY CAR ANALOGY

I use the analogy to a bank robber's getaway car to teach about how catecholaldehydes, the products of enzymatic deamination of cytoplasmic catecholamines, can explain the aging-related loss of catecholamine neurons in Parkinson's disease and other neurodegenerative diseases.

The engine of a car converts energy to movement. A controller—the driver—regulates the process. The fuel injector squirts fuel into the combustion chamber, where the fuel is combusted. When the car is idling, the fuel injector squirts the gasoline into the combustion chamber at a slow, continuous rate.

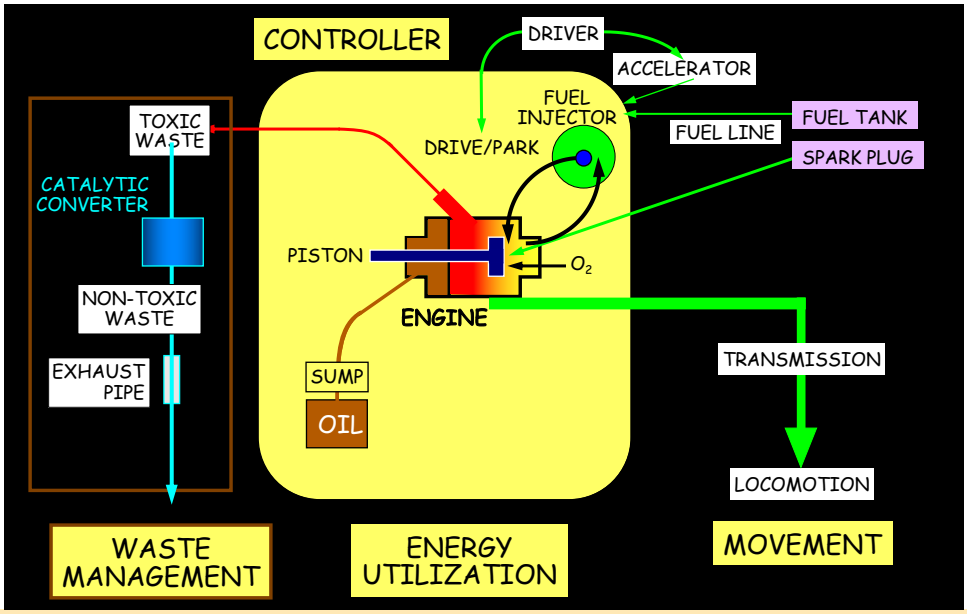


Fig. 394: The getaway care analogy.

Combustion is an oxidative process. The products of the combustion may be harmful, but they are converted to non-toxic waste products by the catalytic converter, which exit the car via the tailpipe. For the sake of analogy, let's say the amount of fuel in the combustion chamber is limited by recycling back into the fuel injector. The pistons in the engine are lubricated by oil supplied by a reservoir crankcase.

What if the getaway car had a faulty catalytic converter? The toxic byproducts of combustion might back up and potentially harm the engine. What if there were deficient recycling of the gasoline back into the fuel injector? Then there would be more production of the toxic byproducts of combustion.

If you were a bank robber your getaway car would be kept idling at the curb outside the bank. If the ignition were off, it would take longer for you to get away just when you had to,

and if the ignition happened to fail at that crucial time, that would be the end of your career as a bank robber. After several months, just from the wear and tear of having had the car in idle all that time, the engine's life span probably would be shortened because of a buildup of harmful deposits—gunk—inside. The engine might fail completely.

If you did a "post-mortem" on the engine and crankcase, you would find gunk deposits. No amount of analysis of the gunk would pinpoint the root cause of the engine failure. Maybe the catalytic converter had a design or manufacturing flaw, or something interfered with the fuel injector recycling the non-combusted fuel, or the oil had the wrong viscosity, or the driver habitually "floored" the accelerator. You wouldn't be able to tell.

Even if none of these factors alone would have ever caused a problem in the normal life span of the car, together they could have built up sufficient gunk to kill the engine.

Catecholamine neurons such as nigrostriatal dopaminergic neurons and cardiac sympathetic noradrenergic neurons are "on" continuously, in the sense that dopamine is being synthesized in the cytoplasm, and dopamine and norepinephrine (which is synthesized in the vesicles from dopamine taken up from the cytoplasm) are always leaking from the vesicles into the cytoplasm.

Catecholamine neurons are like little idling getaway car engines. Catecholamines in the vesicles leak continuously into the cytoplasm, where they are oxidized spontaneously (auto-oxidation, if you'll excuse the pun) or enzymatically (by

monoamine oxidase-A, or MAO-A). Catecholamines are being "combusted" all the time.

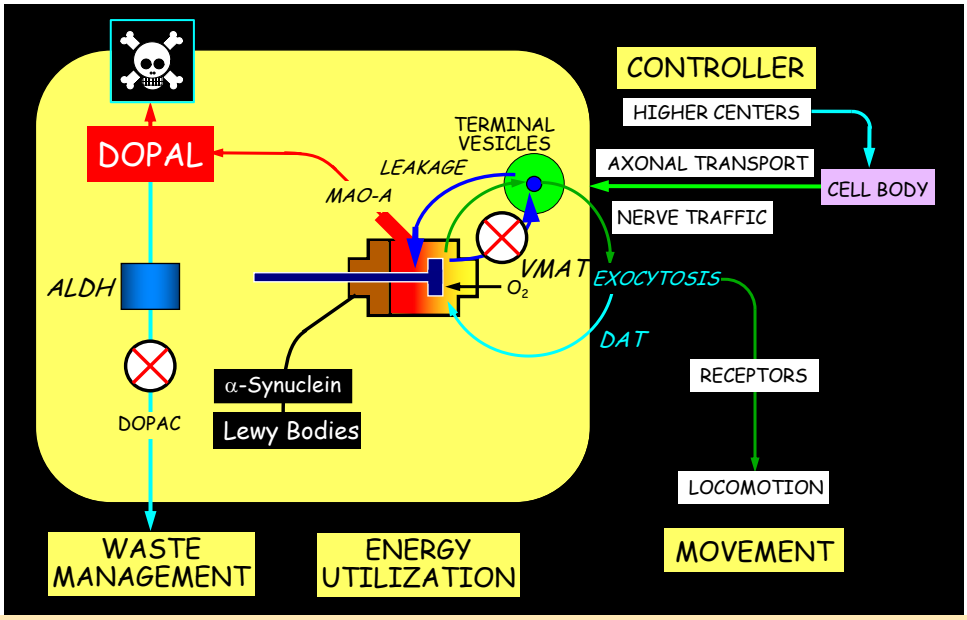


Fig. 395: Catecholamine neurons are like getaway car engines. *Catecholamines are being made and "combusted" all the time. Here the getaway car analogy is used to convey the catecholaldehyde hypothesis.*

DOPAL is the toxic aldehyde produced when MAO-A acts on cytoplasmic dopamine. The harmful byproducts of catecholamine oxidation are to a large extent detoxified by enzymes, the catalytic converters in neurons. DOPAL is detoxified by ALDH, which converts DOPAL to DOPAC, and DOPAC, the non-toxic waste product, then exits the cell.

The type 2 vesicular monoamine transporter (VMAT2) recycles the cytoplasmic catecholamines, so that levels of cytoplasmic catecholamines are kept very low. The cytoplasm of the neurons contains a variety of dissolved proteins, including the

protein, alpha-synuclein.

What if a dopaminergic neurons had decreased ALDH activity? Then DOPAL would tend to accumulate. What if there a vesicular storage defect? Then for a given rate of dopamine synthesis in the cytoplasm, there would be a higher rate of DOPAL production.

Catecholamine neurons are like little getaway car engines.

Most of the cytoplasmic dopamine that escapes vesicular uptake is oxidized enzymatically to form DOPAL. If there were a deficiency of ALDH, DOPAL would build up, and if there were a vesicular storage defect, then for a given rate of dopamine synthesis the rate of DOPAL production would be increased. Evidence for all these abnormalities has been obtained.

What about the "gunk" in the getaway car engine? DOPAL causes the protein, alpha-synuclein, to precipitate inside the neurons. Lewy bodies, the pathologic hallmark of Parkinson's disease, contain abundant alpha-synuclein deposits. DOPAL may be a key link between catecholamine depletion and Lewy bodies.

DOPAL also potently oligomerizes alpha-synuclein, and oligomerized alpha-synuclein interferes with vesicular functions, which shunts cytoplasmic dopamine toward oxidative deamination to form DOPAL—a positive feedback loop. DOPAL may be the missing link between catecholamine

deficiency and alpha-synuclein.

THE CATECHOLALDEHYDE HYPOTHESIS

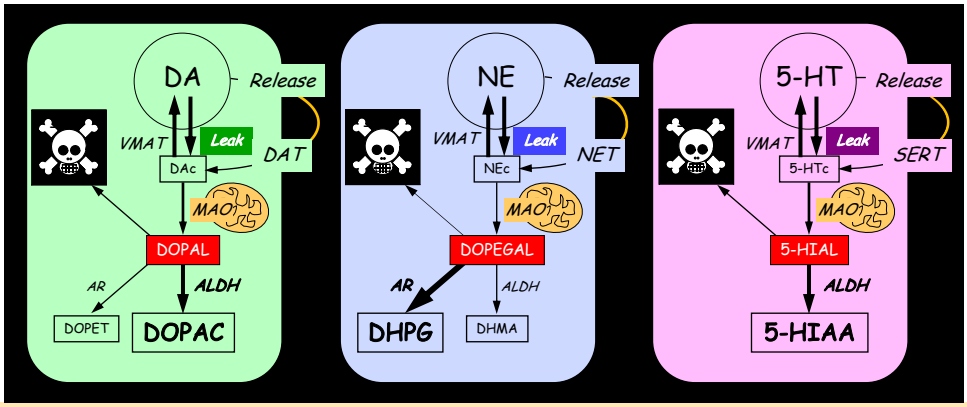


Fig. 396: Monoamine aldehyde toxicity. *Aldehydes produced by the action of monoamine oxidase (MAO) on dopamine, norepinephrine, and serotonin (5-HT) are toxic.*

Just as dopamine and norepinephrine are metabolized by MAO to form potentially toxic aldehydes, serotonin (5-hydroxytryptamine, 5-HT) which is a monoamine that is not a catecholamine, is metabolized by MAO to form another aldehyde, 5-HIAL. Because of this, the catecholaldehyde hypothesis can be expanded to the "monoamine aldehyde hypothesis." In Parkinson's disease, not only are dopamine neurons lost but so are norepinephrine and serotonin neurons. The monoamine aldehyde hypothesis explains this in terms of autotoxicity evoked by DOPAL, DOPEGAL, and 5-HIAL.

Normally monoamine aldehydes are metabolized efficiently by enzymes—aldehyde dehydrogenase (ALDH), for DOPAL and 5-HIAL and aldehyde/aldose reductase (AR) for DOPEGAL. In PD and MSA, however, ALDH activity is decreased, and

DOPAL is built up with respect to dopamine.

For ALDH to work requires a co-factor called NAD^+. NAD^+ in turn is made in the mitochondria by an important process called complex 1. Drugs that inhibit complex 1 are toxic. Part of the toxicity in dopamine neurons may come from decreased availability of NAD^+ for ALDH to do its job in preventing buildup of DOPAL. Complex 1 activity has been reported to be decreased in PD.

DOPAL-SYNUCLEIN INTERACTIONS

DOPAL interacts with a variety of intracellular proteins, altering their functions. This is where alpha-synuclein, the major protein in Lewy bodies, comes in. DOPAL potently oligomerizes alpha-synuclein, meaning that it converts the protein monomer to dimers, trimers, etc. DOPAL-induced alpha-synuclein oligomers impede vesicular functions. This means a shift in the fate of cytoplasmic dopamine from vesicular sequestration to oxidative deamination catalyzed by MAO, which increases DOPAL formation—a positive feedback loop. DOPAL also forms quinone-protein adducts with ("quinonizes") alpha-synuclein and many other intra-cellular proteins, interfering with their functions.

DOPAL also causes alpha-synuclein to come out of solution and precipitate. In particular, in oligodendrocytes, a type of glial cells, DOPAL causes alpha-synuclein to aggregate in the cytoplasm. This could be a model of the glial cytoplasmic inclusions that are a histopathologic hallmark of MSA.

Although the catecholaldehyde hypothesis can explain the unusual susceptibility of catecholamine neurons in Lewy body diseases, so far it has not been tested experimentally.

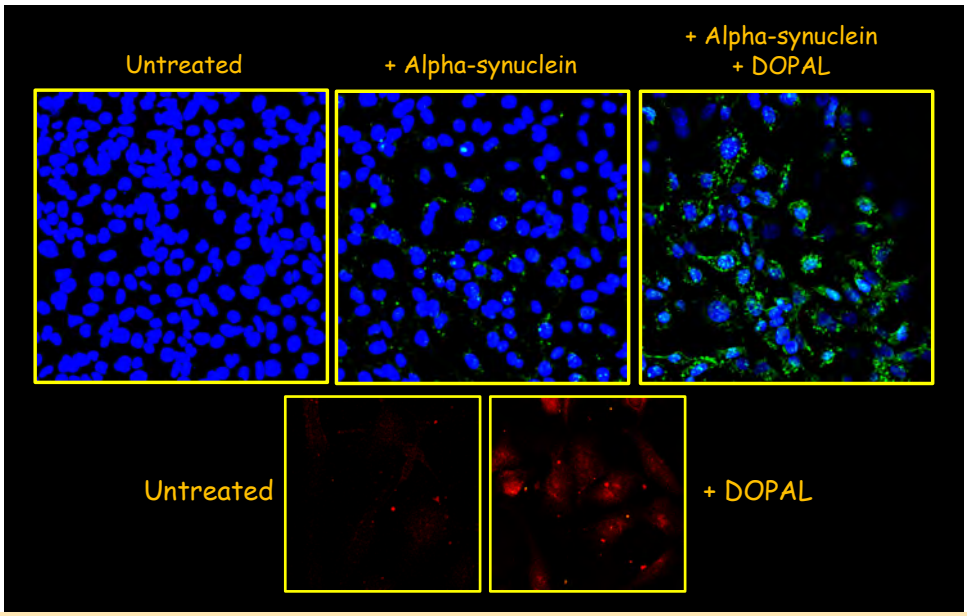


Fig. 397: DOPAL-induced protein modifications. *The top panel shows DOPAL-induced aggregation of alpha-synuclein (green) in the cytoplasm of oligodendrocytes, a type of glial cell (nuclei are blue). The bottom panel shows DOPAL-induced intra-cellular formation of quinoproteins (red).*

The concept diagram in Fig. 398 summarizes the catecholamine autotoxicity theory.

TREATMENT IMPLICATIONS OF THE CATECHOLALDEHYDE HYPOTHESIS

The notion of catecholaldehyde autotoxicity has several implications for treatment, disease modification, and prevention. Conversely, disease modification clinical trials

would provide key tests of the catecholaldehyde hypothesis.

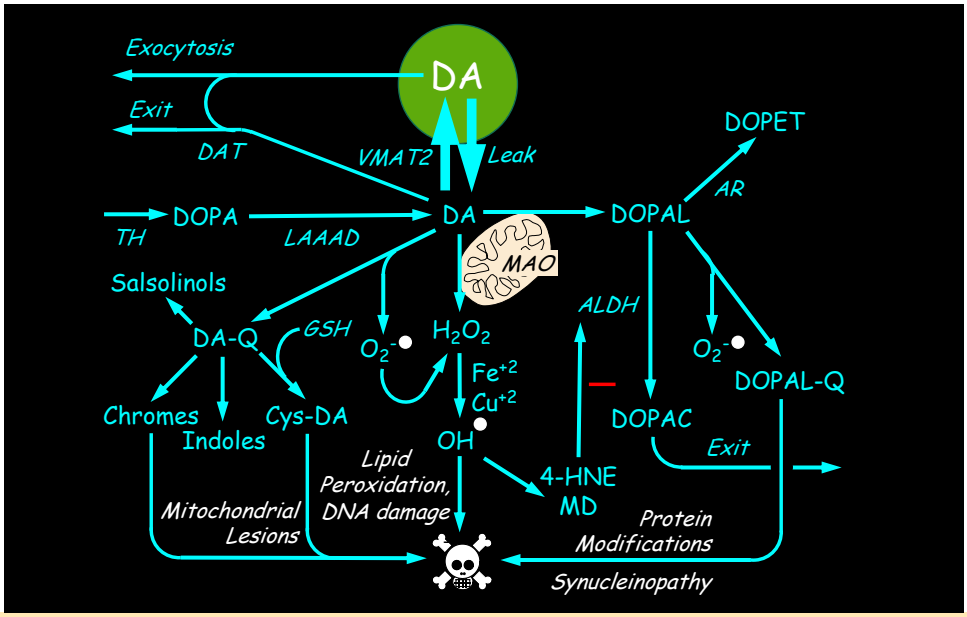


Fig. 398: Catecholamine autotoxicity. *This concept diagram shows some of the routes by which enzymatic or spontaneous oxidation of cytoplasmic dopamine may be toxic.*

The sick-but-not-dead phenomenon

Profound depletion of the catecholamines dopamine and norepinephrine in the brain, heart, or both characterize Lewy body diseases such as Parkinson disease, dementia with Lewy bodies, and pure autonomic failure. Although one might presume that catecholamine deficiency in these disorders results directly and solely from loss of catecholaminergic neurons, there is increasing evidence for functional abnormalities in extant residual neurons contributing to the neurotransmitter deficiencies. I call this the “sick-but-not-dead” phenomenon.

Recent research has begun to flesh out the meaning of “sick”

here. These diseases all involve decreased vesicular sequestration of cytoplasmic catecholamines, decreased catecholamine recycling by neuronal reuptake, and decreased ALDH activity, all in line with the getaway car analogy. In addition, there is decreased catecholamine biosynthesis, and DOPAL inhibits both of the synthetic enzymes tyrosine hydroxylase and L-aromatic-amino-acid decarboxylase.

The catecholaldehyde hypothesis and getaway car analogy lead straightforwardly to testable ideas about how to delay the onset of or slow the rate of aging-related loss of catecholamine neurons. The discovery of specific paths mediating the sick-but-not-dead phenomenon offers novel targets for multi-pronged therapeutic approaches.

First, inhibit MAO-A, since this would decrease formation of the toxic metabolite, DOPAL. Second, treat with an anti-oxidant that is bioavailable to catecholaminergic neurons, since this would attenuate spontaneous and enzymatic oxidation of cytoplasmic catecholamines and interfere with synuclein oligomerization. One such anti-oxidant may be N-acetylcysteine (NAC).

In general, the sick-but-not-dead phenomenon may apply to several degenerative diseases involving catecholamine systems.

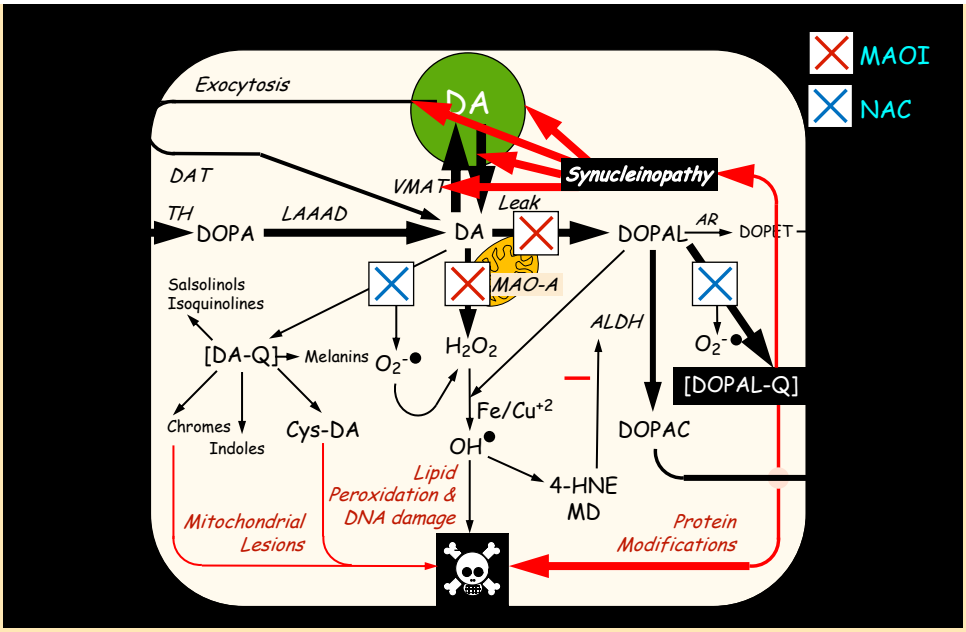


Fig. 399: Treatment implications of the catecholaldehyde hypothesis. *The catecholaldehyde hypothesis predicts that treatment to inhibit DOPAL production (by a monoamine oxidase, MAOI) and DOPAL oxidation (by the anti-oxidant N-acetylcysteine, NAC) should slow the progression of catecholaminergic neurodegeneration.*

EXTENSION OF THE MEANING OF "AUTONOMIC"

I envision further evolution of the homeostasis theory to encompass integration of autonomic nervous with behavioral, endocrine, autocrine/paracrine, and cytokine effectors. The general proposal is that all these systems mediate automatic adjustments that maintain health, and disintegration of these systems causes disorders of regulation in disease.

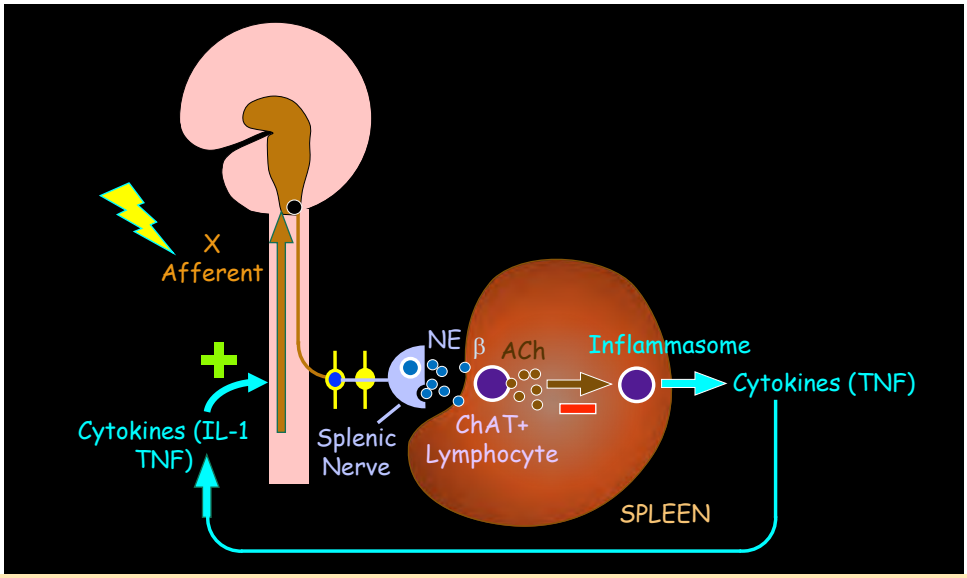


Fig. 400: Vagal-inflammasome negative feedback loop. *This is an example of extension of "autonomic" to include the immune system. Vagus nerve stimulation offers a biocybernetic approach that might treat inflammatory disorders.*

There is a large repertoire of cytokines that reciprocally interact with autonomic components (e.g., vagal-immunosome interactions, adrenaline-induced increases in interleukin-6 levels).

The separation of the central autonomic network from the cortical motor control system seems artificial, given the hard wiring of cortical motor centers to the adrenal medulla revealed by rabies virus trans-synaptic tract tracing.

This integrated view may help unravel the pathogenetic mystery of POTS, which while considered to be a dysautonomia may have neuroendocrine and autoimmune aspects.

It is time to extend the meaning of "autonomic."

Over the decades since Walter B. Cannon's extension of Langley's autonomic nervous system to include a hormonal component, here called the sympathetic adrenergic system (SAS), additional neuroendocrine systems have been described that figure prominently in regulation of internal variables. Examples are the hypothalamic-pituitary-adrenocortical (HPA) system, the renin-angiotensin-aldosterone system (RAS), and the arginine vasopressin (AVP)/anti-diuretic hormone (ADH) system. There also are autocrine-paracrine systems such as the renal DOPA-dopamine system, locally released and acting nitric oxide in response to parasympathetic nervous system (PNS)-mediated acetylcholine release, endogenous opiates, co-transmitters, and a large array of cytokines. All of these systems work unconsciously, automatically, and involuntarily. If their coordinated activities, which are regulated by the brain, don't have the "purpose" of maintaining homeostasis, then at least they act that way.

FLIPPING THE CLINIC

The term, "flip the clinic," refers to an initiative by the Robert Wood Johnson Foundation (RWJF). RWJF considers this to be less a full-fledged program than a "conversation" in progress.

Flipping the clinic is an attempt to achieve two goals. The first goal is to empower patients, family, and caregivers to be more informed and engaged in their own health and health care. The second goal is to enable healthcare providers to improve the ways they communicate with patients and support them better during and between office visits.

I hope this book is a step in "flipping the clinic" in the area of autonomic medicine.

The notion of flipping the clinic draws inspiration from Sal Khan, founder of the Khan Academy, the well-known not-for-profit organization that aims to offer "free world-class education" online, through an extensive library of videos and lectures as well as interactive challenges and assessments.

Khan Academy has sought to "flip" the classroom. Instead of listening to lectures in the classroom and doing "homework" at home, students listen to lectures at home and do "homework" in class, where the teacher can help students who are having difficulty. Students can also proceed at their own pace, mastering the material on their own schedule, not the teacher's or the classroom's.

From a scientific point of view, flipping the clinic will be especially valuable for patients with multi-system disorders of regulation, such as dysautonomias. A system of education, lifestyle adjustments, support groups, and internet-based outcomes research can be compared with the standard medical practice models, in terms of both cost-efficiency and patient satisfaction.

Flipping the clinic applies similar principles to medical practice. I envision an internet-based, mutually educational system that is accessible by patients suffering from, students learning about, and practitioners managing autonomic disorders.

I hope this book is a step in that direction.

GLOSSARY

^{18}F-DA *(Abbreviation for 6-[^{18}F]fluorodopamine) A drug that is dopamine with a positron-emitting isotope of fluorine attached. ^{18}F-dopamine is used to visualize sympathetic innervation.*

^{18}F-DOPA *(Abbreviation for 6-[^{18}F]fluorodopa) A drug that is DOPA with a positron-emitting isotope of fluorine attached. ^{18}F-DOPA is used to visualize dopaminergic innervation in the brain.*

^{131}I-Albumin *Albumin that is tagged with a trace amount of radioactive iodine (^{131}I). Injection of ^{131}I-albumin is the basis for a test to measure the blood volume.*

^{123}I-Metaiodobenzylguanidine *(^{123}I-MIBG) A particular type of radioactive drug that is used to visualize sympathetic nerves such as in the heart.*

^{123}I-MIBG *(Abbreviation for ^{123}I-Metaiodobenzylguanidine)*

3-Methoxy-4-hydroxyphenylglycol (MHPG) *A major end-product in the metabolism of norepinephrine.*

3,4-Dihydroxyphenylacetaldehyde (DOPAL) *An intermediate metabolite of dopamine.*

3,4-Dihydroxyphenylacetic acid (DOPAC) *The main intra-neuronal metabolite of dopamine.*

3,4-Dihydroxyphenylglycol (DHPG) *The main intra-neuronal metabolite of norepinephrine.*

3,4-Dihydroxyphenylglycolaldehyde (DOPEGAL) *An intermediate metabolite of norepinephrine.*

5-HIAA *(Abbreviation for 5-hydroxyindoleacetic acid) 5-HIAA is the main end-product in the metabolism of serotonin.*

5-HTP *(Abbreviation for 5-hydroxytryptophan) 5-HTP is the amino acid precursor of serotonin.*

5-Hydroxyindoleacetic acid (5-HIAA) *The main end-product in the metabolism of serotonin.*

5-Hydroxytryptophan (5-HTP) *The amino acid precursor of serotonin.*

6-[^{18}F]Fluorodopa (^{18}F-DOPA) *A drug that is the catechol amino acid, DOPA, with a fluorine atom attached that is a type of radioactive isotope called a positron emitter. Positron-emitting fluorodopa is used to visualize sites of dopaminergic innervation in the brain.*

6-[^{18}F]Fluorodopamine (^{18}F-DA) *A drug that is the catecholamine, dopamine, with a fluorine atom attached that is a radioactive isotope called a positron emitter. Positron-emitting fluorodopamine is used to visualize sites of sympathetic innervation such as in the heart.*

-A-

A5 *A region in the pons that contains norepinephrine-producing neurons.*

AAD *(Abbreviation for autoimmunity-associated autonomic denervation)*

AAG *(Abbreviation for autoimmune autonomic ganglionopathy)*

ABPM *(Abbreviation for ambulatory blood pressure monitoring)*

ACE *(Abbreviation for angiotensin-converting enzyme) ACE is an enzyme of the renin-angiotensin-aldosterone system that converts angiotensin I to angiotensin II.*

Acetate *A small organic molecule that is a common building block in the body.*

Acetyl coenzyme A *A small organic molecule that is combined with choline to form the chemical messenger acetylcholine.*

Acetylcholine *A chemical that functions as the messenger of the parasympathetic nervous system and the sympathetic cholinergic system. Acetylcholine is also the mediator of transmission in ganglia.*

Acetylcholinesterase (AChE) *An enzyme that rapidly breaks down acetylcholine in the extracellular fluid.*

ACh *(Abbreviation for acetylcholine)*

AChE *(Abbreviation for acetylcholinesterase)*

Adenosine triphosphate (ATP) *The main source of chemical energy in the body.*

ADH *(Abbreviation for antidiuretic hormone)*

Adie's pupil (also called Adie's tonic pupil) *A condition in which a pupil is relatively large and constricts slowly in bright light.*

Adrenal gland *A gland near the top of the kidney that produces important hormones such as cortisol and adrenaline.*

Adrenal medulla *The "marrow," or core, of the adrenal gland.*

Adrenalectomized *Having the adrenal glands removed.*

Adrenaline *The same as epinephrine.*

Adrenergic *Referring to cells or neurons that use adrenaline or norepinephrine as chemical messengers.*

Adrenoceptors *Specialized proteins in cell membranes of various tissues that bind to the catecholamines norepinephrine (noradrenaline) or epinephrine (adrenaline), resulting in changes in the state of activity of the cells.*

Adrenocortical *Referring to the adrenal cortex. The adrenal cortex is the outer layer of the adrenal gland.*

Adrenomedullary hormonal system (AHS) *The part of the autonomic nervous system where epinephrine (adrenaline) is released from the adrenal medulla. Synonymous with sympathetic adrenergic system (SAS).*

AHS (*Abbreviation for adrenomedullary hormonal system), synonymous with the sympathetic adrenergic system (SAS).*

AIDS *(Abbreviation for acquired immunodeficiency syndrome) The final stage of HIV disease.*

^{131}I-Albumin *Albumin that is tagged with a trace amount of radioactive iodine (^{131}I). Injection of ^{131}I-albumin is the basis for a test to measure the blood volume.*

Albumin *A prominent protein in the bloodstream.*

Alcohol dehydrogenase *An enzyme that breaks down alcohol.*

Aldehyde dehydrogenase (ALDH) *An enzyme involved in the intra-neuronal metabolism of dopamine.*

Aldehyde/aldose reductase (AR) *An enzyme that converts some aldehydes to glycols.*

Aldehyde *A type of chemical containing a -CHO group. Aldehydes formed within cells are very reactive.*

ALDH *(Abbreviation for aldehyde dehydrogenase) ALDH is an important enzyme in the metabolism of dopamine in neurons.*

Aldomet *Brand name of a drug that resembles levodopa and is an effective drug to treat high blood pressure.*

Aldosterone *The body's main sodium-retaining hormone. Aldosterone is steroid produced in the adrenal gland.*

Algorithm *A step by step procedure for solving a problem.*

Alizarin red *A pigment powder that turns purple when wet, used in sweat testing.*

Alkali *A base that dissolves in water and produces a pH more than 7.*

Alkalinizing *Referring to making a solution more alkaline. This is the same as raising the pH or making the solution more basic.*

Allostasis *A concept according to which goal values for internal variables can change as a function of*

circumstances.

Allostatic load *Cumulative wear and tear from allostasis.*

Alpha-1 adrenoceptors *A particular type of adrenoceptors that are prominent in blood vessel walls. Stimulation of alpha-1 adrenoceptors in blood vessel walls causes the vessels to constrict.*

Alpha-2 adrenoceptor blocker *A drug that blocks alpha-2 adrenoceptors.*

Alpha-2 adrenoceptors *A type of adrenoceptor that is present on particular cells in the brain, in blood vessel walls, in several organs, and on sympathetic nerve terminals.*

Alpha-adrenoceptor *One of the two types of receptors for norepinephrine (noradrenaline) and epinephrine (adrenaline).*

Alpha-methylDOPA (Aldomet™) *A drug that resembles levodopa and is an effective drug to treat high blood pressure.*

Alpha-synuclein *A protein found in Lewy bodies and glial cytoplasmic inclusions.*

Alzheimer's disease *A common neurodegenerative disease causing dementia.*

Amaurosis fugax *Transient, painless loss of vision, usually due to a problem with blood flow to part of the brain.*

Amine *A chemical containing a nitrogen atom with hydrogen atoms attached.*

Amino acid *A particular type of chemical that contains an amino chemical group and a carboxylic acid chemical group and is a "building block" of proteins.*

Amphetamines *Drugs that share a particular chemical structure and cause decreased appetite, increased attention, decreased sleep, and behavioral activation.*

AMY *(Abbreviation for amygdala)*

Amygdala *A structure of the limbic system in the brain, involved with emotional responses.*

Amyloidosis *Any of a variety disorders in which a type of protein called amyloid is deposited within body organs.*

Anaphylaxis *A severe, rapidly developing allergic response.*

Anemia *A decreased amount of red blood cells. Anemic patients look pale and feel tired.*

Angina pectoris *An unpleasant squeezing or pressure sensation due to inadequate delivery of oxygenated blood to the heart muscle, such as from coronary artery disease.*

Angiokeratoma *A benign tumors of skin capillaries. Angiokeratomas are characteristic of Fabry disease.*

Angiotensin II *A particular peptide hormone that produces blood vessel constriction. Angiotensin II is a key part of the renin-angiotensin-aldosterone system.*

Angiotensin-converting enzyme (ACE) *An enzyme of the renin-angiotensin-aldosterone system that converts angiotensin I to angiotensin II.*

Anhidrosis *Medical term for the lack of sweating.*

Anoxia *Absence of oxygen.*

ANP *(Abbreviation atrial natriuretic peptide)*

ANS *(Abbreviation for autonomic nervous system)*

Antecubital *Referring to the elbow crease area.*

Anterior cingulate cortex *A part of the frontal lobe of the cerebral cortex that plays a role in the emotions.*

Anti-Hu *An antibody produced in the setting of some cancers.*

Antibody *A large, Y-shaped protein produced mainly by plasma cells that is used by the immune system to identify and neutralize pathogens such as bacteria and viruses.*

Anticipatory control *A form of predictive or anticipatory regulation, largely synonymous with feed-forward regulation.*

Antidiuretic hormone (ADH) *Same as vasopressin.*

Anti-nAChR *Antibody that targets nicotinic acetylcholine receptors.*

AP *(Abbreviation for area postrema) The AP in the back of the medulla has no blood-brain barrier and is the site of the "vomiting center."*

Apical *Describing the apex or tip. The apical left ventricle is the tip of the heart.*

Apnea *Temporary cessation of breathing.*

Aquaporins *A family of membrane channels that transport water.*

AR *(Abbreviation for aldehyde/aldose reductase)*

Arachnodactyly *A condition in which a person has long, thin fingers (like a spider).*

ARC *(Abbreviation for arcuate nucleus)*

Arcuate nucleus *A cluster of nerve cells in the hypothalamus near the third ventricle.*

Area postrema (AP) *A region in the back of the medulla that has no blood-brain barrier and is the site of the "vomiting center."*

Arginine vasopressin *(Synonymous with vasopressin)*

Arachnodactyly *A condition in which a person has long, thin fingers.*

Arrector pili Small muscles that cause the hair to stand up.

Arrestins *A family of chemicals that help turn off the intracellular cascade that activates cells when G-protein-coupled receptors such as beta-adrenoceptors are occupied.*

Arrhythmia *Abnormal rhythm, usually referring to abnormal heart rhythm.*

Arterial baroreflex *A rapid reflex that keeps arterial blood pressure within bounds. The reflex is evoked when the*

baroreceptors in arteries are stretched.

Arterial blood sampling *Obtaining blood from a large blood vessel that moves blood away from the heart.*

Arterial pressure *The blood pressure in an artery.*

Arteries *Large blood vessels that carry blood from the heart.*

Arteriole *Tiny arteries that carry blood from the heart, like "twigs" of the arterial tree. The overall amount of constriction of arterioles is the main determinant of the total resistance to blood flow in the body. Constriction of arterioles therefore increases the blood pressure, just like tightening the nozzle of a garden hose increases the pressure in the hose.*

Arteriosclerosis *Hardening of arteries.*

Artery *A large blood vessel that carries blood from the heart. Arteries (with the exception of the arteries to the lungs) carry oxygen-rich blood at high pressure.*

AS *(Abbreviation for alpha-synuclein)*

Ascorbic acid *(Synonymous with vitamin C)*

Ashkenazi *Referring to people of Eastern European Jewish ethnicity.*

ASIC *(Abbreviation for acid-sensing ion channel) Acid-sensing ion channels are involved with both chemoreceptor and baroreceptor functions.*

Aspartame *A type of artificial sweetener. Aspartame is a methyl ester of aspartic acid/phenylalanine.*

Asphyxiation *Severe, sudden loss of oxygen supply due to lack of breathing, such as in suffocation.*

Aspiration *Inhalation of a foreign body into an airway.*

Asthma *A disease of the airways that involves episodes of airway spasm, producing wheezing, coughing, and shortness of breath.*

Asystole *A state of no electrical activity and therefore no*

pumping activity of the heart. Asystole is a cause of sudden death.

ATP *(Abbreviation for adenosine triphosphate)*

ATP7A *The gene that encodes a copper ATPase. ATP7A mutation causes Menkes disease.*

ATPase *An enzyme that breaks down ATP, releasing energy.*

Atropine *A drug that blocks muscarinic acetylcholine receptors.*

Auerbach's plexus *A nerve network in the wall of the gastrointestinal tract, part of the enteric nervous system.*

Autocrine/paracrine *A type of arrangement where a chemical messenger acts on the same or nearby cells from the site of its release.*

Autoimmune *Referring to an abnormal immune response against substances or tissues in the body.*

Autoimmune autonomic ganglionopathy (AAG) *A rare form of autonomic failure associated with high levels of antibodies to the neuronal nicotinic receptor, resulting in impaired transmission of autonomic nerve impulses in ganglia.*

Autoimmune autonomic neuropathy *A form of autonomic failure associated with an "attack" of the immune system on a part of the autonomic nervous system.*

Autoimmunity-associated autonomic denervation *A rare form of autonomic failure associated with generalized autonomic denervation.*

Autonomic *Referring to the autonomic nervous system.*

Autonomic dysreflexia *A condition after a spinal cord injury in which afferent stimulation, such as from filling of the urinary bladder, evokes a large increase in blood pressure.*

Autonomic function testing *Testing of one or more functions of the autonomic nervous system.*

Autonomic medicine *A medical discipline that focuses on*

clinical disorders of the autonomic nervous system.

Autonomic myasthenia *Nickname for a form of chronic autonomic failure associated with an antibody to the acetylcholine receptor responsible for transmission of nerve impulses in ganglia.*

Autonomic nerve supply *The amount of autonomic nerve fibers and terminals in a tissue or organ.*

Autonomic nervous system (ANS) *The body's "automatic" nervous system, responsible for many automatic, usually unconscious processes that keep the body going.*

Autonomically mediate syncope *Syncope due to alterations in activities of the components of the autonomic nervous system. A fainting reaction is an example of autonomically mediated syncope.*

Autosomal dominant *A situation where even one copy of the mutated gene is sufficient to produce the disease.*

Autosomal recessive *A situation where copies of the mutated gene on each chromosome produce the disease.*

Autotoxic *A characteristic of chemicals that harm the cells in which they are produced.*

Autotoxicity *A process by which a chemical harms the cells in which it is produced.*

AVP *(Abbreviation for arginine vasopressin)*

Axon reflex *A type of reflex where stimulation of nerves going towards the brain leads directly to a change in nerve activity towards a nearby site.*

-B-

B cell (also known as B lymphocyte) *A particular type of lymphocyte white blood cell. B cells secrete antibodies and also present antigen and secrete cytokines.*

Baroreceptor reflex *The same as baroreflex.*

Baroreceptors *Stretch or distortion receptors in the walls of large blood vessels such as the carotid artery and in the heart muscle.*

Baroreflex *A rapid reflex where an increase in blood pressure sensed by the brain leads to relaxation of blood vessels and a decrease in heart rate. The baroreflex keeps blood pressure stable.*

Baroreflex failure *A disorder in which the baroreceptor reflex fails, resulting in variable blood pressure and orthostatic intolerance.*

Baroreflex-cardiovagal failure *A situation where there is a lack of the normal change in the cardiac interbeat interval for a given change in systolic blood pressure.*

Baroreflex-cardiovagal gain *The change in cardiac interbeat interval for a given change in systolic blood pressure.*

Baroreflex-sympathoneural failure *A situation where there is a lack of the normal reflexive increase in sympathetic noradrenergic outflow for a given decrease in blood pressure.*

Baroreflex-sympathoneural gain *The change in sympathetic outflow for a given change in arterial blood pressure.*

Barostat *The conceptual homeostatic comparator that keeps the blood pressure stable.*

Basal *Referring to the upper part of the heart.*

Basal ganglia *Structures in the brain that are below the cortex and above the brainstem.*

Basic *Having an alkaline pH.*

BAT *(Abbreviation for brown adipose tissue)*

Beighton score *A scoring system for rating joint hyperextensibility.*

Benign prostatic hypertrophy (BPH) *Long-term enlargement of*

the prostate gland that does not result from a cancer.

Benzodiazepine *A type of drug with a particular chemical structure that causes sedation, an anti-anxiety effect, relaxation of skeletal muscle, and decreased seizure activity.*

Beta-adrenoceptor *One of the two types of receptors for norepinephrine (noradrenaline) and epinephrine (adrenaline).*

Beta-1 adrenoceptors *One of the three types of beta-adrenoceptors, prominent in the heart muscle.*

Beta-2 adrenoceptors *One of the three types of beta-adrenoceptors, prominent in blood vessel walls in skeletal muscle, in the heart muscle, and on sympathetic nerve terminals.*

Beta-3 adrenoceptors *One of the three types of beta-adrenoceptors, prominent in fatty tissue.*

Beta-adrenoceptor blocker *A type of drug that blocks one or more types of beta-adrenoceptors.*

Beta-Adrenoceptors *One of the two types of receptors for the norepinephrine (noradrenaline) and epinephrine (adrenaline).*

Beta-blocker *A shorter form of the term beta-adrenoceptor blocker.*

Bethanechol (Urecholine™) *A drug that stimulates some receptors for acetylcholine, mimicking the effects of stimulating the parasympathetic nervous system.*

BH4 *(Abbreviation for tetrahydrobiopterin)*

Bicuspid aortic valve *A congenital abnormality in which the aortic valve has two rather than the normal three leaflets.*

Biomarker *An objective measure of a biological or disease process.*

Blood glucose *The concentration of the important metabolic*

fuel, glucose (dextrose), in the blood.

Blood pressure (BP) *The pressure in arteries. Systolic blood pressure is the maximum pressure while the heart is beating, and diastolic blood pressure is the minimum pressure between heartbeats.*

Blood volume *The total volume of blood in the body. Most of the blood volume is in veins.*

Blood-brain barrier *A physical and chemical barrier that keeps compounds in the bloodstream from entering the substance of the brain.*

Botulinum toxin *A toxic chemical released from a particular bacterium. Botulinum toxin blocks release of acetylcholine.*

BP *(Abbreviation for blood pressure)*

BPH *(Abbreviation for benign prostatic hypertrophy)*

Bradykinesia *Slow movement, especially slow initiation of movement.*

Brain fog *Decreased ability to concentrate, remember, or carry out executive functions.*

Brainstem *The part of the central nervous system between the brain and the spinal cord. The brainstem includes the hypothalamus, midbrain, pons, and, just at the top of the spinal cord, the medulla oblongata.*

BRK *(Abbreviation for bradykinin and other kinins)*

Bromocriptine *A drug that blocks a class of dopamine receptors. In post-partum women, injection of bromocriptine prevents lactation.*

Bronchioles *Small airway tubes in the lungs.*

Bronchoconstriction *Constriction of the airways.*

Bruit *A whooshing sound that can be heard with a stethoscope, due to turbulent blood flow through an area of arterial narrowing.*

Buccal *Referring to the cheek.*

Buffering *In homeostatic systems theory, a process that diminishes the impact of an external disturbance on the level of a monitored variable.*

-C-

Cachectic *Having the appearance of wasting, as in end-stage cancer.*

CAF *(Abbreviation for chronic autonomic failure)*

Caffeic acid *A particular chemical found in coffee beans that is not caffeine.*

Caffeine *A chemical found in high concentrations in coffee beans.*

cAMP *(Abbreviation for cyclic adenosine monophosphate)*

Carbidopa *A drug that inhibits the conversion of L-DOPA (levodopa) to dopamine. Carbidopa does not enter the brain from the bloodstream and blocks the conversion of L-DOPA to dopamine outside the brain.*

Cardiac output *The amount of blood pumped by the heart in one minute.*

Cardiac sympathetic neuroimaging *A clinical laboratory test designed to visualize the sympathetic innervation of the heart.*

Cardiovagal *Referring to effects of the vagus nerve on the heart (usually on the heart rate).*

Cardiovascular *Referring to the heart and blood vessels.*

Carotid arteries *The main arteries in the neck. In the upper neck, the common carotid artery splits into the external and internal carotid arteries.*

Carotid sinus *A region at the split of the common carotid artery into the internal and external carotid arteries. In humans, the carotid sinus contains distortion receptors called*

baroreceptors.

Carotid sinus nerve *(Also called Hering's nerve) A branch of the glossopharyngeal nerve that carries nerve fibers from the carotid sinus and carotid body.*

Carotid sinus stimulation *A method to control high blood pressure using a device that electrically stimulates the carotid sinus.*

CASS *(Abbreviation for Composite Autonomic Severity Scale) A scale to rate the severity of autonomic failure.*

Catechol-O-methyltransferase (COMT) *A major enzyme that metabolizes catechols.*

Catecholaldehyde *A type of chemical that contains a catechol group and an aldehyde. DOPAL is a catecholaldehyde.*

Catecholaldehyde hypothesis *A concept in which aldehyde metabolites of catecholamines cause or contribute to neuronal death, such as in Parkinson's disease.*

Catecholamine *A member of an important chemical family that includes adrenaline.*

Catecholamine autotoxicity *A concept in which spontaneous or enzyme-catalyzed oxidation of cytoplasmic catecholamines causes or contributes to neuronal death, such as in Parkinson's disease.*

Catecholamines *Norepinephrine (noradrenaline) epinephrine (adrenaline), and dopamine.*

Catechol *A chemical that has a catechol structure in it. Dopamine, norepinephrine, adrenaline, and DOPA are catechols.*

Catechol-O-methyltransferase (COMT) *An enzyme that breaks down catechols in non-neuronal cells.*

Catechols *Chemicals that have a particular structure in them called catechol. Dopamine, norepinephrine, adrenaline, and DOPA are catechols.*

Caudal ventrolateral medulla (CVLM) *A region in the lower, outer part of the medulla. The CVLM is part of the central autonomic network.*

Caudate *A brain structure that is part of the striatum, in the basal ganglia.*

CCHS *(Abbreviation for Congenital Central Hypoventilation Syndrome) A disease in which patients breathe normally while awake but hypoventilate when sleeping.*

Cell membrane norepinephrine transporter (NET) *The transporter responsible for "recycling" of norepinephrine back into sympathetic nerves.*

CellCept (or Mycophenolic acid) *A drug that inhibits part of the immune system.*

Central nervous system (CNS) *The brain and spinal cord.*

Central Sympathetic Hyperactivity *A condition where there is an increase in the rate of sympathetic nerve traffic in the body as a whole.*

Cerebellar *Referring to the cerebellum.*

Cerebellar atrophy *A decrease in size of the cerebellum, a part of the brain.*

Cerebellum *A part of the brain, located above and behind the brainstem, that plays important roles in coordination of movement and the sense of orientation in space.*

Cerebrospinal fluid (CSF) *The clear fluid that bathes the brain and spinal cord.*

Cervical spinal cord *The spinal cord at the level of the neck.*

ChAT *(Abbreviation for choline acetyltransferase) ChAT catalyzes the production of acetylcholine from choline and acetyl coenzyme A.*

Cheese effect *Side effects such as paroxysmal hypertension from eating tyramine-containing foodstuffs in the setting of monoamine oxidase inhibition.*

Chemoreflex *A reflex initiated by stimulation of chemical receptors, such as those in the carotid body, that respond to changes in blood concentrations of carbon dioxide, hydrogen ion, and oxygen.*

Chiari malformation *An anatomic abnormality where part of the brainstem falls below the hole between the brain and spinal cord.*

Chief Complaint *A single phrase or sentence that describes in the patient's own words what has been bothering the patient that has led to the patient coming in for evaluation.*

Choline *A small organic molecule that is used in the body to produce acetylcholine.*

Choline acetyltransferase (ChAT) *The enzyme that catalyzes the production of acetylcholine from choline and acetyl coenzyme A.*

Chorea *A type of quick abnormal movement of the hands or feet.*

Choroid plexus *A web-like network of cells in the brain that are the source of the cerebrospinal fluid.*

Chromosome *Organized structures of DNA in cells. Humans have 23 pairs of chromosomes, including 2 sex chromosomes (X and Y in males, 2 X chromosomes in women).*

Chronic autonomic failure (CAF) *Long-term failure of the autonomic nervous system.*

Chronic fatigue syndrome *A condition where the patient has a sense of persistent fatigue for more than six months, without an identified cause.*

Chronic orthostatic intolerance (COI) *Long-term inability to tolerate standing up.*

Ciliary ganglion *A parasympathetic ganglion at the back of the eye socket.*

CING *(Abbreviation for cingulate cortex)*

Cingulate cortex (CING) *A region of the brain that lies above the corpus callosum and is involved with processing emotions and emotional behaviors.*

Classical conditioning *A form of association learning where two stimuli are repeatedly paired; a response that is at first elicited by the second stimulus (unconditioned stimulus) is eventually elicited by the first stimulus alone (conditioned stimulus). Same as Pavlovian conditioning.*

Clearance *The volume of fluid cleared of a substance in a given amount of time.*

Clonidine *A drug that stimulates alpha-2 adrenoceptors in the brain, in blood vessel walls, and on sympathetic nerve terminals. Clonidine decreases release of norepinephrine from sympathetic nerves and decreases the blood pressure.*

Clonidine suppression test *A test based on effects of clonidine administration on blood pressure and plasma levels of chemicals such as norepinephrine (noradrenaline).*

CNS *(Abbreviation for the central nervous system)*

Coat hanger phenomenon *Pain in the back of the neck and shoulders during standing. This can be a symptom of chronic orthostatic intolerance.*

COL *(Abbreviation for collagen-related genes)*

Cold pressor test *An autonomic function test in which the patient dunks a hand into a bucket of ice-cold water and keeps the hand immersed.*

Common carotid artery *A large artery on each side of the neck that supplies blood to the head and neck.*

Common faint *The same as neurocardiogenic syncope, autonomically mediated syncope, and reflex syncope.*

COMPASS *(Abbreviation for Composite Autonomic Symptom Score) The "COMPASS 31" scale contains a total of 31*

questions in 6 domains and yields an overall autonomic symptom score from 0 to 100.

Compensatory activation *A situation where failure of one effector system compensatorily activates another effector system, allowing a degree of control of a monitored variable.*

Complex 1 (NADH:ubiquinone oxidoreductase) *The first enzyme in the mitochondrial respiratory chain.*

Composite Autonomic Severity Scale (CASS) *A scale to rate the severity of autonomic failure.*

Composite Autonomic Symptom Score 31 (COMPASS 31) *An autonomic symptom scale that contains a total of 31 questions in 6 domains, yielding an overall autonomic symptom score from 0 to 100.*

CO *(Abbreviation for cardiac output)*

COI *(Abbreviation for chronic orthostatic intolerance)*

COMT *(Abbreviation for catechol-O-methyltransferase) COMT is an important enzyme that breaks down catechols in non-neuronal cells.*

Conductance *A measure of how easily electricity flows along a particular path.*

Congenital *Present from birth.*

Congenital central hypoventilation syndrome (CCHS) *A rare inherited disease in which the patients do not have the normal reflexive respiratory responses.*

Congestive heart failure (CHF) A *condition in which the heart doesn't pump blood adequately and the blood backs up into the lungs.*

Conjunctival injection *Swollen blood vessels in the whites of the eyes, giving the appearance of being "blood shot."*

Constipation *Infrequent and difficult bowel movements.*

Contraction band necrosis *A particular microscopic pathologic*

appearance of dead heart muscle that can result from high levels of adrenaline.

Conversion reaction *Neurological symptoms such as numbness, blindness, or paralysis without an identified organic cause.*

CoQ *(Abbreviation for coenzyme Q) CoQ is synonymous with ubiquinone.*

COQ2 *A gene that encodes for the mitochondrial enzyme para-hydroxybenzoate-polyprenyltransferase.*

Core temperature *The temperature at the core of your body, such as the temperature of the arterial blood.*

Coronary arteries *The arteries that deliver blood to the heart muscle.*

Coronary artery disease *A condition where the coronary arteries become narrowed or blocked by fatty deposits and thickening of the blood vessel walls.*

Coronary ischemia *Lack of adequate blood flow to heart muscle via the coronary arteries.*

Corpora cavernosa *A pair of sponge-like highly vascularized structures in the penis that when engorged with blood produces erection.*

Corpus striatum (synonymous with striatum) *The caudate and putamen in the basal ganglia of the brain.*

CPAP *(Abbreviation for continuous positive airway pressure). A method to treat sleep apnea by preventing airways from collapsing.*

CPVT *(Abbreviation for catecholaminergic polymorphic ventricular tachycardia) CPVT is a genetic disorder in which life-threatening abnormal heart rhythms can result from catecholamines.*

Cranial nerves *The twelve nerves that come through holes in the skull from the brainstem and go to many organs, from the eyes to the gastrointestinal tract.*

CSF *(Abbreviation for cerebrospinal fluid)*

CTK *(Abbreviation for cytokines)*

CYB561 The gene that encodes cytochrome b561. Mutation of the CYB561 is a rare cause of neurogenic orthostatic hypotension.

Curare *A poison that paralyzes by blocking nicotinic acetylcholine receptors at neuromuscular junctions in skeletal muscle.*

CVLM (*Abbreviation for caudal ventrolateral medulla)*

CYB561 The gene that encodes cytochrome b561. Mutation of the CYB561 is a rare cause of neurogenic orthostatic hypotension.

Cybernetics *The science of communications and automatic control systems in machines and living things.*

Cybernetic Medicine *(Synonymous with Scientific Integrative Medicine) A conceptual framework for linking systems biology with integrative physiology in order to understand disease mechanisms.*

Cyclic adenosine monophosphate (cAMP) *A key chemical "second messenger" inside cells.*

Cys-DOPA *(Abbreviation for 5-S-cysteinylDOPA) A catechol in which cysteine and DOPA are bonded.*

Cys-DA *(Abbreviation for 5-S-cysteinyldopamine) A catechol in which cysteine and dopamine are bonded.*

Cytokine *A type of protein that is secreted by cells of the immune system and exerts effects on other cells. Examples of cytokines are interferons, interleukins, and tumor necrosis factors.*

Cytoplasm *The gel-like solution that fills cells.*

-D-

d-Amphetamine *The dextro- mirror image form of amphetamine.*

DA *(Abbreviation for dopamine)*

DAN *(Abbreviation for diabetic autonomic neuropathy)*

DAT *(Abbreviation for the cell membrane dopamine transporter)*

DAT scan *A type of scan of the brain that is used to detect loss of dopamine terminals in the striatum, as in Parkinson's disease.*

DBH *(Abbreviation for dopamine-beta-hydroxylase)*

DDA *(Abbreviation for DOPA-dopamine autocrine-paracrine system)*

DDAVP *A synthetic form of vasopressin, the anti-diuretic hormone.*

DDC *(Abbreviation for DOPA decarboxylase)*

DDD *(Abbreviation for DOPA-responsive dystonia)*

Desmopressin (DDAVP) *A synthetic form of vasopressin, the anti-diuretic hormone.*

Dehydration *Abnormal lack of water in the body.*

Delayed orthostatic hypotension *A fall in the blood pressure after prolonged standing.*

Dementia with Lewy bodies (DLB, synonymous with Lewy body dementia, LBD) *A form of dementia in which the brain contains abundant Lewy bodies.*

Denervated *Having no nerves.*

Denervation supersensitivity *Increased sensitivity of a process as a result of loss of delivery of a chemical messenger to its receptors that normally mediate the process.*

Dermis *The layer of beneath the epidermis. The dermis contains fat, connective tissue, blood vessels, arrector pili (pilomotor) muscles, and sweat glands.*

Dermographia *A condition in which lightly scratching the skin*

causes raised, red lines where the skin was scratched.

Desmopressin *(DDAVP) A synthetic form of vasopressin, the anti-diuretic hormone.*

Detrusor *A smooth muscle in the wall of the urinary bladder that causes the urinary bladder to contract.*

Dextro-amphetamine *(Same as d-amphetamine)*

DHPG *(Abbreviation for 3,4-dihydroxyphenylglycol) DHPG is the main intra-neuronal metabolite of norepinephrine.*

DHPR *(Abbreviation for dihydropteridine reductase)*

Diabetes *A disease state with excessive volume of urination and excessive water intake.*

Diabetes mellitus *A form of diabetes that results from lack of insulin effects in the body.*

Diabetes insipidus *A form of diabetes that results from lack of antidiuretic hormone (vasopressin) in the body.*

Diabetic autonomic neuropathy (DAN) *Dysautonomia in the setting of diabetes mellitus.*

Diagnosis *A decision about the cause of a specific case of disease.*

Diastolic *The bottom number in a blood pressure reading.*

Diastolic pressure *Minimum pressure at which the heart fills with blood between beats.*

Dihydrocaffeic acid *A particular chemical that is a breakdown product of caffeic acid.*

Dihydropteridine reductase (DHPR) deficiency *A rare, atypical form of phenylketonuria (PKU).*

Dishabituation *A return to the initial magnitude of response after habituation has taken place.*

Distal *Further away from the center or point of attachment in the body.*

Distress *A form of stress that is consciously experienced.*

DLB *(Abbreviation for dementia with Lewy bodies)*

DLB+OH *(Abbreviation for dementia with Lewy bodies and orthostatic hypotension)*

DMNX *(Abbreviation for dorsal motor nucleus of the vagus)*

DMX *(Abbreviation for dorsal motor nucleus of the vagus)*

DNA *A long molecule, in the shape of a double helix, that contains genetic instructions.*

DOPA *(Abbreviation for 3,4-dihydroxyphenylalanine, levodopa) DOPA, a catechol amino acid, is the precursor of the catecholamines.*

DOPA decarboxylase (DDC, LAAAD) *The enzyme responsible for conversion of L-DOPA to dopamine in the body.*

DOPA-responsive dystonia *A neurological disease resulting from decreased activity of an enzyme required for synthesizing tetrahydrobiopterin.*

DOPAC *(Abbreviation for 3,4-dihydroxyphenylacetic acid) DOPAC is the main intra-neuronal metabolite of dopamine.*

DOPAL *(Abbreviation for 3,4-dihydroxyphenylacetaldehyde) DOPAL is the catecholaldehyde metabolite of dopamine.*

Dopamine *One of the body's three catecholamines. Dopamine deficiency in the striatum causes the movement disorder in Parkinson's disease.*

Dopamine sulfate *A particular metabolite of dopamine.*

Dopamine-beta-hydroxylase (DBH) *The enzyme responsible for conversion of dopamine to norepinephrine in the body.*

Dopamine-beta-hydroxylase deficiency *A rare cause of neurogenic orthostatic hypotension due to lack of the enzyme required for producing norepinephrine from dopamine.*

DOPEG *(Another abbreviation for DHPG)*

DOPET *(Abbreviation for 3,4-dihydroxyphenylethanol) DOPET is a minor metabolite of dopamine.*

DOPS *(Abbreviation for dihydroxyphenylserine)*
Dorsal *Referring to the back part.*
Dorsal motor nucleus *The nucleus of the vagus nerve in the back of the medulla of the brainstem.*
Dorsal root ganglion *A particular cluster of nerve cell bodies in a posterior root of a spinal nerve. The neurons receive input from sense organs and project to the spinal cord.*
Dorsomedial *Toward the back and central. The dorsomedial medulla contains the nucleus of the solitary tract.*
Droxidopa *Synonymous with L-DOPS. Droxidopa is converted in the body to norepinephrine.*
Dysautonomia *A condition in which a change in the function of one or more components of the autonomic nervous system adversely affects health.*
Dysautonomias *Conditions in which a change in the function of one or more components of the autonomic nervous system adversely affects health.*
Dysphoria *Sour mood; a state of unease or generalized dissatisfaction with life.*
Dyspnea *Shortness of breath.*

-E-

Eaton-Lambert syndrome *A rare autoimmune condition in which there is decreased acetylcholine release at neuromuscular junctions, resulting in weakness.*
ECF *(Abbreviation for extracellular fluid)*
Edinger-Westphal nucleus *A cluster of nerve cells in the midbrain from which parasympathetic nerves travel to the eye.*
EDS *(Abbreviation for Ehlers-Danlos syndrome)*
Effector *An entity that influences the level of a monitored*

variable. The sympathetic noradrenergic system is an example of an effector for controlling the blood pressure.

Effector sharing *A situation in which two homeostats use the same effector.*

Ehlers-Danlos syndrome *A type of inherited disease of structural tissue that involves the protein, collagen. Some signs of Ehlers-Danlos syndrome are stretchy skin and overly flexible joints.*

Endocytosis *Vesicular recycling by the vesicles coming off the membrane surface and re-entering to the cytoplasm.*

Endogenous *Referring to something that is made in the body.*

Endothelial *Referring to the innermost layer in a blood vessel wall.*

Endothelial cells *Cells that make up the innermost wall of blood vessels.*

Enkephalins *A class of compounds made in the body that bind to opiate receptors.*

Enophthalmos *A posterior displacement of the eyeball within the orbit.*

ENS *(Abbreviation for enteric nervous system) The ENS component of the autonomic nervous system found in the walls of the gastrointestinal tract.*

Enteric *Referring to the gastrointestinal tract.*

Enteric nervous system (ENS) *A component of the autonomic nervous system found in the walls of the gastrointestinal tract.*

Enzyme *A type of protein that accelerates a biochemical process.*

EOS *(Abbreviation for endogenous opioid system)*

Ephedrine *A particular drug that acts in the body as a sympathomimetic amine.*

EPI *(Abbreviation for epinephrine) EPI is the main hormone*

released from the adrenal medulla.

Epinephrine (adrenaline) *The main hormone released from the adrenal medulla. Epinephrine is one of the body's three catecholamines.*

Erectile failure *Impotence from failure to have or sustain erection of the penis.*

Ergotamine *A particular drug that constricts blood vessels.*

Ergotropic *W.R. Hess's term referring to particular behaviors evoked by hypothalamic stimulation that seem to be directed outwards towards the environment.*

Error control regulation *Reflexive regulation via negative feedback in a homeostatic system.*

Erythromelalgia *A condition in which the patients complain of burning pain in the skin.*

Erythropoietin *A hormone that stimulates the bone marrow to produce red blood cells.*

ETS *(Abbreviation for endoscopic thoracic sympathectomy)*

Eustress *Selye's term for stress that is not harmful.*

Exocytosis (or exocytotic release) *Release of the contents of vesicles into the extracellular fluid, after fusion and poration of the vesicles with the cell membrane.*

Express *In molecular biology expression means that the cells are translating their cellular mRNA in order to make functional protein.*

Extracellular fluid (ECF) *The fluid outside cells of the body. The ECF is composed of the interstitial fluid and the blood plasma.*

Extravasation *Leakage of fluid from blood vessels into the surrounding tissues.*

-F-

Fabry disease *A lipid storage disease due to deficiency of the enzyme alpha-galactosidase-A. The disease is manifested by angiokeratomas and anhidrosis.*

Factitious *False symptoms without secondary gain.*

Fainting *Relatively rapid loss of consciousness that is not caused by heart disease.*

False-positive test *A positive test result when the patient does not actually have the disease.*

Familial Dysautonomia (FD) *A rare inherited disease that features abnormalities in sensation and in functions of the autonomic nervous system.*

FAC *(Abbreviation for familial amyloid cardiomyopathy)*

FAP *(Abbreviation for familial autonomic polyneuropathy)*

FBF *(Abbreviation for forearm blood flow)*

FD *(Abbreviation for Familial Dysautonomia) FD is a rare inherited disease that features abnormalities in sensation and in functions of the autonomic nervous system.*

FDA *(Abbreviation for the U.S. Food and Drug Administration)*

F-DA *(Abbreviation for fluorodopamine) ^{18}F-DA is used to image sympathetic innervation by PET scanning.*

F-DOPA *Fluorinated DOPA. ^{18}F-DOPA is used to image the striatum in the brain by PET scanning.*

Feed-forward regulation *A form of predictive or anticipatory regulation (synonymous with anticipatory control).*

Fenfluramine *A particular drug that acts in parts of the nervous system where serotonin is the chemical messenger.*

Fibromyalgia *A condition that involves widespread, chronic pain and tenderness of muscle or connective tissues.*

First messenger *A hormone or other chemical messenger that acts on receptors on target cells. Second messengers within the target cells mediate the changes in cell*

functions.

Flipping the clinic *A term referring to empowerment and responsibility of people in their medical care.*

Florinef™ *(Brand name for fludrocortisone)*

Fludrocortisone (Florinef™) *A type of artificial salt-retaining steroid drug.*

Fluorodopamine *A drug that is the catecholamine dopamine with a fluorine atom attached.*

Forearm blood flow (FBF) *The rate of inflow of blood into the forearm, usually expressed in terms of blood delivery per 100 cc of tissue volume per minute.*

Forearm vascular resistance (FVR) *The extent of resistance to blood flow in the forearm blood vessels.*

Free fatty acids *Chemicals that are breakdown products of triglycerides. Free fatty acids can be used as an energy source in some organs.*

Fungiform papillae *Particular taste buds on the tongue.*

FVR *(Abbreviation for forearm vascular resistance)*

-G-

Galvanic skin response (GSR) *A physiological change in the amount of sweat, an index of ability of the skin to conduct electricity.*

Ganglia *Plural of ganglion; clumps of nerve cells in the autonomic nervous system.*

Ganglion *A clump of cells where autonomic nerve impulses are relayed between the spinal cord and target organs such as the heart.*

Ganglion blocker *A type of drug that inhibits the transmission of nerve impulses in ganglia.*

Gastrin *A hormone secreted through the bloodstream that*

stimulates secretion of gastric stomach juices.

Gastroesophageal reflux *A condition in which stomach contents and acid go backward up the swallowing tube, the esophagus.*

Gastroparesis *Poor stomach motility, so that food does not pass through the stomach properly.*

Gaucher disease *An inherited disease in which mutation of a enzyme called glucocerebrosidase causes accumulation of a type of fat called glucocerebroside in body organs.*

GBA *The gene encoding glucocerebrosidase. GBA mutations cause Gaucher disease.*

GCH1 *(Abbreviation for GTP cyclohydrolase 1) GCH1 is an enzyme in the biosynthetic cascade leading to tetrahydrobiopterin.*

GCI *(Abbreviation for glial cytoplasmic inclusion)*

GDNF *(Abbreviation for glial cell line-derived neurotrophic factor)*

Gene *A segment of DNA that directs development and behavior in an organism. If the genetic material were an encyclopedia, the genes would be sentences.*

GH *(Abbreviation for growth hormone)*

GLA *The gene encoding alpha-galactosidase A. Alpha-galactosidase A deficiency causes Fabry disease.*

Glands *Body structures that release chemicals.*

Glial cell *A type of non-neuronal "helper" cell in the brain.*

Glial cell line-derived neurotrophic factor (GDNF) *A nerve growth factor produced by glial cells.*

Glial cytoplasmic inclusions (GCIs) *Inclusion bodies in the cytoplasm of glial cells.*

Glomerular filtrate *The fluid in kidney tubules after filtration of the blood in the glomeruli.*

Glomeruli *Plural of glomerulus. The glomeruli in the kidney*

filter the blood.

Glomerulus *A microscopic tuft of arterioles that filters the blood in the kidneys.*

Glossopharyngeal nerve *The ninth cranial nerve.*

Glucagon *A hormone that plays a major role in regulation of glucose levels.*

Glucocerebrosidase *A particular enzyme. Mutation of the gene encoding glucocerebrosidase (GBA) causes Gaucher disease.*

Glucocorticoid *A type of steroid made in the adrenal cortex that increases glucose levels.*

Glucose *One of the body's main fuels. The same as dextrose.*

Glucostat *The conceptual homeostatic comparator that keeps the blood glucose level stable.*

Glycogen *A multibranched polysaccharide of glucose that serves as a form of energy storage.*

Glycopyrrolate *A particular anti-cholinergic drug that is a muscarinic cholinergic antagonist.*

GON *(Abbreviation for gonadotropin)*

Gonadotropin (GON) *A type of hormone released by the pituitary gland that stimulates gonad activity.*

G-protein coupled receptor kinase (GRK) *A member of a class of enzymes that are activated by G-proteins.*

GPCR *(Abbreviation for G-protein coupled receptor)*

Grinch syndrome *A reference to the Dr. Seuss character who had a heart that was "two sizes too small."*

Growth hormone (GH) *A hormone released by the pituitary gland that promotes growth.*

GSR *(Abbreviation for galvanic skin response) A rapid increase in electrical conduction in the skin as a result of an increase in production of sweat.*

GTP *(Abbreviation for guanosine triphosphate)*

GTPCH *(Abbreviation for GTP cyclohydrolase)*
GTP cyclohydrolase (GTPCH) *An enzyme in the biosynthesis of tetrahydrobiopterin.*
Guillain-Barré syndrome *A condition involving autoimmune attack on neurons of the peripheral nervous system.*
Gustatory *Referring to tasting something.*

-H-

hATTR *(Abbreviation for hereditary ATTR amyloidosis)*
Habituation *The process by which repetition of a stimulus diminishes the physiological or emotional response.*
HACER *(Abbreviation for hypothalamic area controlling emotional responses)*
Heart block *An impediment to conduction of impulses in the electrical conduction pathways of the heart.*
Heart failure *A condition where the heart fails to pump an amount of blood for the tissues of the body.*
Hematocrit *The percent of the blood volume that is the volume of the red blood cells.*
Hemorrhage *Rapid blood loss from the circulation.*
Hereditary sensory and autonomic neuropathy type III (HSAN III) *(Synonymous with Familial Dysautonomia)*
Hereditary sensory and autonomic neuropathy type IV (HSAN IV) *A rare form of inherited disease involving lack of ability to sense pain and lack of sweating.*
Hereditary transthyretin amyloidosis *A rare cause of chronic autonomic failure.*
Heroin *A type of opiate drug.*
Heterozygous *A situation in which a genetic mutation is found on one chromosome but not the other.*
5-HIAA *(Abbreviation for 5-hydroxyindoleacetic acid) 5-HIAA*

is the main breakdown product of serotonin.

5-Hydroxyindoleacetic acid (5-HIAA) *The main breakdown product of serotonin.*

Hirschsprung's disease *A disease of newborns in which there is failure to pass meconium or stool due to a loss of enteric ganglion neurons.*

Histamine flare reaction *A particular appearance of the skin after local injection of histamine.*

History of the Present Illness (HPI) *A narrative history of a medical condition. The HPI is a key part of the medical history.*

HIV *(Abbreviation for human immunodeficiency virus)*

HIV disease *A disease caused by the human immunodeficiency virus. The final stage of HIV disease is AIDS (acquired immunodeficiency syndrome).*

Holmes-Adie syndrome *A condition in which there is Adie's pupil combined with a loss deep tendon reflexes.*

Homeostasis *A condition in which levels of constituents of body fluids and of core temperature are kept within bounds.*

Homeostat *A general term for a metaphorical physiological comparator.*

Homovanillic acid (HVA) *The main end-product of dopamine metabolism.*

Homozygous *A situation in which the same genetic mutation is found on both chromosomes*

Hormone *A chemical released into the bloodstream that acts at remote sites in the body.*

Horner's syndrome *A syndrome of lid lag (ptosis), constricted pupil (miosis), and decreased sweating (anhidrosis) due to disruption of sympathetic nerve traffic.*

HPA *(Abbreviation for hypothalamic-pituitary-adrenocortical) The HPA axis plays an important role in distress and*

immunity.

HPI *(Abbreviation for history of the present illness)*

HR *(Abbreviation for heart rate)*

HRV *(Abbreviation for heart rate variability)*

HSAN *(Abbreviation for hereditary sensory and autonomic neuropathy)*

Huntington's disease *An inherited, progressive neurodegenerative disease of adults that involves involuntary limb movements and dementia.*

HVA *(Abbreviation for homovanillic acid) HVA is the main end-product of dopamine metabolism.*

Hyperadrenergic orthostatic intolerance *A condition where an inability to tolerate standing up is combined with signs or symptoms of excessive levels of catecholamines such as epinephrine (adrenaline).*

Hypercarbia *An excessive increase in the blood concentration of carbon dioxide.*

Hyperdynamic circulation syndrome *A condition in which the rate and force of the heartbeat are abnormally increased.*

Hyperglycemia *A condition in which there is a high blood glucose level.*

Hyperhidrosis *A condition in which there is excessive sweating.*

Hypernoradrenergic hypertension *Long-term high blood pressure associated with increased release of norepinephrine from sympathetic nerves.*

Hypertension *A condition where the blood pressure is persistently increased.*

Hypertrophied *Characterized by an increase in the volume of an organ or tissue, due to enlargement of the component cells.*

Hypertrophy *An increase in the volume of an organ or tissue, due to enlargement of the component cells.*

Hypoglycemia *A condition where there is an abnormally low blood glucose level.*

Hypothalamic-pituitary-adrenocortical system (HPA) *A major neuroendocrine system involving the hypothalamus, pituitary gland, and adrenal cortex.*

Hypothalamus *A region of the brain above the brainstem.*

Hypothermia *A condition where there is an abnormally low body temperature.*

Hypoxia *Oxygen deficiency.*

-I-

IBS *(Abbreviation for irritable bowel syndrome)*

Idiopathic hyperhidrosis *Excessive sweating that has no known cause.*

IgE *An immunoglobulin that plays a key role in acute allergic reactions.*

IKAP *(Abbreviation for IkappaB kinase-associated protein)*

IkappaB kinase-associated protein (IKAP) *The protein product encoded by the gene, IKBKAP. FD patients have decreased levels of this protein in nervous system tissue.*

IKBKAP *A particular gene, a type of mutation of which causes Familial Dysautonomia.*

ILBD *(Abbreviation for incidental Lewy body disease) ILBD is thought to be a form of pre-symptomatic Parkinson's disease.*

Ileus *Distention of the bowel due to lack of propulsive movement of contents.*

Imidazoline *A particular chemical structure.*

Immunoglobulin *A type of glycoprotein produced by immune cells that acts as an antibody.*

Immunosome *The effector part of the immune system.*

Impedance plethysmography *A non-invasive medical test that measures small changes in electrical resistance. Impedance plethysmography can be used to measure changes in local blood flow.*

Impotence *Inability to have erection of the penis or ejaculation of semen.*

Inappropriate sinus tachycardia *Fast heart rate because of too rapid firing of the heart's pacemaker in the sinus node.*

Incidental Lewy body disease (ILBD) *The occurrence of Lewy bodies found at autopsy in clinically healthy people. ILBD is thought to be a form of pre-symptomatic Parkinson's disease.*

Incontinence *Sudden involuntary urination or bowel movement.*

Inderal™ *(Brand name of propranolol)*

Indirectly acting sympathomimetic amines *A type of drug that produces effects similar to those of stimulating sympathetic nerves.*

Inflammasome *A multi-protein intracellular complex that detects pathogenic microorganisms and stressors and activates pro-inflammatory cytokines.*

Infused *Administered by infusion. Drugs can be infused via an intravenous catheter.*

Innervation *Nerve supply.*

INS *(Abbreviation for insulin)*

Instrumental conditioning *A type of learning in which the organism's behavior is shaped based on the likelihood of reinforcement. Instrumental and operant conditioning are virtually synonymous.*

Insular cortex *(Also called the insula and insular lobe) A part of the cerebral cortex folded deep within the fissure separating the temporal from the parietal and frontal lobes.*

Insulin *An important hormone released from the pancreas that helps to control the blood glucose level.*

Insulin neuritis *A form of acute painful neuropathy due to rapid improvement in glucose levels by insulin treatment.*

Interleukin *A member of a group of cytokines.*

Intermediolateral columns *The middle outer part of the spinal cord that contains sympathetic pre-ganglionic neurons.*

Interoceptive *Referring to input from sensors within body organs (especially the gut).*

Intima *The innermost layer of a blood vessel wall.*

Intravenous (IV) *Inside a vein. Drugs can be infused or blood can be sampled via an IV catheter.*

Intravenous immunoglobin (IVIG) *Therapy using a mixture of antibodies administered by vein.*

Intravenous saline *Physiological salt-in-water solution that is given by vein.*

Intron *A segment of a DNA or RNA molecule that does not code for a protein and interrupts the sequence of genes.*

Ionotropic *Referring to movement of ions across the cell membrane.*

Iontophoresis *A way of using electricity to deliver a drug to the skin surface.*

Irritable Bowel Syndrome (IBS) *A gastrointestinal disorder consisting of symptoms of abdominal pain and altered bowel movements.*

Ischemic *Restriction of blood supply to tissues.*

Isoproterenol *(Isuprel™) A particular drug that stimulates beta-adrenoceptors.*

Isoproterenol infusion test *A test where isoproterenol is given by vein, to see if this affects the ability to tolerate tilting or to measure the body's responses to stimulation of beta-adrenoceptors.*

Isuprel™ *The brand name of isoproterenol.*
IV *(Abbreviation for intravenous)*
IVIG *(Abbreviation for intravenous immunoglobulin)*

-J-

JBC *(Abbreviation for Journal of Biological Chemistry)*
JPET *(Abbreviation for Journal of Pharmacology and Experimental Therapeutics)*
Juxtaglomerular apparatus *A specialized structure near the glomeruli of the kidneys that is involved with regulating renal blood flow and the rate of glomerular filtration.*

-K-

Kinky hair disease *The same as Menkes disease.*

-L-

LAAAD *(Abbreviation for L-aromatic-amino-acid decarboxylase)*
L-aromatic-amino-acid decarboxylase (LAAAD) *The enzyme that converts levodopa to dopamine in the body.*
L-dihydroxyphenylalanine *(Levodopa, L-DOPA) L-dihydroxyphenylalanine is the precursor of the catecholamines in the body.*
L-Dihydroxyphenylserine (L-DOPS) *A particular amino acid that is converted to norepinephrine by the action of L-aromatic-amino-acid decarboxylase.*
L-DOPA *(Abbreviation for L-dihydroxyphenylalanine, the same as levodopa) L-DOPA is the precursor of the catecholamines in the body.*

L-DOPS *(Abbreviation for L-dihydroxyphenylserine, brand name Northera™) L-DOPS is turned into norepinephrine in the body.*

Lacrimal *Referring to tears.*

Lacrimation *Secretion of tears.*

Lambert-Eaton syndrome *(Same as Eaton-Lambert syndrome) A neuromuscular disease resulting from autoimmunity to calcium channels.*

LBD *(Abbreviation for Lewy body dementia)*

LC *(Abbreviation for locus ceruleus)*

Lesion *A damaging abnormality in a tissue.*

Levodopa *The same as L-DOPA and L-dihydroxyphenylalanine.*

Lewy body *A type of inclusion body in the cytoplasm of neurons. Lewy bodies contain abundant precipitated alpha-synuclein.*

Lewy body dementia *(LBD; synonymous with dementia with Lewy bodies)*

Lewy body diseases *A group of diseases characterized by Lewy bodies. The autonomic synucleinopathies Parkinson's disease with orthostatic hypotension and pure autonomic failure are examples.*

LH *(Abbreviation for lateral hypothalamus)*

Limbic system *A group of brain structures above the level of the brainstem and below the level of the cerebral cortex.*

Livedo reticularis *A skin finding consisting of a mottled lattice-like pattern of purplish discoloration.*

Locus ceruleus (LC) *A cluster of nerve cells in the pons of the brainstem. The LC is the main source of norepinephrine in the brain.*

Log *Mathematical way to express numbers with a base of 10.*

Low pressure baroreceptors *Distortion receptors in the walls of the atria of the heart and great veins.*

LRRK2 *(Abbreviation for leucine-rich repeat kinase 2) A particular enzyme. Mutation of the gene encoding LRRK2 is a cause of familial Parkinson's disease.*

Lumbar puncture *A procedure where a needle is inserted into the lower back, such as to sample cerebrospinal fluid.*

Lymphocytes *A family of white blood cells that play important roles in immunity.*

-M-

Ma-huang Chinese name for an herbal remedy that is ephedrine.

MCAS *(Abbreviation for Mast Cell Activation Syndrome)*

Macula densa *An area of specialized cells in the juxtaglomerular apparatus that are sensitive to sodium chloride.*

Malingering *Falsification of symptoms with secondary gain.*

MAO *(Abbreviation for monoamine oxidase)*

MAO-A *(Abbreviation for monoamine oxidase type A)*

MAO- B *(Abbreviation for monoamine oxidase type B)*

MAP *(Abbreviation for mean arterial pressure)*

Marfanoid *Having the characteristics of being tall and thin, with long arms and legs and thin fingers, as in Marfan syndrome.*

MAST *(Abbreviation for military anti-shock trousers)*

Mast cell *A particular type of immune cell that plays a role in rapid immune responses.*

Mast Cell Activation Syndrome (MCAS) *A condition in which mast cells are activated inappropriately or excessively.*

MCAS *(Abbreviation for Mast Cell Activation Syndrome)*

Mean arterial pressure (MAP) *The average blood pressure in the arteries.*

Meconium *The earliest stool of a newborn.*

Meissner's plexus *A network of neurons in the submucosal layer of the wall of the small intestine.*

Melanin *A black pigment formed from oxidation of tyrosine or catechols.*

Menkes disease *A rare inherited disease of copper metabolism that causes death in early childhood.*

Mesolimbic *Referring to a nervous pathway from the midbrain to the limbic system.*

Metabolism *The chemical processes that occur within a living organism.*

Metabotropic receptor *A type of membrane receptor that acts through a second messenger. The muscarinic cholinergic receptor is an example of a metabotropic receptor.*

Metanephrine (MN) *The O-methylated metabolite of epinephrine.*

Metanephrines *A general term for the O-methylated metabolites of norepinephrine and epinephrine.*

3-Methoxytyramine *The O-methylated metabolite of dopamine.*

3-Methoxytyrosine *The O-methylated metabolite of DOPA.*

Methylphenidate (Ritalin™) *A particular drug in the family of amphetamines.*

Metoclopramide *A drug that is an antagonist at dopamine receptors. Metoclopramide is used clinically to treat gastroesophageal reflux and delayed gastric emptying (gastroparesis).*

MHPG *(Abbreviation for 3-methoxy-4-hydroxyphenylglycol). MHPG is a major end-product of norepinephrine metabolism.*

MIBG *(Abbreviation for metaiodobenzylguanidine)* ^{123}*I-MIBG is used for cardiac sympathetic neuroimaging.*

Midodrine (Proamatine™) *A particular drug that can be taken*

as a pill and constricts blood vessels by way of stimulation of alpha-adrenoceptors, used commonly in the treatment of orthostatic hypotension and orthostatic intolerance.

Milieu intérieur Claude Bernard's concept of the fluid environment of nearly constant composition that bathes and nourishes the cells of the body.

Military anti-shock trousers (MAST) suit *A type of inflatable trousers that decreases pooling of blood in the legs.*

Mineralocorticoid *A type of steroid that causes the body to retain sodium.*

Miosis *Constriction of the pupil.*

Mitochondria *Intra-cellular organelles that produce chemical energy.*

mmHg *Abbreviation for millimeters of mercury, a measure of pressure.*

MN *(Abbreviation for metanephrine)*

Monitored variable *A biological activity that can be sensed and the level of which can be controlled by effectors.*

Monoamine *A type of biochemical that contains a component called an amine group. Serotonin, norepinephrine, dopamine, and adrenaline are monoamines.*

Monoamine oxidase *An enzyme localized to the outer mitochondrial membrane that metabolizes catecholamines and related chemicals.*

Moxonidine *A particular drug that decreases blood pressure by decreasing sympathetic nerve traffic.*

MSA *(Abbreviation for multiple system atrophy) MSA is a rare progressive disease of the brain.*

MSA-C *(Abbreviation for the cerebellar form of multiple system atrophy)*

MSA-P *(Abbreviation for the parkinsonian form of multiple system atrophy)*

MSNA *(Abbreviation for muscle sympathetic nerve activity)*

Multiple system atrophy (MSA) *A rare progressive disease of the brain that includes failure of the autonomic nervous system.*

Muscarine *A chemical found in some mushrooms that stimulates muscarinic cholinergic receptors.*

Muscarinic *Referring to one of the two types of acetylcholine receptors. The other is nicotinic.*

Muscle sympathetic nerve activity (MSNA) *Pulse-synchronous traffic in sympathetic post-ganglionic fibers in peripheral nerves.*

Mutation *A rare genetic change, like a "typo" in the genetic encyclopedia.*

Myasthenia gravis *An autoimmune neuromuscular disease usually associated with circulating antibodies to the skeletal muscle nicotinic receptor.*

Mycophenolic acid *A drug that inhibits the immune system.*

Mydriasis *Dilation of the pupil.*

Myelin *A fatty, electrically insulating material found in sheaths surrounding nerve fibers.*

Myelinated *Having a myelin sheath.*

Myocardium *Muscle tissue of the heart.*

Myocytolysis *A microscopic pathologic finding in the heart that can reflect death of heart muscle cells due to exposure to catecholamines.*

-N-

nAChR *(Abbreviation for nicotinic acetylcholine receptor)*

NAD+ *(Abbreviation for the oxidized form of nicotinamide adenine dinucleotide) A type of co-enzyme required for some enzymes to function. NAD+ is an oxidizing agent that*

accepts electrons.

NE *(Abbreviation for norepinephrine) NE is one of the body's three catecholamines.*

Negative feedback *A situation where the output from a system is fed back into the system.*

Negative feedback loop *A type of control system in which alteration in the input about a monitored variable leads to an opposing alteration in the output via an effector.*

Nerve growth factor (NGF) *A particular factor that is trophic for sympathetic nerves and dorsal root ganglion cells.*

Nerve terminal *The end of a nerve fiber, from which chemical messengers are released.*

Nerve traffic *Electrical signals conducted within a nerve.*

NET *(Abbreviation for the cell membrane norepinephrine transporter)*

NET deficiency *A rare cause of orthostatic intolerance resulting from decreased activity of the cell membrane norepinephrine transporter.*

Neurally mediated hypotension (NMH) *A sudden fall in blood pressure during provocative tilt table testing.*

Neurally mediated syncope *A condition that includes sudden loss of consciousness from a change in the function of the autonomic nervous system.*

Neurasthenia *(Same as neurocirculatory asthenia) A condition closely related to chronic fatigue syndrome that features exercise intolerance without identified cause.*

Neuritis *Inflammation of nerves.*

Neurocardiogenic syncope *(Same as Neurally Mediated Syncope and Autonomically Mediated Syncope).*

Neurochemical *A chemical released from nervous tissue.*

Neurocirculatory asthenia *A condition closely related to chronic fatigue syndrome that features exercise intolerance without*

identified cause.

Neurodegeneration *Progressive loss of structure or function of neurons.*

Neuroendocrine *Relating to the nervous and endocrine systems functioning as a unit.*

Neuroendocrine system *A type of system in which chemical messengers released from nerve terminals act on cells that in turn release hormones into the bloodstream.*

Neurogenic orthostatic hypotension *A form of orthostatic hypotension due to an inadequate reflexive increase in release of norepinephrine.*

Neuroimaging tests *Tests based on visualizing the nervous system.*

Neuroimmunology *A field of medical science that focuses on interactions between the nervous system and the immune system.*

Neuroleptic *A type of tranquilizer drug used to treat schizophrenia or other psychiatric conditions.*

Neuromelanin *A dark pigment in the cytoplasm of catecholaminergic neurons.*

Neuronal nicotinic receptor (nAChR) *The form of acetylcholine receptor that mediates ganglionic neurotransmission.*

Neuronal reuptake *Reuptake of a neurotransmitter into the cytoplasm of the neuron.*

Neuropathic POTS *A form of postural tachycardia syndrome (POTS) thought to result from local or patchy loss of sympathetic nerves.*

Neuropathy *An abnormality of one or more peripheral nerves.*

Neuropharmacologic *A type of drug effect that acts on nervous tissue or mimics chemicals released in nervous tissue.*

Neurotransmitter *A chemical released from nerve fibers or terminals that produces effects on nearby cells.*

NGF *(Abbreviation for nerve growth factor)*

NIDDM *(Abbreviation for non-insulin-dependent diabetes mellitus)*

NIH *(Abbreviation for the National Institutes of Health)*

Nicotine *A chemical in tobacco that stimulates a particular type of receptor for the chemical messenger acetylcholine.*

Nicotinic *Referring to one of the two types of receptors for the chemical messenger acetylcholine. The other is muscarinic.*

Nigrostriatal system *A dopaminergic network involving the substantia nigra of the midbrain and the striatum in the basal ganglia.*

Nitric oxide (NO) *A gas produced in the body that acts as a vascular relaxing factor.*

Nitroglycerine *A particular drug that relaxes walls of veins in the body.*

NMH *(Abbreviation for neurally mediated hypotension)*

NMN *(Abbreviation for normetanephrine)*

NO *(Abbreviation for nitric oxide)*

nOH *(Abbreviation for neurogenic orthostatic hypotension)*

Non-dipping *Absence of the normal nocturnal decrease in blood pressure.*

Non-myelinated *Lacking a myelin sheath.*

Non-selective beta-adrenoceptor blockers *A type of drug that blocks all types of beta-adrenoceptors.*

Noradrenaline *(Synonymous with norepinephrine) Noradrenaline is one of the body's three catecholamines.*

Noradrenergic *Referring to norepinephrine. Noradrenergic neurons use norepinephrine as their chemical messenger.*

Norepinephrine (noradrenaline) *The main chemical messenger of the sympathetic nervous system that is responsible for much of regulation of the cardiovascular system by the*

brain.

Normal saline *A dilute solution of sodium chloride (table salt) that has the same concentration as in the serum.*

Normetanephrine (NMN) *The O-methylated metabolite of norepinephrine.*

NTRK1 *(Abbreviation for neurotrophic tyrosine kinase receptor type 1) Mutation of the gene encoding NTRK1 is a cause of type IV hereditary sensory and autonomic neuropathy.*

NTS *(Abbreviation for nucleus of the solitary tract) The NTS is the brainstem site of the initial synapse in the arterial baroreflex and other autonomic reflexes.*

Nucleus accumbens *A region at the bottom of the brain in front of the pre-optic area of the hypothalamus. The nucleus accumbens is thought to play important roles in motivation, pleasure, reward, reinforcement learning, and addiction.*

Nucleus of the solitary tract (NTS) *The brainstem site of the initial synapse in the arterial baroreflex and other autonomic reflexes.*

-O-

Oculogyric crisis *A reaction to certain drugs or medical conditions in which there is prolonged, involuntary upward deviation of the eyes.*

OH *(Abbreviation for orthostatic hypotension) OH is a fall in blood pressure during standing.*

Oligomerization *A chain addition reaction process in which a protein molecule links covalently to one or more other molecules of the same protein.*

O-methylated *Having an O-methyl (methoxy) group, OCH_3.*

This is a characteristic of common breakdown products of catecholamines.

Ondine's curse *A term used to refer to congenital central hypoventilation syndrome.*

Ontogenetic *Referring to the development of an organism from egg fertilization through the lifespan.*

Operant conditioning *A type of learning where behavior is controlled by consequences. Operant and instrumental conditioning are virtually synonymous.*

Ophthalmic nerve *One of the three branches of the trigeminal nerve. The ophthalmic nerve carries sympathetic fibers to the iris dilator muscle for pupil dilation.*

Opioid *A type of drug that acts on opioid receptors to produce morphine-like effects.*

Optic nerve *The second cranial nerve, which transmits visual from the retina of the eye to the brain.*

Organic compound *A chemical containing carbon atoms that are bound to other atoms of other elements, especially hydrogen, nitrogen, or oxygen.*

Orthostasis *Standing up.*

Orthostatic hypotension (OH) *A fall in blood pressure when a person stands up. OH has been defined by a fall in systolic blood pressure of 20 mm Hg or more or a fall in diastolic blood pressure of 10 mm or more after the person stands up for at least 3 minutes.*

Orthostatic intolerance *An inability to tolerate standing up, due to a sensation of lightheadedness or dizziness.*

Orthostatic tachycardia *An excessive increase in pulse rate when a person stands up.*

Osmolality *A measure of the amount of particles dissolved in a fluid.*

Osmopressor *Referring to an increase in blood pressure after*

drinking water without solute.

Osmostat *The conceptual homeostatic comparator that keeps serum osmolality within bounds.*

Oxidation *The loss of electrons during a chemical reaction. This happens when oxygen is added to a compound.*

Oxymetazoline *A drug that is an imidazoline like clonidine but does not readily enter the brain. Oxymetazoline is commonly used in over the counter nasal decongestant sprays.*

-P-

Pacemaker *Something that spontaneously produces electrical impulses on a regular basis.*

PAF *(Abbreviation for pure autonomic failure) PAF is a disease that manifests with orthostatic hypotension.*

PAG *(Abbreviation for peri-aqueductal gray) The PAG in the back of the midbrain is involved autonomic outflows, pain, and instinctive behaviors.*

Palpitation *A symptom where the patient notes a forceful, rapid heartbeat or a sensation of the heart "flip-flopping" in the chest.*

Pancreas *An organ in the abdomen that secretes hormones such as insulin and digestive enzymes.*

Pancreatic polypeptide *A hormone released from the pancreas. Pancreatic polypeptide levels can provide an indirect index of vagal outflow.*

Pandysautonomia *Failure of all components of the autonomic nervous system, such as in autoimmune autonomic ganglionopathy.*

Panic disorder *A condition that features a rapid buildup of fear or anxiety that the patient cannot control.*

Parabrachial nucleus *A region at the junction of the pons and midbrain of the brainstem. The parabrachial region is part of the central autonomic network.*

Paracrine *A type of arrangement where a chemical messenger acts on the same or nearby cells from the site of its release.*

Paraneoplastic *A consequence of cancer that is not due to the local presence of cancer cells.*

Parasympathetic nerve traffic *The rate of traffic in parasympathetic nerves.*

Parasympathetic nervous system (PNS) *One of the two branches of the autonomic nervous system, responsible for many "vegetative" functions such as gastrointestinal movements after a meal.*

Parasympathetic neurocirculatory failure *Failure to regulate the heart rate appropriately, such as during normal breathing or in response to the Valsalva maneuver.*

Paraventricular nucleus (PVN) *A cluster of neurons in the hypothalamus located near the third ventricle. The PVN is the source of important chemical messengers such as vasopressin, oxytocin, and corticotropin-releasing hormone.*

PARK1 *A form of familial Parkinson's disease due to A53T mutation of the gene encoding alpha-synuclein.*

PARK4 *A form of familial Parkinson's disease due to triplication of the gene encoding alpha-synuclein.*

Parkinson disease *Same as Parkinson's disease.*

Parkinson's disease (PD) *A disease that involves slow movement due to the loss of dopamine-containing nerve terminals of the nigrostriatal system.*

Parkinson's disease with orthostatic hypotension (PD+OH) *Parkinson's disease with a fall in blood pressure when the patient stands up.*

Parkinsonian *Having one or more features of Parkinson's disease.*

Parkinsonian form of MSA (MSA-P) *A form of multiple system atrophy that includes one or more features of Parkinson's disease.*

PARM *(Abbreviation for polyalanine repeat expansion mutation)*

Partial dysautonomia *(Same as Neuropathic POTS)*

Pathogenic *Capable of causing disease.*

Pavlovian conditioning *A form of association learning where two stimuli are repeatedly paired; a response that is at first elicited by the second stimulus (unconditioned stimulus) is eventually elicited by the first stimulus alone (conditioned stimulus). Pavlovian conditioning is synonymous with classical conditioning.*

PD *(Abbreviation for Parkinson's disease)*

PD+D *(Abbreviation for Parkinson's disease with dementia)*

PD+OH *(Abbreviation for Parkinson's disease with orthostatic hypotension)*

Pectus excavatum *A condition in which a person is born with the breastbone (sternum) that is indented or sunken in.*

Pentolinium *A particular type of drug that blocks chemical transmission in ganglia.*

Peptide *A short chain of amino acids.*

Percutaneous *Through the skin.*

Peri-aqueductal gray *A region of the back of the midbrain. The peri-aqueductal gray region is part of the central autonomic network.*

Percutaneous *Through the skin.*

Perfusate *A fluid used in perfusion, which is the passage of fluid through the circulatory system or lymphatic system to an organ or a tissue.*

Peripheral nervous system *The nerves and ganglia outside the central nervous system (brain and spinal cord).*

Peristalsis *Gastrointestinal movements such as after a meal that move digested material.*

Peroneal *Located outside the knee and lateral calf.*

Peripheral nervous system *The nerves and ganglia outside the central nervous system (brain and spinal cord).*

PET scanning *(Abbreviation for positron emission tomographic scanning)*

PGP 9.5 *(Abbreviation for protein gene product 9.5, also known as ubiquitin C-terminal hydrolase 1, or UCHL-1) A protein expressed by nerves that is used to visualize nerve fibers in tissue samples.*

pH *The negative log of the hydrogen ion concentration in an aqueous solution.*

Phen-Fen *Two drugs, phentermine and fenfluramine, prescribed together to decrease appetite and promote weight loss.*

Phentermine *A particular drug that acts in the body as a sympathomimetic amine.*

Phenylalanine *A particular amino acid.*

Phenylalanine hydroxylase *The enzyme that converts phenylalanine to tyrosine. Phenylketonuria patients typically have low phenylalanine hydroxylase activity.*

Phenylephrine *(Brand name Neo-Synephrine™) A particular drug that constricts blood vessels by stimulating alpha-1 adrenoceptors.*

Phenylethanolamine-N-methyltransferase (PNMT) *The enzyme catalyzing the conversion of norepinephrine to epinephrine.*

Phenylketonuria (PKU) *A disease of children that results from lack of activity of a particular enzyme, phenylalanine hydroxylase, resulting in a toxic buildup of phenylalanine*

in the body.

Phenylpropanolamine (PPE) *A particular drug that acts in the body as a sympathomimetic amine.*

Pheo *(slang for pheochromocytoma)*

Pheochromocytoma *An abnormal growth that produces the catecholamines norepinephrine (noradrenaline) or epinephrine (adrenaline).*

Phosphoprotein *A protein that contains phosphorus.*

Phosphorylation *A biochemical process that involves the addition of phosphate to an organic compound.*

PHOX2B *(Abbreviation for the Paired-like homeobox gene, type 2B) PHOX2B is necessary for normal development of the autonomic nervous system. Mutation of the PHOX2B gene is required to diagnose Congenital Central Hypoventilation Syndrome (CCHS).*

Phylogenetic *Referring to development and diversification of a species in the course of evolution.*

Physiognomic *Assessing from physical appearance.*

Physiological *Referring to a body function, as opposed to a body part.*

Piloerection *Hair standing upright or bristling, often associated with "goosebumps."*

Pilomotor *Referring to the hair standing up.*

Pituitary gland *A gland located at the end of a stalk at the base of the brain that releases a variety of hormones.*

PKU *(Abbreviation for phenylketonuria)*

Plasma *The part of the blood that is left after anti-coagulated blood settles or is centrifuged (spun at a high rate in a tube).*

Plasma cell *A type of white blood cell that produces antibodies.*

Plasma epinephrine level *The concentration of epinephrine (adrenaline) in the plasma.*

Plasma metanephrines *Plasma levels of the free (unconjugated) O-methylated metabolites of norepinephrine (normetanephrine) and epinephrine (metanephrine).*

Plasma norepinephrine level *The concentration of norepinephrine (noradrenaline) in the plasma.*

Plasmapheresis *Synonymous with plasma exchange. Plasmapheresis is a process that filters the blood to remove harmful antibodies.*

Platelets *Tiny particles in the blood that when activated clump together. Platelet plugs stop bleeding from punctures in blood vessel walls.*

Pleiotropic *A situation in which one gene affects multiple, seemingly unrelated traits.*

PNMT *(Abbreviation for phenylethanolamine-N-methyltransferase) PNMT is the enzyme that catalyzes the conversion of norepinephrine to epinephrine.*

PNS (*Abbreviation for parasympathetic nervous system)*

Polymorphism *A genetic change that is not as rare as a mutation but not so common as to be considered normal.*

Polysaccharide *A carbohydrate that consists of multiple sugar molecules bonded together.*

Polysomnography *A type of sleep test in which multiple parameters are monitored.*

Portal vein *A large vein coming from the spleen, stomach, pancreas, and intestines and going to the liver.*

Positive feedback loop *A situation in which a change in input about a monitored variable leads to output that makes the change in input even larger.*

Positron emission tomographic scanning (PET scanning) *A type of nuclear medicine scan where a positron-emitting form of a drug is injected and the radioactivity in different organs is detected by a special type of scanner called a PET*

scanner.

Positron emitter *A chemical that releases a special type of radioactivity called positrons.*

Post-ganglionic *Occurring distal to ganglia.*

Post-ganglionic nerves *Nerves from the ganglia that deliver signals to nerve terminals in target tissues such as the heart.*

Post-prandial hypotension *A fall in blood pressure after eating a meal.*

Postural tachycardia syndrome (POTS) *A condition where the patient has a long-term inability to tolerate standing up and has an excessive increase in pulse rate in response to standing.*

Potassium *An important element and electrolyte found in all cells of the body.*

POTS *(Abbreviation for postural tachycardia syndrome)*

Post-ganglionic nerves *Nerves that originate in ganglia. Sympathetic and parasympathetic nerves are examples of post-ganglionic nerves.*

Power spectral analysis of heart rate variability *A special type of test based on changes in the heart rate over time.*

PPE *(Abbreviation for phenylpropanolamine)*

PPI *(Abbreviation for proton pump inhibitor)*

Prednisone *The name of a steroid drug commonly used to treat disorders involving inflammation.*

Prefrontal cortex *The part of the cerebral cortex at the front of the frontal lobe. The prefrontal cortex is thought to play key roles in a variety of complex behaviors and higher thought processes.*

Pre-ganglionic nerves *Nerves of the autonomic nervous system that come from cell bodies in the spinal cord and travel to the ganglia.*

Pre-symptomatic *Before symptoms occur.*

Presyncope *A feeling of near-fainting.*

Primitive specificity *A concept according to which each stressor has a neurochemical signature with distinct central and peripheral mechanisms.*

Prion *A protein that can cause infection or spread in the body like an infectious agent.*

PRO *(Abbreviation for prolactin)*

Proamatine™ *(Brand name of midodrine)*

Procrit™ *(Brand name of erythropoietin)*

Pro-drug *A drug that works by being converted in the body to an active compound. L-DOPS is a norepinephrine pro-drug.*

Prognostic *Predictive of disease or survival.*

Progressive Supranuclear Palsy (PSP) *A type of neurological syndrome with particular abnormalities of gaze.*

Prolactin *A protein hormone released from the anterior pituitary gland that stimulates milk production.*

Propranolol (Brand name Inderal™) *A drug that is the classical non-selective beta-adrenoceptor blocker.*

Proton *A sub-atomic particle with a positive electric charge and mass of about 1 atomic mass unit.*

Proton pump inhibitor (PPI) *A type of drug that inhibits secretion of acid in the stomach.*

Provocative test *A test designed to evoke an abnormal response of the body.*

Pseudogene *A section of a chromosome that is an imperfect copy of a functional gene.*

Pseudopheo *Slang for pseudopheochromocytoma.*

Pseudopheochromocytoma *A condition in which a patient has episodes of severe high blood pressure and symptoms suggestive of a pheochromocytoma but does not have the tumor.*

Pseudephedrine (Sudafed™) *A particular drug that acts in the body as a sympathomimetic amine.*

Psilocybin *A psychedelic chemical found in some mushrooms.*

Ptosis *Droopy eyelid.*

Pulmonary edema *A pathologic condition in which the lungs fill up with fluid. A common cause of pulmonary edema is heart failure.*

Pupillometry *A test involving measuring the diameter of the pupils.*

Pupillomotor *Referring to constriction or dilation of the pupils.*

Pure autonomic failure (PAF) *A form of long-term failure of the autonomic nervous system that is manifested by orthostatic hypotension with no evidence for degeneration of the brain.*

Putamen *A brain structure that is part of the striatum, in the basal ganglia.*

PUT/OCC *The ratio of putamen to occipital cortex radioactivity after injection of ^{18}F-DOPA.*

Pyridostigmine (Mestinon™) *A drug that works by blocking the enzyme that breaks down acetylcholine.*

-Q-

QSART *(Abbreviation for Quantitative Sudomotor Axon Reflex Test)*

Quantitative Sudomotor Axon Reflex Test (QSART) *A type of test of autonomic nervous system function based on the ability of drugs to evoke sweating.*

Quaternary ammonium ion *A particular chemical arrangement in which a nitrogen atom is bonded to 4 organic groups and is therefore positively charged regardless of the pH of the solution.*

Quinone *A chemical in which an even number of =O group is*

attached to the benzene ring of the molecule. In dopamine quinone, the adjacent –OH groups of the catechol are replaced by =O groups.

Quinonization *Formation of a quinone-protein covalent adduct.*

-R-

Radiofrequency ablation *Destruction of a tissue by applying radiofrequency energy, which burns the tissue.*

Raphe nuclei *Clusters of neurons in the middle of the lower brainstem. Raphe nuclei are a major source of serotonin in the brain.*

RAS *(Abbreviation for renin-angiotensin-aldosterone system)*

Rasagiline *A drug that inhibits monoamine oxidase-B.*

RBD *(Abbreviation for REM behavior disorder) In RBD, the patients act out their dreams and thrash about in bed. Sleep studies show failure of the limbs to be flaccid during REM sleep.*

Receptors *Special proteins in the walls of cells that bind chemical messengers such as hormones.*

Reflex *An involuntary, rapid response to a stimulus, mediated by a reflex arc.*

Reflex syncope *(Synonymous with neurocardiogenic syncope, vasovagal syncope, autonomically mediated syncope, and fainting)*

REM Behavior Disorder (RBD) *A condition in which the limbs fail to stay relaxed during REM sleep. The patient acts out his or her dreams.*

REM sleep *(Abbreviation for rapid eye movement sleep) A stage of sleep involving active dreaming, in which the eyes move rapidly.*

Renal nerve ablation *A technique to treat hypertension by destroying sympathetic nerves of the kidneys.*

Renin *An enzyme of the renin-angiotensin-aldosterone system that converts angiotensinogen to angiotensin I.*

Renin-Angiotensin-Aldosterone system *A system that plays an important role in maintaining the correct amount of blood volume and sodium in the body.*

Reserpine *A drug that blocks the vesicular monoamine transporter and thereby depletes stores of monoamines such as catecholamines and serotonin.*

Respiratory sinus arrhythmia *The normal changes in pulse rate that occur with breathing.*

RET *The gene encoding a protein that is involved in signaling within cells. The RET protein is involved with development of autonomic neurons.*

Retrotrapezoid nucleus (RTN) *A brainstem region that plays an important role in regulation of respiration.*

Review of Systems (ROS) *An inventory of symptoms based on querying about functions of different body systems.*

Riley-Day syndrome *An eponym for Familial Dysautonomia, or FD.*

Ritalin™ *(Brand name of methylphenidate) A particular drug that resembles amphetamine.*

Rituximab *An anti-autoimmune drug that destroys antibody-producing B cells.*

RNA *(Abbreviation for ribonucleic acid) RNA is vital for producing proteins based on genetic instructions in the DNA.*

ROS *(Abbreviation for Review of Systems)*

Ross's syndrome *A condition in which there is Adie's pupil, loss deep tendon reflexes, and altered sweating.*

Rostral ventrolateral medulla (RVLM) *The outer upper part of*

the medulla of the brainstem. The RVLM is a major source of nerve fibers that descend in the spinal cord to the sympathetic pre-ganglionic neurons.

RPG *(Abbreviation for respiratory pattern generator) A region in the brainstem that generates a respiratory pattern.*

RTN *(Abbreviation for retrotrapezoid nucleus)*

RVLM *(Abbreviation for rostral ventrolateral medulla) The RVLM is a major source of nerve fibers that descend in the spinal cord to the sympathetic pre-ganglionic neurons.*

Ryanodine receptor *A member of a class of receptors that act as intra-cellular calcium channels.*

-S-

S-adenosyl methionine (SAMe) *A molecule that is a source of methyl groups in some biochemical reactions. SAMe is the methyl donor for the O-methylation of catecholamines by catechol-O-methyltransferase (COMT).*

Sacral *Referring to the triangular bone in the lower back between the two hip bones of the pelvis.*

Sacral nerve *A spinal nerve coming from the lower-most portion of the spinal cord.*

SAI *(Abbreviation for sympathoadrenal imbalance)*

Saline *A solution of salt in water.*

Salivary glands *Glands in the head that produce saliva.*

Salivation *Formation of spit.*

Salivary glands *Glands in the head that produce saliva.*

SAMe *(Abbreviation for S-adenosyl methionine)*

SAS *(Abbreviation for sympathetic adrenergic system) The SAS is the part of the sympathetic nervous system for which adrenaline is the main chemical messenger. The SAS is also called the adrenomedullary hormonal system.*

Scientific Integrative Medicine *(Synonymous with Cybernetic Medicine and Systems Medicine) A conceptual framework for linking systems biology with integrative physiology in order to understand disease mechanisms.*

SCN9A *A gene that encodes a sodium channel in peripheral neurons.*

Scotoma *A blind spot in the visual field, surrounded by an area of more normal vision. Scintillating scotoma is also called visual migraine.*

SCS *(Abbreviation for sympathetic cholinergic system) The SCS is the part of the sympathetic nervous system for which acetylcholine is the main chemical messenger. The SCS is especially involved in sweating.*

SEC *(Abbreviation for skin electrical conductance)*

Second messengers *Molecule that relay signals received at receptors on the cell surface to target molecules in the cytoplasm or nucleus.*

Secretomotor *Referring to secretion from a gland, such as salivation, tear production, and sweating.*

Segawa's disease *Synonymous with DOPA-responsive dystonia.*

Selective Serotonin Reuptake Inhibitor (SSRI) *A type of drug that inhibits neuronal uptake of serotonin.*

Selegiline *A drug that inhibits monoamine oxidase-B.*

Senescent *Aging.*

Sensitization *The process by which repetition of a stimulus amplifies the physiological or emotional response.*

Sepiapterin reductase *An enzyme in the synthetic cascade leading to tetrahydrobiopterin.*

Sepsis *A life-threatening condition from generalized infection in the body.*

Serotonin *(Synonymous with 5-hydroxytryptamine, 5-HT) A particular chemical messenger in a family called*

monoamines.

Short-Lasting Unilateral Neuralgiform Headache with Conjunctival Injection and Tearing *(SUNCT) A syndrome involving episodic painful headache with conjunctival injection and tearing.*

Shy-Drager syndrome *(Eponym for multiple system atrophy with orthostatic hypotension) A form of nervous system disease where different pathways of the brain degenerate and the patient has a fall in blood pressure during standing.*

Sign *Something a doctor can observe or measure that provides objective evidence of a disease.*

Sinemet™ *Brand name of levodopa combined with carbidopa.*

Sinus node *The pacemaker area of the heart that normally generates the electrical impulses resulting in a coordinated heartbeat.*

Sinus node ablation *Destruction of the sinus node in the heart, usually as a treatment for excessively rapid heart rate.*

Sjogren's syndrome *An autoimmune condition characterized by dry mouth and dry eyes.*

Skin electrical conductance (SEC) *A measure of the ability of the skin to conduct electricity. Because of the electrolytes found in sweat, when a person sweats, SEC increases.*

Skin sympathetic test (SST) *A type of test of the sympathetic nervous system based on the ability of various drugs or environmental manipulations to increase secretion of sweat.*

SLC6A2 The gene that encodes the cell membrane norepinephrine transporter.

SLC18A2 The gene that encodes the type 2 vesicular monoamine transporter.

Smooth muscle cells *The type of muscle cells in the heart and in*

blood vessel walls.

SNARE *(Abbreviation for the SNAP REceptor) Proteins that facilitate fusion of vesicles to cell membranes.*

SNCA The gene encoding the protein alpha-synuclein.

SNS *(Abbreviation for sympathetic noradrenergic system) The SNS is the part of the sympathetic nervous system for which norepinephrine is the chemical messenger.*

Sodium *An important chemical element found in all body fluids.*

Somatic nervous system *The somatic nervous system is the main way the body deals with the "outside world," by way of its main target organ, skeletal muscle.*

Somatization *Recurrent, multiple medical symptoms without a discernible organic cause.*

Somatostatin (Octreotide™) *A type of drug that when injected can raise the blood pressure in patients with autonomic failure.*

Sphincter *A circular smooth muscle that normally maintains constriction of a body passage.*

Sphingolipid *Any of a class of compounds that are fatty acid derivatives of sphingosine. Sphingolipids are components of nerve cell membranes.*

Sphingosine *An 18-carbon amino alcohol with an unsaturated hydrocarbon chain.*

Spillover *The estimated rate of entry of an endogenous compound into the bloodstream. Cardiac norepinephrine spillover is the rate of entry of norepinephrine into the venous drainage of the heart.*

Spinal nerve *A nerve that carries motor, sensory, and autonomic signals between the spinal cord and the body.*

Splanchnic *Referring to internal organs especially in the abdomen.*

SSRI *(Abbreviation for selective serotonin reuptake inhibitor)*

SSRIs block one of the main ways of inactivating and recycling the chemical messenger serotonin.

SST *(Abbreviation for skin sympathetic test)*

Steady-state *A condition in which the level of something is kept at a plateau.*

Stereoisomer *A mirror image structure of a chemical.*

Strain gauge *A testing device that sensitively measures stretch.*

Stress *A condition in which the brain senses a challenge to physical or mental stability that leads to altered activities of body systems to meet that challenge.*

Stress cardiopathy *Heart dysfunction or failure due to distress.*

Stressor *That which results in a state of stress.*

Striata *Plural of striatum.*

Striatal *Referring to the striatum in the basal ganglia of the brain.*

Striatonigral degeneration *A form of nervous system disease where the patient seems to have Parkinson's disease but does not respond well to treatment with levodopa.*

Striatum *(Same as corpus striatum) A structure in the basal ganglia of the brain that includes the caudate and putamen.*

Stridor *A harsh inspiratory, crowing noise caused by obstruction or dysregulation of the vocal cords.*

Stroke Index *The cardiac stroke volume adjusted for body surface area.*

Stroke volume (SV) *The amount of blood pumped by the heart in one heartbeat.*

Subcortical *Below the level of the cerebral cortex. The brainstem is subcortical.*

Substantia nigra *A black pigmented region of the midbrain that is the major source of dopamine in the brain.*

Sudafed™ *(Brand name of pseudephedrine)*

Sudomotor *Referring to the ability to secrete sweat.*

Sulci *Grooves in the surface of the brain.*

SUNCT *(Abbreviation for Short-Lasting Unilateral Neuralgiform Headache with Conjunctival Injection and Tearing)*

Superior cervical ganglion *A sympathetic ganglion in the upper neck.*

Supine *Lying down on one's back.*

SV *(Abbreviation for stroke volume) The SV is the volume of blood ejected by the heart in one heartbeat.*

Sympathectomy *Surgical removal or destruction of ganglia, which results in absence of traffic in sympathetic nerves.*

Sympathetic adrenergic system *A part of the sympathetic nervous system for which adrenaline is the main chemical messenger. Synonymous with adrenomedullary hormonal system.*

Sympathetic cholinergic system (SCS) *A part of the sympathetic nervous system for which acetylcholine is the chemical messenger. This part is especially important for regulation of sweating.*

Sympathetic innervation *The supply of sympathetic nerves in a tissue or organ.*

Sympathetic nerve terminals *Endings of sympathetic nerves, from which the chemical messenger, norepinephrine (noradrenaline) is released.*

Sympathetic nerve traffic *Nerve impulses in sympathetic nerve fibers.*

Sympathetic nerves *Nerves of the sympathetic nervous system.*

Sympathetic nervous system *One of the branches of the autonomic nervous system, responsible for many "automatic" functions such as constriction of blood vessels when a person stands up.*

Sympathetic neurocirculatory failure *Failure of regulation of the heart and blood vessels by the sympathetic nervous system.*

Sympathetic neuroimaging *Visualization of the sympathetic nerves in the body.*

Sympathetic noradrenergic system (SNS) *A part of the sympathetic nervous system for which norepinephrine is the chemical messenger. The SNS is especially important for regulation of the heart and blood vessels.*

Sympathetic vasoconstrictor tone *The status of constriction of blood vessels as a result of traffic in sympathetic nerves.*

Sympathetically-mediated hypertension *High blood pressure due to increased sympathetic noradrenergic system activity.*

Sympathin *A word used by Walter B. Cannon to refer to a chemical produced by stimulating sympathetic nerves.*

Sympathoadrenal imbalance (SAI) *A situation in which plasma epinephrine levels increase to a greater extent than do plasma norepinephrine levels. SAI is a typical finding before or at the time of fainting.*

Sympathoadrenal system *(also called the sympathetic adrenergic system, sympathico-adrenal system, or sympathoadrenomedullary system) A name for the sympathetic nervous system and adrenomedullary hormonal system acting as a unit.*

Sympathomimetic amine *A type of drug that acts in the body like stimulation of the sympathetic nervous system.*

Sympathotonic orthostatic intolerance *Inability to tolerate standing up that is associated with excessive activity of the sympathetic nervous system.*

Symptom *A complaint about something abnormal a person notices that provides subjective evidence of a disease.*

Syncope *Sudden loss of consciousness associated with loss of*

muscle tone and the regaining of consciousness within seconds to minutes.

Syndrome *A set of symptoms that occur together.*

Synuclein *A particular protein found especially in nervous tissue.*

Synucleinopathies *A family of diseases characterized by deposition of the protein, alpha-synuclein, in the cytoplasm of affected cells. Parkinson's disease is an example of a synucleinopathy.*

Systems biology *Systems biology has been defined variously. One definition is the study of dynamic interactions within biological networks.*

Systolic pressure *The peak blood pressure while the heart is pumping out blood.*

-T-

T cell (also called T lymphocyte) *A type of lymphocyte white blood cell that plays a central role in cell-mediated (as opposed to antibody-mediated) immunity.*

Tachycardia *Excessively fast heart rate.*

Takotsubo cardiopathy A form of stress-related acute heart failure that is most common in post-menopausal women and probably due to high catecholamine levels.

Tardive dyskinesia *A complication of dopamine receptor antagonists that involves involuntary movements of the jaw or tongue.*

TBZ *(Abbreviation for tetrabenazine)*

TEH *(Abbreviation for tilt-evoked hypotension)*

Teleological *Explaining actions by their goals. Teleology is a reason or explanation for something in terms of its purpose or goal.*

Teleology *The explanation of something in terms of its goal, purpose, or end.*

Teleonomic *A description of goal-directed behaviors or processes where the goal-directedness depends on the operation of a program.*

Temperomandibular joint disorder (TMJ) *A condition involving pain and decreased movement of the jaw joint.*

Tetrabenazine (TBZ) *A drug that blocks the type 2 vesicular monoamine transporter.*

Tetrahydrobiopterin (BH4) *A key co-factor for some enzymes, including tyrosine hydroxylase.*

TH *(Abbreviation for tyrosine hydroxylase) TH is the rate-limiting enzyme in catecholamine biosynthesis.*

Thermoregulatory sweat test (TST) *A test based on the ability of the patient to produce sweat in response to an increase in environmental temperature.*

Thermostat *The conceptual homeostatic comparator that keeps core temperature within bounds.*

Thoracolumbar *The mid-portion of the spinal cord from which sympathetic nerves emerge.*

THY *(Abbreviation for thyroid)*

Thyroid *Paired glands in the neck that produce the hormone, thyroxine.*

Tilt table testing *A test where the patient is tilted on a platform, to assess the ability of the patient to tolerate and respond appropriately to standing up.*

Tinnitus *A sense of high-pitched ringing in the ears.*

Tissue *A group of cells within an organ that carry out specific functions.*

TLoC *(Abbreviation for transient loss of consciousness)*

TMJ *(Abbreviation for temperomandibular joint)*

TNF *(Abbreviation for tumor necrosis factor) TNF-α is a type*

of cytokine.

Tomographic scan *A type of scan where a part of the body is visualized in slices.*

Tomography *A type of scan where a part of the body is visualized in slices.*

Total peripheral resistance (TPR) *The total amount of resistance to blood flow in the body.*

Total peripheral vascular resistance *Synonymous to total peripheral resistance, or the total amount of resistance to blood flow in the body.*

TPR *(Abbreviation for total peripheral resistance) TPR is the total amount of resistance to blood flow in the body.*

Transcription factor *A type of protein that affects the process of converting, or transcribing, DNA into RNA*

Trans-synaptic *Taking place across nerve synapses.*

Transthyretin (TTR) *A protein related to amyloidosis. Mutation of the TTR gene results in accumulation of the abnormal protein in a variety of organs and tissues.*

Tremor *Involuntary shaking.*

Tricyclic *A particular chemical structure of a drug. Tricyclics include some commonly used anti-depressants.*

Trigeminal nerve *The fifth cranial nerve, which supplies the face.*

Triglyceride *A type of chemical derived from glycerol and a fatty acid. Triglycerides are the main constituents of body fat in humans.*

Trimethaphan *(Arfonad™) A particular type of drug that blocks chemical transmission in ganglia.*

Trophic *Causing a growth effect.*

Tropic *Causing a change in, or affecting.*

Tryptase *An enzyme found in granules of mast cells that has been used as a marker for mast cell activation.*

TST *(Abbreviation for thermoregulatory sweat test)*

TTR *(Abbreviation for transthyretin) A protein related to amyloidosis.*

Tuberoinfundibular (or tuberohypophyseal) system *A neurochemical system in the brain in which dopamine is delivered from the hypothalamus to the pituitary gland.*

TYR *(Abbreviation for tyramine)*

Tyramine (TYR) *A sympathomimetic amine found in foodstuffs such as hard cheese and red wine.*

Tyramine infusion test *An autonomic function test in which tyramine is given IV and the physiological or neurochemical effects are measured.*

Tyrosinase *An enzyme involved in the production of melanin from tyrosine.*

Tyrosine *An essential amino acid. Tyrosine is converted to DOPA by tyrosine hydroxylase.*

Tyrosine hydroxylase (TH) *An important enzyme required for production of the catecholamines in the body.*

-U-

Ubiquinone *A metabolite in the electron transport chain in mitochondria.*

UCNS *(Abbreviation for the United Council for Neurological Subspecialties)*

Unmyelinated *Same as non-myelinated or lacking a myelin sheath. Post-ganglionic autonomic neurons are unmyelinated.*

UPSIT *(Abbreviation for the University of Pennsylvania Smell Identification Test)*

Uptake-1 *Uptake of norepinephrine and related chemicals by way of the cell membrane norepinephrine transporter, such*

as uptake into sympathetic nerves.

Uptake-2 *Uptake of norepinephrine and related chemicals by way of a transporter on non-neuronal cells such as myocardial cells.*

Urecholine™ *A brand of bethanechol, a drug that stimulates muscarinic cholinergic receptors.*

Urine retention *The inability to start a urinary stream or empty the bladder completely.*

-V-

VAChT *(Abbreviation for vesicular acetylcholine transporter)* The VAChT is *a protein in the walls of storage vesicles in cholinergic neurons that transports acetylcholine into the vesicles.*

Vagal *Having to do with the vagus nerve, one of the main nerves of the parasympathetic nervous system.*

Vagal-gastrin *Vagus nerve-mediated gastrin release.*

Vagal parasympathetic outflow *Traffic in the vagus nerve, a main nerve of the parasympathetic nervous system.*

Vagus nerve *The tenth cranial nerve. The vagus is the main nerve of the parasympathetic nervous system.*

Valsalva maneuver *A type of maneuver in which the person blows against a resistance or strains as if trying to have a bowel movement, resulting in an increase in pressure in the chest and a decrease in the ejection of blood by the heart.*

Vanillylmandelic acid (VMA) *A major end-product of norepinephrine metabolism.*

Vascular resistance *Resistance to blood flow.*

Vasoactive intestinal peptide (VIP) *A small protein produced in the gut, brain, and other organs and used to identify*

sympathetic cholinergic neurons.

Vasoconstriction *Tightening of blood vessel walls.*

Vasodepressor syncope (*Same as Autonomically Mediated Syncope, Reflex Syncope, Neurocardiogenic syncope, and Neurally Mediated Syncope)*

Vasodilation *Widening of blood vessels due to relaxation of smooth muscle cells within the vessel walls.*

Vasomotor *Referring to constriction of blood vessels.*

Vasopressin *(the same as antidiuretic hormone) A hormone released from the pituitary gland at the base of the brain that stimulates retention of water by the kidneys and increases blood pressure by constricting blood vessels.*

Vein *A type of blood vessel that carries blood toward the heart.*

Venlafaxine (Effexor™) *A drug that acts as a combined serotonin and norepinephrine reuptake inhibitor.*

Venous return *Return of blood to the heart by the veins.*

Ventricles *The main pumping chambers of the heart. The right ventricle contains blood pumped by the heart to the lungs. The left ventricle contains blood pumped by the heart to the rest of the body. The left ventricular myocardium is the main pumping muscle of the heart.*

Ventricular arrhythmia *An abnormal rhythm of the heart ventricles.*

Ventriculogram *A radiologic procedure in which a radio-opaque dye is injected to reveal the ventricular cavity in the heart.*

Ventromedial hypothalamus (VMH) *Small region of the hypothalamus that plays a major role in hunger.*

Vertebrae *Bones of the backbone. Each vertebra has sites for articulation and muscle attachment and a hole through which the spinal cord passes.*

Vertebral column *The backbone.*

Vesicle *Tiny bubble-like structure inside nerves and endocrine cells. Vesicles store chemical messengers such as norepinephrine.*

Vesicular acetylcholine transporter (VAChT) *A particular type of protein in the walls of storage vesicles that transports acetylcholine into the vesicles.*

Vesicular monoamine transporter (VMAT) *A particular type of protein in the walls of storage vesicles that transports chemicals such dopamine into the vesicles.*

Vesicular sequestration *The uptake or retention of neurochemicals in vesicles.*

VIP *(Abbreviation for vasoactive intestinal peptide)*

Viscera *A term referring to the internal organs in the cavities of the body.*

Vitamin *An organic compound that an organism requires in limited amounts and is obtained through the diet.*

VMA *(Abbreviation for vanillylmandelic acid) VMA is a major breakdown product of norepinephrine.*

VMAT *(Abbreviation for the vesicular monoamine transporter) VMATs are proteins in the walls of vesicles in monoaminergic neurons that transport monoamines from the cytoplasm into the vesicles.*

VMAT2 *(Abbreviation for the type 2 vesicular monoamine transporter) VMAT2 is important for the storage of catecholamines in vesicles in sympathetic nerves and in the brain.*

VMH *(Abbreviation for ventromedial hypothalamus)*

Voltage-gated *A characteristic of membrane ion channels that are activated by changes in the electrical membrane potential near them.*

Volustat *The conceptual homeostatic comparator that keeps blood volume within bounds.*

VTA *(Abbreviation for ventral tegmental area) The VTA is adjacent to the substantia nigra in the midbrain.*

-X-

X-Chromosome *One of the two sex-determining chromosomes.*
X-linked *A mode of inheritance in which the genetic abnormality is on the X chromosome.*

-Y-

Yohimbe bark *A naturally occurring form of yohimbine that is available as an over-the-counter herbal remedy.*
Yohimbine *A drug that blocks alpha-2 adrenoceptors in the brain, in blood vessel walls, and on sympathetic nerve terminals.*
Yohimbine challenge test *A type of autonomic function test in which yohimbine is administered and blood pressure and plasma levels of norepinephrine or other neurochemicals are measured.*