

**WHAT
IS
THE
AUTONOMIC
NERVOUS
SYSTEM?**

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? 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.

The autonomic nervous system is the body’s “automatic nervous system.”

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.

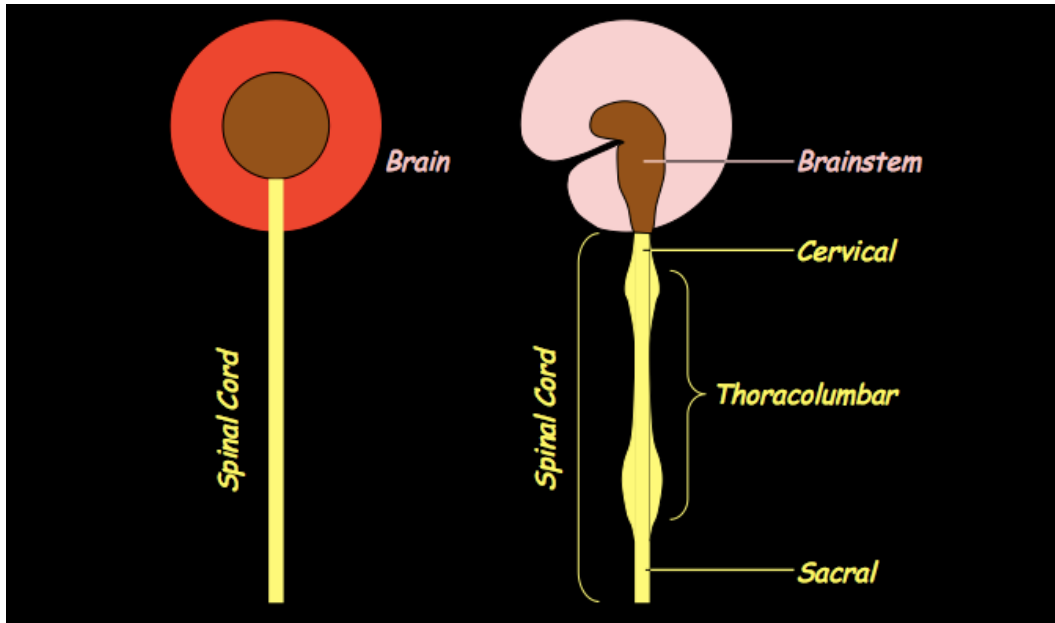
THE TOOTSIE ROLL POP

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.

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 central nervous system is like a Tootsie Roll Pop.

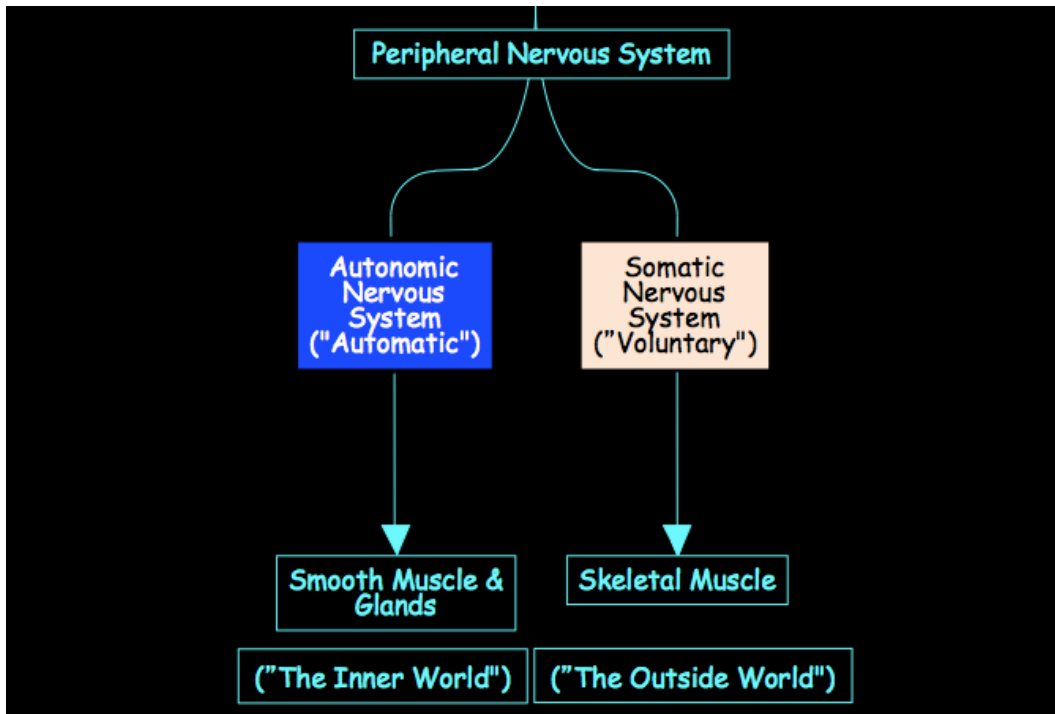


The brainstem is in the brain at the top of the spinal cord.

The Autonomic Nervous System Isn't Autonomic (It's Automatic).

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.

The peripheral nervous system has two main divisions—somatic and



The peripheral nervous system consists of the autonomic nervous system and the somatic nervous system.

autonomic. The somatic nervous system deals with the “outside world” of everything around us. It uses sense organs for you to detect what is going on outside you, and it uses skeletal muscles for you to move.

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

organismic integrity. The task is accomplished because of the component of the peripheral nervous system that helps regulate the inner world—the autonomic nervous system.

The autonomic nervous system is the main way the brain regulates the “inner world” of your body.

The autonomic nervous system deals with the inner world by delivering chemical messengers that change functions of body organs. The organs contain a type of muscle called smooth muscle. Smooth muscle is found in blood vessel walls and glands, such as the thyroid gland, salivary glands, adrenal glands, pancreas, and sweat glands. (Heart muscle cells have a unique structure.) The autonomic nervous system sends signals from the brain to the heart and smooth muscle cells that cause changes in their muscle tone. All of this happens automatically, all day and night, to keep your body functioning. In contrast, the target organ of the somatic nervous system is skeletal muscle.

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

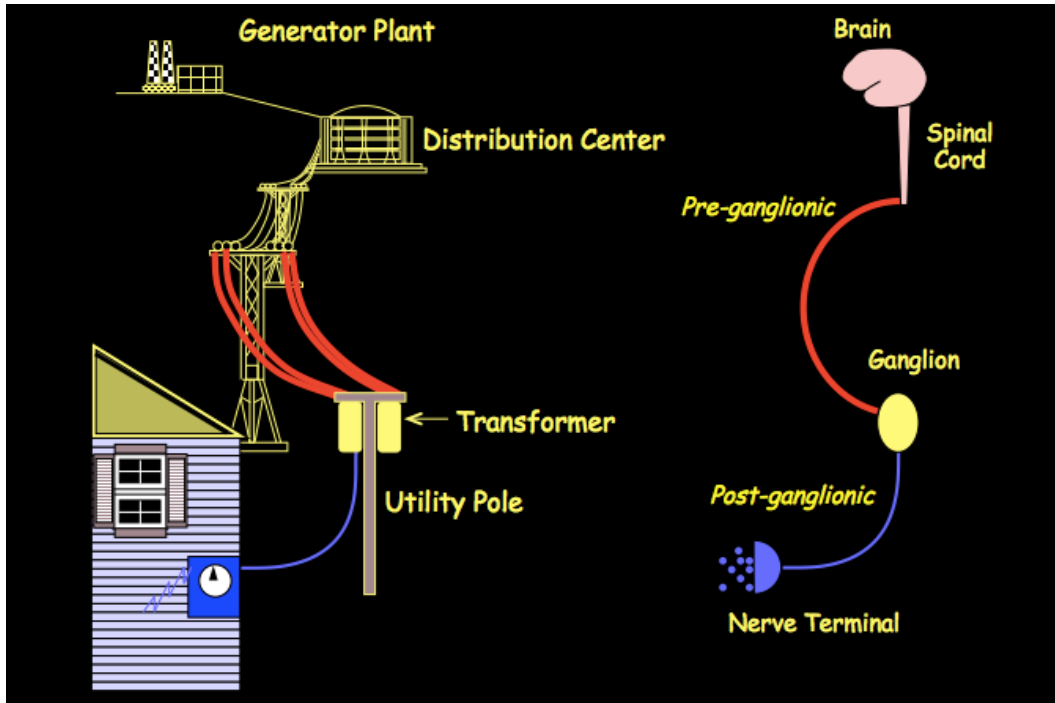
In general, voluntary and automatic body functions are linked. When you clench your fists, after several seconds your blood pressure increases. When you get out of a hot shower and walk into a cool locker room, you develop goose bumps. When you stand up from

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. It does function automatically, unconsciously, and involuntarily. That's why I prefer the phrase, automatic nervous system.

You will be learning that the autonomic nervous system (ANS) has several component systems. These include the enteric nervous system (ENS), the parasympathetic nervous system (PNS), the sympathetic cholinergic system (SCS), the sympathetic adrenergic system (SAS), and the sympathetic noradrenergic system (SNS). You will also be learning that each of these components has associated chemical messengers. The main chemical messengers of the autonomic are the neurotransmitters acetylcholine (ACh) and norepinephrine (NE) and the hormone, epinephrine (EPI, synonymous with adrenaline).

Knowing about these components and chemical messengers is important, because abnormalities of particular components or chemical messengers result in different symptoms and signs, with different meanings in terms of diagnosis, treatment, and outlook.

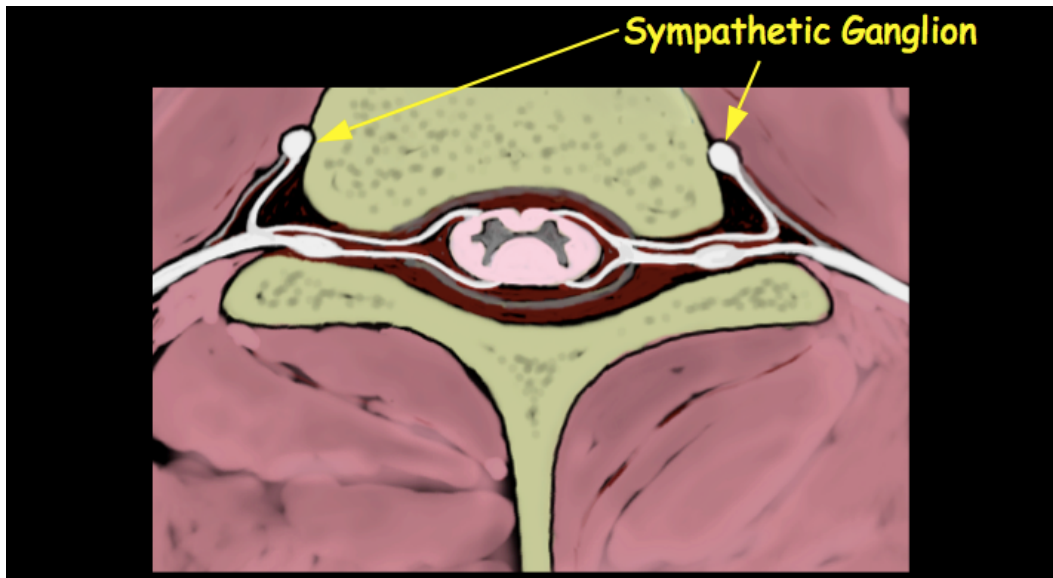
The Utility Pole Outside Your House



Ganglia are like transformers on the utility pole outside your house.

Nerves that travel to skeletal muscle to regulate movement come directly from the central nervous system. Nerves of the autonomic nervous system that travel to internal organs come indirectly, via clumps of cells called “ganglia.”

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



This cross-sectional diagram shows the location of sympathetic ganglia on each side of the spinal column.

physical distinction originally led to the view that the nerves coming from the ganglia were also functionally distinct from the central nervous system—that is, they were thought to be independent, or “autonomic.”

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

To convey what the ganglia of the autonomic nervous system do, think of how electricity is delivered to your house. 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 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 non-myelinated nerves. The nerves from the ganglia to the target organs are “post-ganglionic.” They are thin, slow conducting, and non-myelinated.

Just like the trunk lines to the utility pole outside your house are thick cables while the lines from the transformer to your house are thin wires, pre-ganglionic nerve fibers from the spinal cord to the ganglia are thick and conduct electricity rapidly, while post-ganglionic nerve fibers from the ganglia to most target organs are thin and transmit electricity slowly.

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, pre-ganglionic fibers, as if there were a direct wiring connection from the electrical

distribution center to the terminal box.

HISTORY OF THE "AUTOMATIC" NERVOUS SYSTEM

On the Risk of Being a Physician's Son

In the early 1890s, an English physician and amateur inventor, Dr. George Oliver, 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 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 in the gauge 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.



George Oliver and E.A. Schäfer, who first reported the cardiovascular actions of adrenal extract in 1894.

According to Sir Henry Dale, an authority who received a Nobel Prize in 1936, the extract had been injected. According to others, based on the writings of both Oliver and Schäfer themselves, the extract had been given orally.

This disagreement relates to the enzymatic “gut-blood barrier” that prevents ingested catecholamines and related compounds from making their way into the bloodstream.

Swallowed adrenaline is broken down efficiently by enzymes in the gut.



You can buy adrenal concentrate as a dietary supplement.

The gastrointestinal tract possesses impressively efficient means for detoxifying ingested catecholamines. Multiple enzymes carry out this crucial task. 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 bloodstream 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?

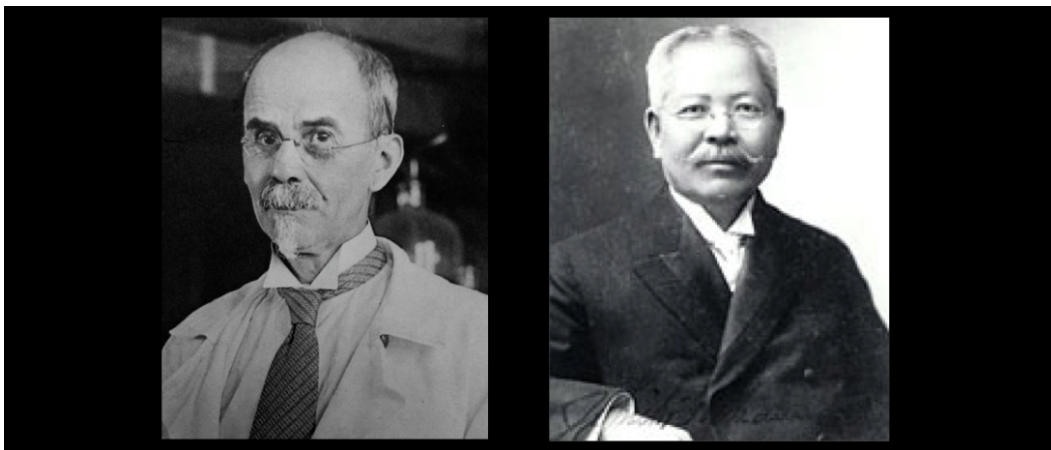
The most famous member of the catecholamine family has two names—adrenaline and epinephrine (EPI). Its chemical father, the chemical messenger of the sympathetic noradrenergic system, also has two names—noradrenaline and norepinephrine (NE). Here is how this came about.

Beginning immediately after Oliver and Schäfer reported the powerful effects of injected adrenal extract, researchers worldwide began a race to identify the “active principle” of the adrenal gland. One of these was John Jacob Abel, of Johns Hopkins, who devoted about a decade of his life to this 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. Keizo Uenaka, whom Takamine had hired as a chemist, successfully crystallized—and therefore isolated in pure form—what Takamine called adrenaline. In 1901, Takamine reported this first successful crystallization of a hormone.

Almost simultaneously, Thomas Aldrich, a colleague of Takamine at



John Jacob Abel and Jokichi Takamine raced to identify the active principle of the adrenal gland around 1900.

Parke-Davis (and, probably not coincidentally, a former assistant of Abel at Johns Hopkins), correctly deduced its chemical structure.

Abel never published the correct chemical structure, and so medical historians gave Takamine and Aldrich the credit for one of the most important medical scientific feats ever—the first identification of a hormone.

Thanks to Takamine, Parke-Davis patented Adrenalin, and Takamine became a millionaire. He founded three companies, one of which, Sankyo Pharmaceutical Company, continues to this day as Daiichi/Sankyo, the second largest drug company in Japan. Takamine also funded the gift of cherry trees that have graced the Tidal Basin in

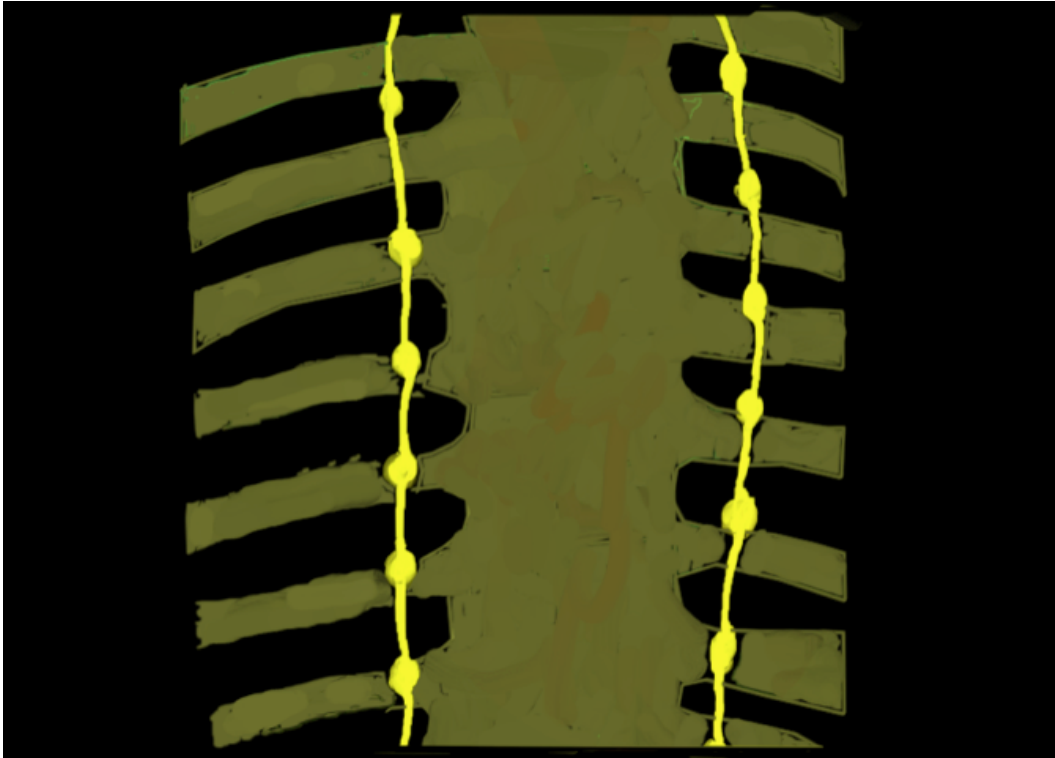


J. Takamine, who discovered adrenaline, funded the Japanese cherry trees at the Tidal Basin in Washington, DC.

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 among the most prestigious journals in pharmacology and biochemistry. Scientific reports in American journals, such as JPET, still use the word that Abel introduced, “epinephrine,” whereas European journals commonly use Takamine's “adrenaline.” For teaching purposes I refer to both epinephrine and adrenaline.

Langley's "Autonomic Nervous System"

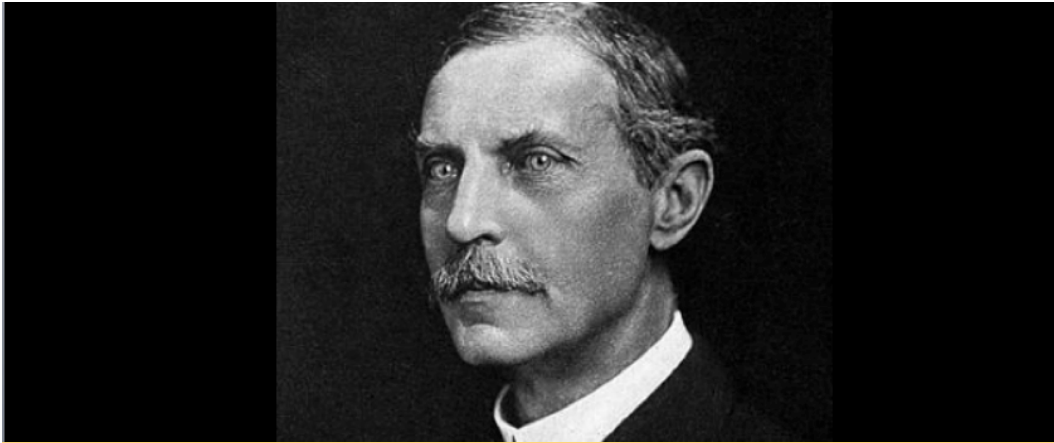


The autonomic nervous system is arranged like pearls on a necklace on each side of the spinal column.

Let's say you opened someone's chest and had a look inside.

If you removed the heart and lungs, then in front of the back ribs, on each side of the spinal column, you'd see glistening strands of nerves arranged like pearls on a necklace.

About the turn of the 20th century, the great English physiologist,

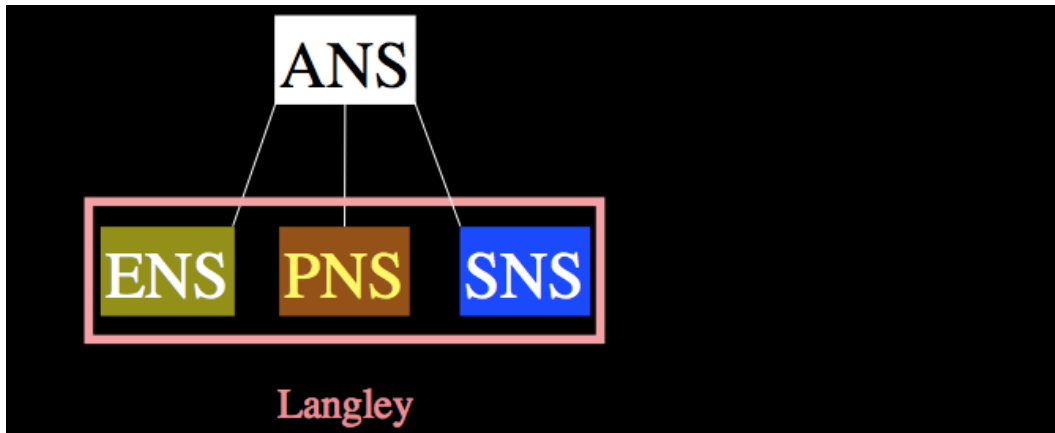


John Newport Langley (1852-1925), father of the “autonomic nervous system.”

John Newport Langley, named this part of the nervous system the “autonomic nervous system,” or ANS.

Langley viewed these nerves as functioning autonomously of the central nervous system.

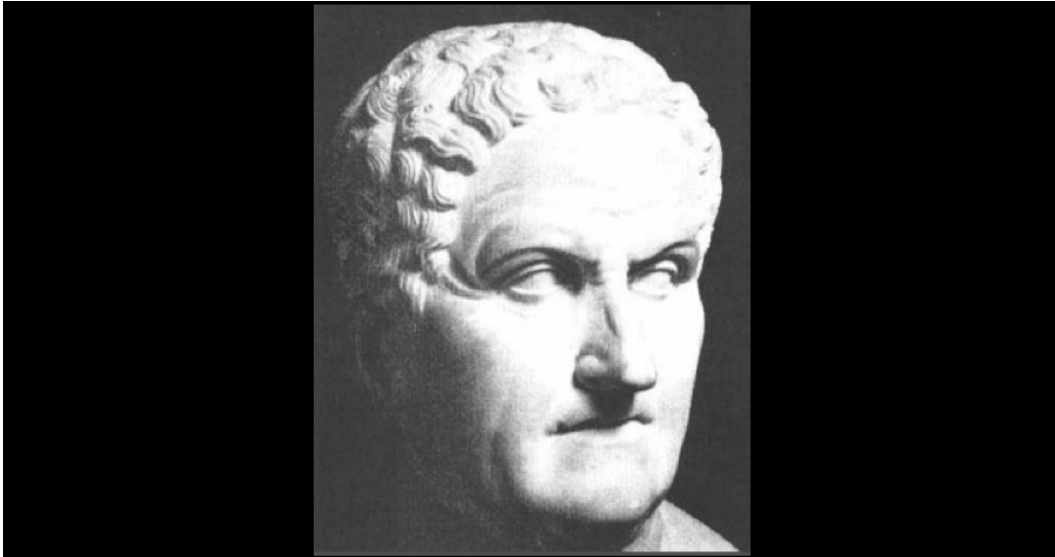
Langley’s autonomic nervous system contains three components. One component is the enteric nervous system, or ENS. “Enteric” refers to the gut, and ENS neurons are in layers of the wall of the gastrointestinal tract. Enteric nerves play a key part in peristalsis, the coordinated movement of gastrointestinal contents through the hollow tube that is the gut.



Langley’s “autonomic nervous system” (ANS) consists of the enteric nervous system (ENS), parasympathetic nervous system (PNS), and sympathetic nervous system (SNS).

A second component of the autonomic nervous system was also named by Langley—the “parasympathetic nervous system,” abbreviated PNS. The parasympathetic nervous system is in several ways a “vegetative” system, involved with digestion and conversion of ingested foodstuffs into usable energy.

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 teachings of Galen, the 2d century Greek physician whose ideas and teachings dominated medical thought and practice for 14 centuries.



Galen (ca. 129-216), father of the “sympathetic nervous system”

Galen, taught that the body has “spirits”—animal, vital, and natural. 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. Although no one ever has come up with evidence for the existence of the spirits, the idea that the sympathetic nervous system coordinates functions of body organs is essentially, ironically correct.

As will be seen, the sympathetic nervous system can be divided into three parts based on the main chemical messengers involved. The first to be identified was adrenaline.

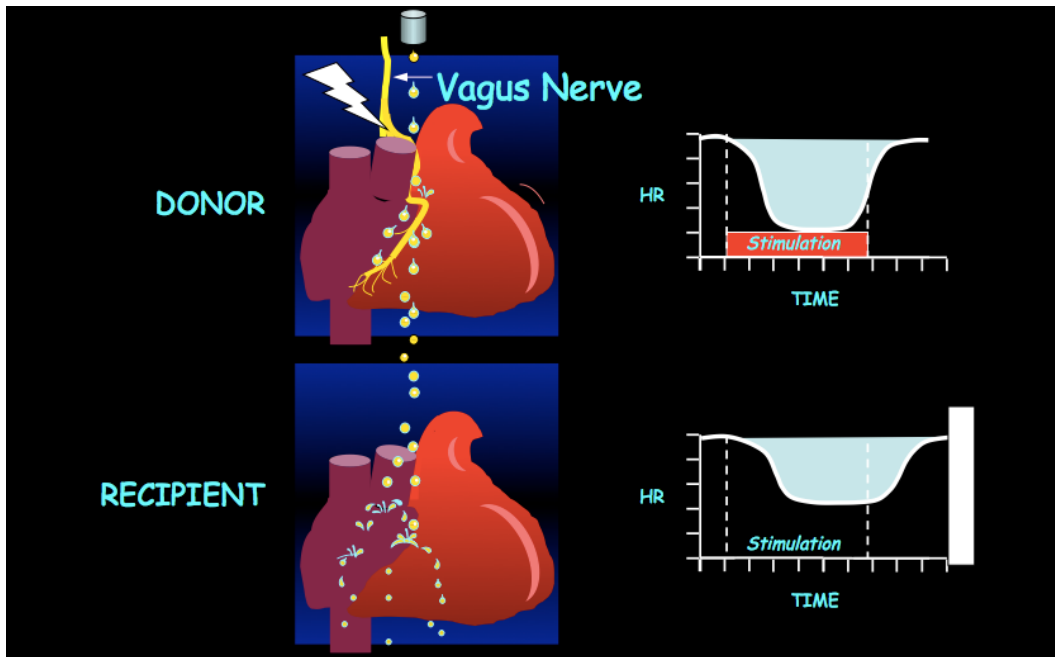
The Heart of a Frog

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



Otto Loewi (Nobel Prize, 1936)

The experimental setup consisted of the exposed, beating hearts of two frogs, a “donor” frog and a “recipient” frog. Loewi bathed the heart of the donor frog in a fluid and let the fluid drip onto the exposed, 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 fluid that dripped from the donor heart onto the recipient heart. Loewi inferred that the nerve stimulation released a chemical substance that caused the recipient frog's heart to slow down too. He



Loewi's experimental setup to demonstrate that stimulation of the vagus nerve releases a chemical messenger.

called that substance the “Vagusstoff” or “substance of the vagus.”

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

Otto Loewi was the first to demonstrate the existence of a chemical messenger coming from nerves—a neurotransmitter. He identified the neurotransmitter as

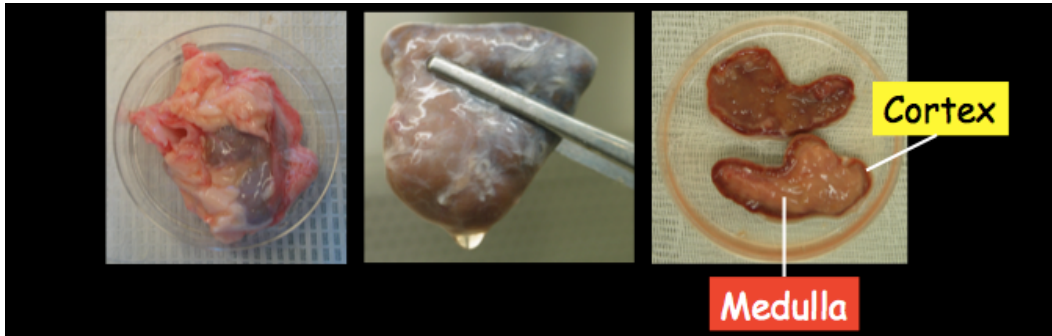
acetylcholine. For this he received a Nobel Prize.

Loewi used virtually the same experimental setup to demonstrate that in frogs stimulation of the sympathetic nervous system supply to the heart releases adrenaline. This was in 1921, a few years before he identified the Vagusstoff. Now we know that in certain situations in humans, such as severe exercise, and in some disorders, such as panic disorder, adrenaline is indeed released by the heart; however, it is likely that the source of this adrenaline is that taken up as a hormone from the bloodstream by sympathetic nerves.

The Fat above the Kidneys

A couple of decades after Langley formulated his idea of the autonomic nervous system, the great American physiologist, Walter B. Cannon, added what can be considered to be a fourth component of the autonomic nervous system—the adrenal gland.

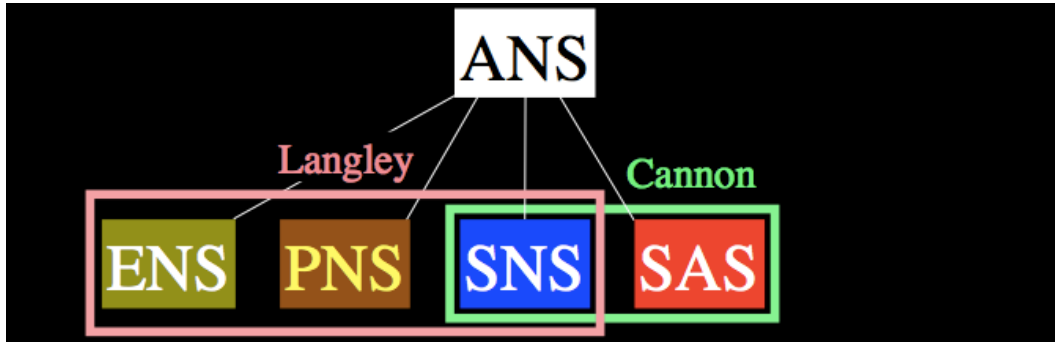
The Bible, in Exodus and Leviticus, describes in detail the rituals of animal sacrifice. Some tissues were specified for ritual burning; eating them was strictly forbidden. One of these tissues was the “fat above the kidneys.” The text stipulates—not once but thirteen times—that the fat above the kidneys was to be burnt and not to be eaten by anyone.



The adrenal glands are in the fat above the kidneys. The medulla contains adrenaline. The cortex contains steroids.

Why was eating the fat above the kidneys proscribed? The fat above the kidneys is unique for its contents. Buried within it are the adrenal glands, which store the powerful hormones cortisol, aldosterone, adrenal androgens, and 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 physiologically active compounds into the bloodstream. Ingestion of adrenal gland tissue repeatedly by the priests over a long period could easily have made them ill.

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; and no one knew about the effects on the body of the chemicals within the adrenal glands until about a century ago.



Relationship between Langley's autonomic nervous system and Cannon's sympathoadrenal system.

Cannon discovered that emotional stress releases a substance from the adrenal gland into the bloodstream—a hormone. The part of the autonomic nervous system involved with adrenaline release by the adrenal gland is called the sympathetic adrenergic system, or SAS.

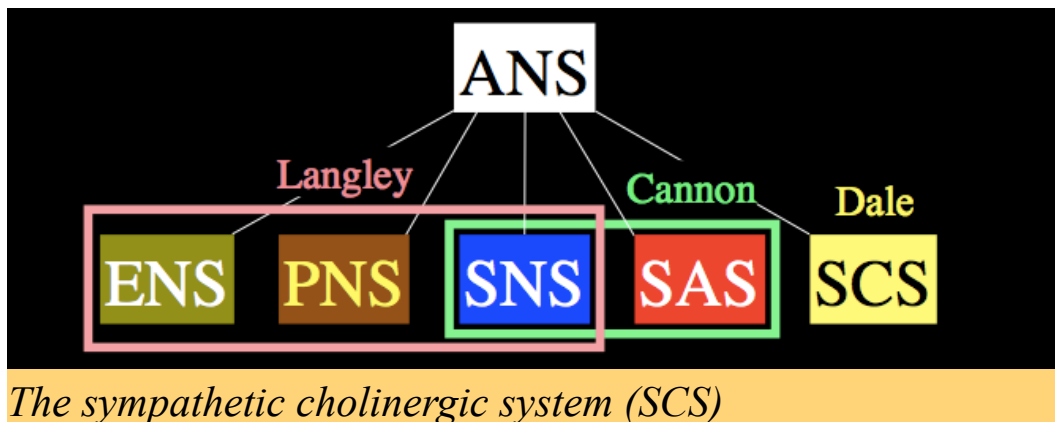
Cannon taught that the sympathetic nervous system and adrenal gland act as a functional unit in emergencies. This functional unit is sometimes called the “sympathico-adrenal” system or “sympathoadrenal system.” According to Cannon, the sympathoadrenal system mediates bodily changes in “fight-or-flight” situations. (“Fight or flight” is a phrase that Cannon introduced.)

Cannon viewed the sympathoadrenal system as the key effector for maintaining “homeostasis,” a word he invented. Homeostasis refers to a situation where all the values for key processes and chemicals of the body are kept within bounds, so that the cells are bathed in a

constant fluid environment. As will be seen, Cannon's notion of homeostasis follows directly on the Claude Bernard's concept of the internal environment—the *milieu intérieur*.

Dale's Sympathetic Cholinergic System

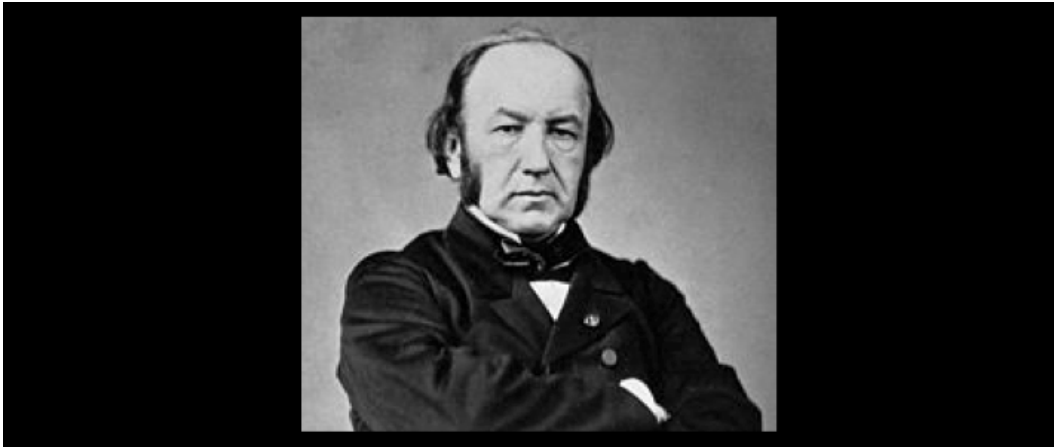
In the 1930s Sir Henry Dale (Nobel Prize, 1936) added what may be considered a fifth component of the autonomic nervous system, the sympathetic cholinergic system, or SCS.



The sympathetic cholinergic system is the main autonomic nervous system component involved with sweating.

Bernard and the "Inner World"

Understanding of the roles of the autonomic nervous system in health

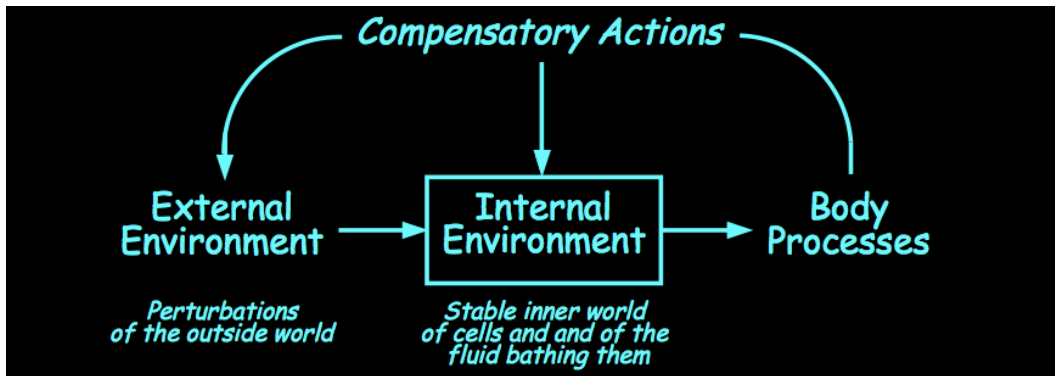


Claude Bernard, father of the milieu intérieur, the internal environment.

and disease begins with the teachings and demonstrations of Claude Bernard.

Bernard introduced the idea of the inner world, when he theorized that body systems function as they do to maintain a constant internal environment—what he called the *milieu intérieur*.

Bernard's conception evolved over several years. First he taught that a fluid environment of nearly constant composition bathes and nourishes the cells of the body. Near the end of his life, in about 1876, he postulated further that the body maintains the constant internal environment by myriad, continual, compensatory reactions. These compensatory reactions would tend to restore a state of



Claude Bernard taught that compensatory actions help maintain the internal environment.

equilibrium in response to any outside changes, enabling independence from the external environment.

Bernard therefore not only introduced the notion of an apparently constant inner world but also a purpose for body processes. One of the most famous passages in the history of physiology is his statement, “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.

Cannon's “Homeostasis”

Beginning about the turn of the twentieth century, Walter B. Cannon expanded on Bernard's theory of the *milieu intérieur*. Bernard's theory addressed the “why” of bodily processes by proposing that they help maintain a constant internal environment. Cannon's work and ideas began to flesh out the “how.” In a series of magnificent experiments over about a quarter century, Cannon demonstrated for the first time the critical role that adrenaline plays in maintaining the constancy of the inner world.

Cannon invented the word, “homeostasis.” By this term he referred to the stability of the inner world. The concept of homeostasis was a direct extension from Bernard’s *milieu intérieur*.

According to Cannon, the brain coordinates body systems, with the aim of maintaining values for key internal variables within bounds. The core temperature is kept at about 98.6°F, the serum sodium level at 140 mEq/L, the blood glucose level at 90 mg/dL, and so forth. Internal or external disturbances threatening homeostasis, by causing large enough deviations from the goal values, arouse internal nervous and hormone systems, induce emotional and motivational states, and generate externally observable behaviors, all of which would have the goal of reestablishing homeostasis.

And according to Cannon, the body responds to all emergencies in the same way, by evoking increased secretion of adrenaline.



Walter B. Cannon, who coined the word, “homeostasis.”

Core temperature, blood levels of oxygen and glucose, concentrations of red blood cells in the bloodstream, amounts of electrolytes, the rate of the heartbeat, blood flows to organs, and many more “variables” of the body normally don’t vary by much. They are kept within ranges.

This regulation does not happen by chance. It is the product of millions of years of evolution. In higher organisms, maintaining the constancy of the internal environment 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.

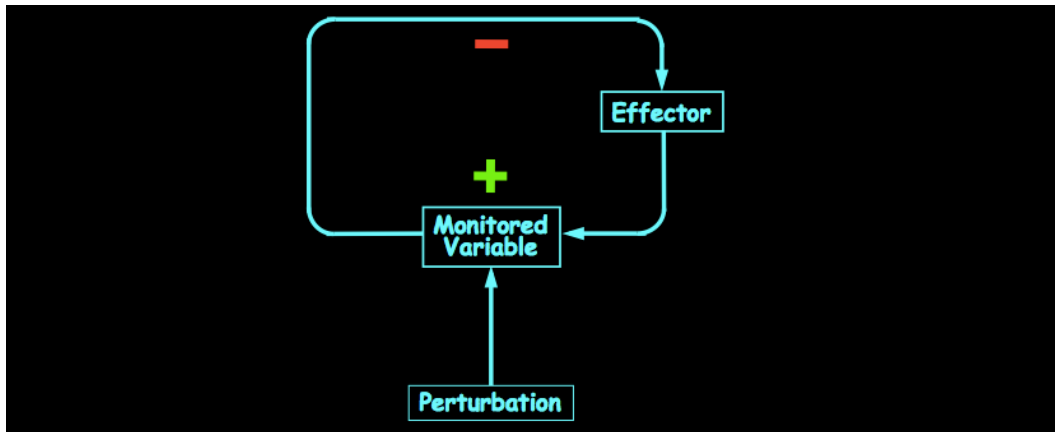
Ashby's "Homeostat"

How does the brain maintain the inner world despite continual challenges to homeostasis? In a single phrase, the brain does so via negative feedback systems.

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. A negative feedback loop has one (or an odd number) of negative relationships in the cycle.

It can be shown mathematically that in a system involving negative feedback regulation, the level of the monitored variable reaches a plateau, or steady state, value.

A thermostat is a device that compares the temperature that is set with the temperature that is sensed. When the discrepancy is sufficiently

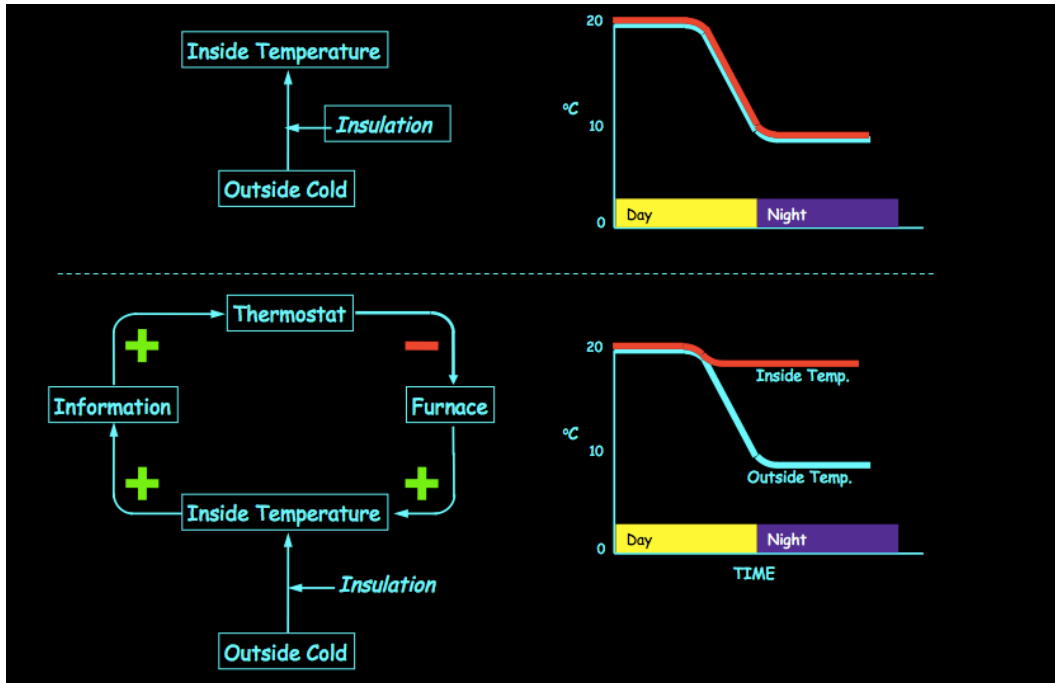


A negative feedback loop

large, the thermostat directs changes in activities of the effector, such as a furnace, reducing the discrepancy.

The level of the monitored variable, in this case the inside temperature, eventually reaches a stable value, which may not necessarily be the temperature actually set, because this would depend on factors such as the power of the furnace and efficiency of the insulation. Eventually, the inside temperature is held somewhere between what is sensed and what is set.

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

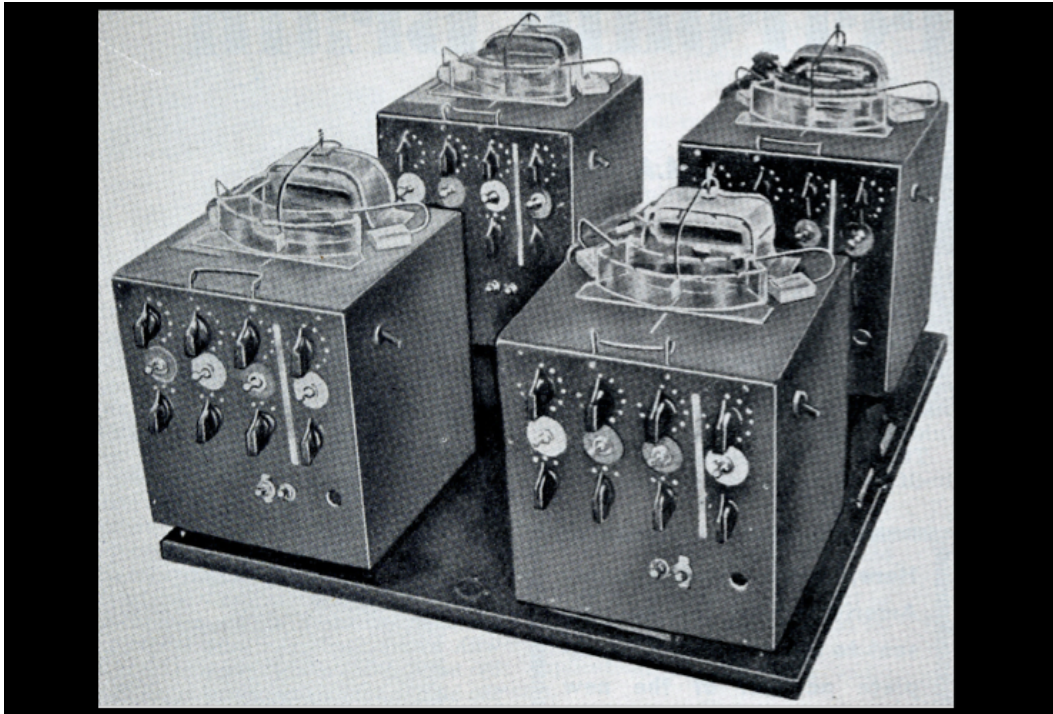


Maintaining the inside temperature via a thermostat is an example of negative feedback regulation.

negative feedback.

In the late 1940s W. Ross Ashby introduced a machine he called the “homeostat”—one of the first devices shown to be capable of adapting itself to the environment and stabilizing the system in the face of introduced disturbances.

The homeostat consisted of four identical, interconnected



Ashby's "homeostat."

electromagnetic units with a pivoted magnet on top of each. A wire hanging off each magnet was immersed in a trough of liquid in such a way that there was a direct relationship between the angle of deviation of the magnet and the current through the liquid. Any perturbation of one of the four units led to opposite changes in the others, resulting in a return of the magnet to its original position.

Ashby recognized the applicability of his machine to physiological homeostasis. In 1949, Time magazine described the homeostat as “the closest thing to a synthetic brain so far designed by man.” In his 1960

book, *Design for a Brain*, he provided several descriptions of how internal homeostats enable adaptation of an organism to its environment.

Selye's "Stress"

Hans Selye popularized stress as a scientific idea.



Hans Selye (1907-1982), father of "the stress response"

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.

Selye proposed that both the experimental and control animals underwent “stress,” which he defined 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 exhaustion.

Selye’s “doctrine of non-specificity” asserts that after all challenges to homeostasis are met by both specific and non-specific responses. The shared element is stress. It took more than a half century before the doctrine of non-specificity was actually tested experimentally, and it was refuted. Nevertheless, Selye's notion of stress as a non-specific syndrome persists and remains widely used today.

Current concepts view stress responses as having a degree of specificity, depending on the particular challenge and on the organism’s perception of and perceived ability to cope with the

stressor. Components of the autonomic nervous system play important roles in all of them.

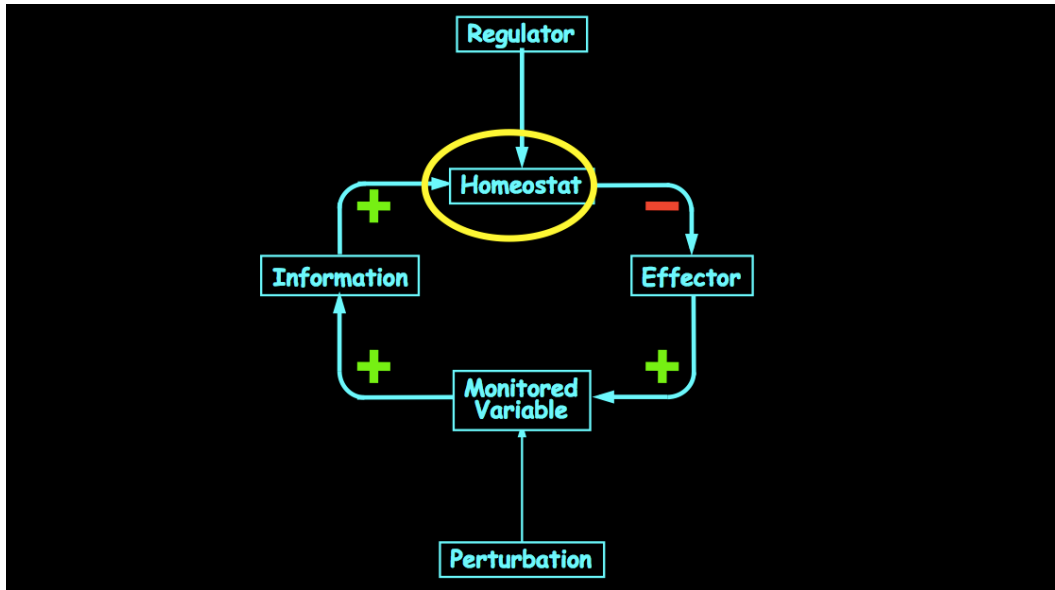
Homeostats and the ANS

Ashby did not include in his homeostat what would correspond to a thermostat in a home heating system—a comparator—to sense a discrepancy between sensed information about the level of the monitored variable and a set point for responding.

Perhaps surprisingly, although the body regulates numerous monitored variables by negative feedback (e.g., blood pressure, glucose, serum osmolality, core temperature), no one has actually identified any physiological comparators.

Instead, for each monitored variable there seems to be a hierarchy of negative feedback loops, from cells to organs to brainstem reflexes to hypothalamic primitive behaviors to higher centers mediating conscious, voluntary behaviors.

One should keep in mind that homeostats such as the “barostat” regulating blood pressure, the “osmostat” regulating serum osmolality, the “glucostat” regulating serum glucose, the “thermostat” regulating core temperature, and so forth, while useful as concepts of integrative physiology, are metaphors.

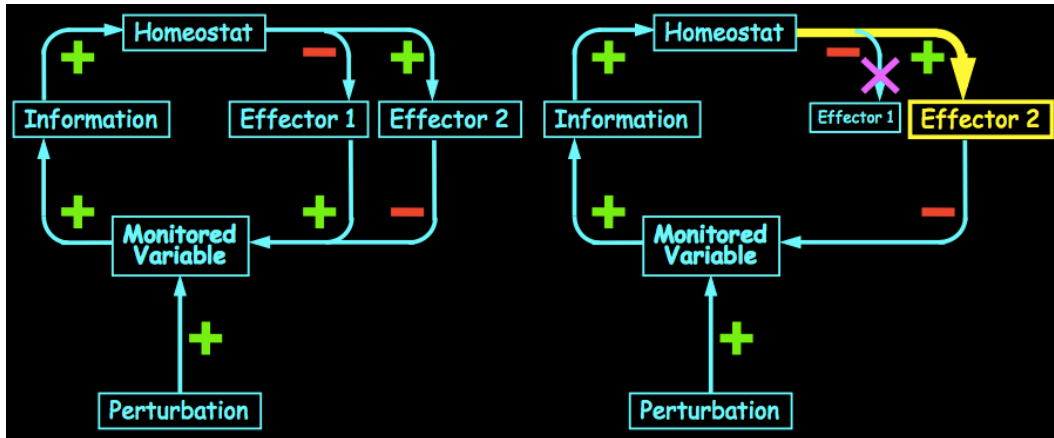


The homeostat as a metaphorical comparator.

The idea of homeostatic comparators leads straightforwardly to a novel definition of stress. Instead of stress being a stimulus or a response pattern, it is a condition, a state in which there is a sensed discrepancy between information about the level of a monitored variable and an algorithm for responding, and the discrepancy leads to alterations in activities of effectors—including components of the autonomic nervous system—that reduce the discrepancy.

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



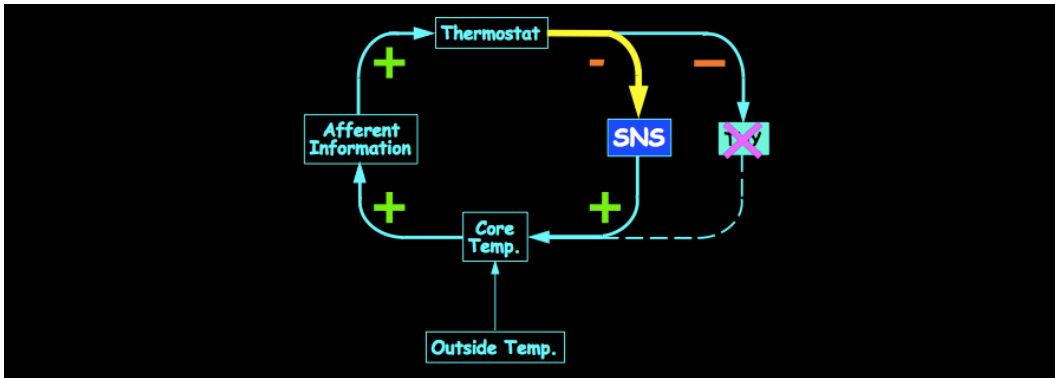
Having multiple effectors enables compensatory activation.

by insulin, glucagon, adrenaline, and cortisol.

Having multiple effectors offers clear survival advantages.

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 activity.

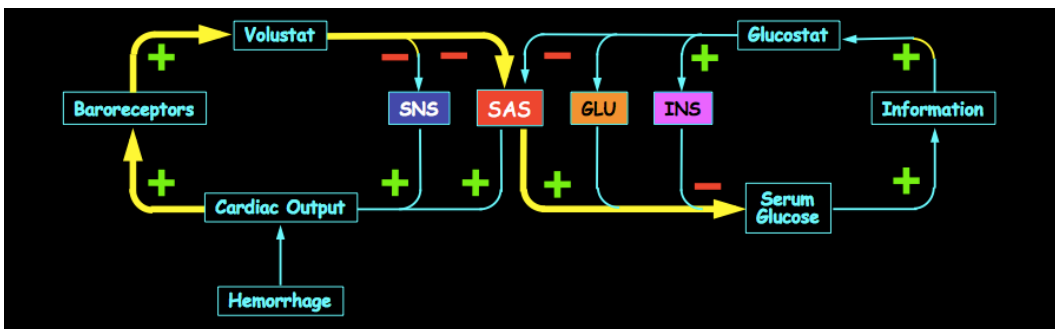
Second, having multiple effectors extends the range of control of the monitored variable. Consider how adding an air conditioner to a furnace extends the range of control of the temperature inside your house.



Compensatory activation of the sympathetic noradrenergic system (SNS) helps explain why hypothyroid patients have increased SNS activity.

Third, having multiple effectors permits the generation of relatively specific patterns of response that are most appropriate for particular stressors.

Multiple Homeostats and Effector Sharing



Sharing of the SAS by two homeostats helps explain why cardiovascular shock is associated with high glucose levels.

The homeostatic systems of the body do not act in isolation from each other. In particular, they can share effectors. For example, a patient who has 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. One may reasonably propose that all medical or surgical emergencies 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 the emergency room.

Analogously, patients with congestive heart failure may have a low serum sodium concentration, because the heart failure stimulates secretion of vasopressin via altered baroreceptor input to the brainstem, while vasopressin is also the anti-diuretic hormone used by the “osmostat” to force the kidneys to retain free water.

ORGANIZATION OF THE ANS

The autonomic nervous system is not one thing. You've learned that it has parts. Langley's autonomic nervous system consists of the enteric nervous system (ENS), parasympathetic nervous system (PNS), and sympathetic nervous system. Cannon added a component, which is the sympathetic adrenergic system (SAS), and Dale added a component, which is the sympathetic cholinergic system (SCS).

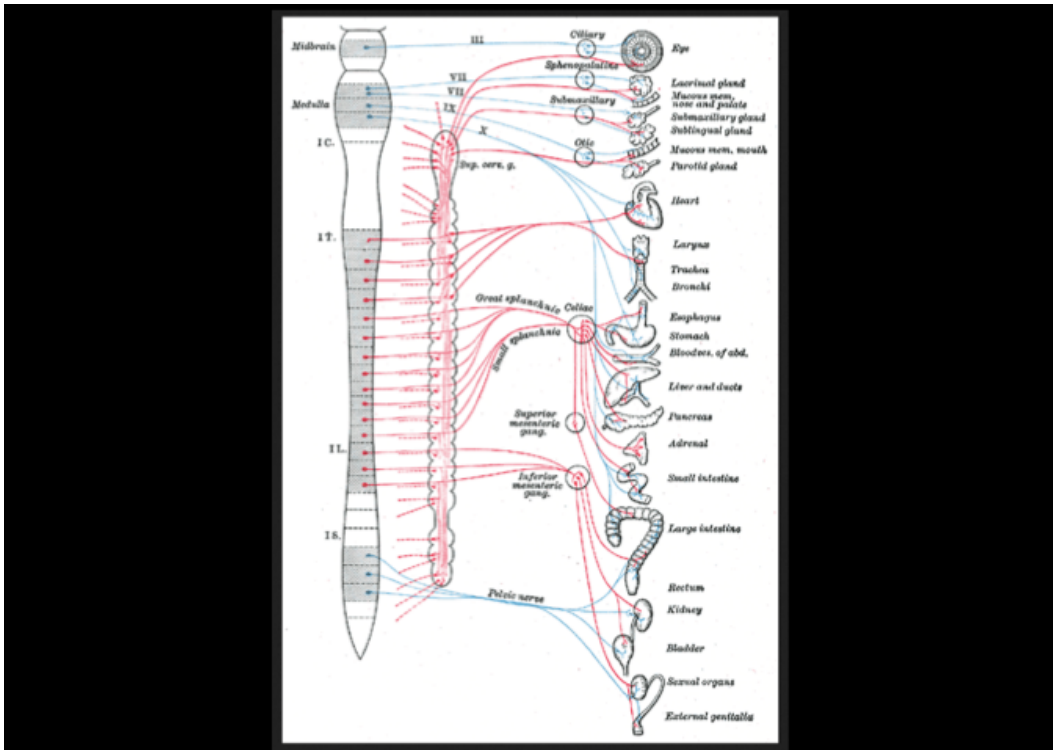
You've also learned that autonomic nerves pass through ganglia, so that there are pre-ganglionic and post-ganglionic autonomic nerves.

Now it's time to consider how the components of the autonomic nervous system are distributed in the body.

The organization of the autonomic nervous system seems impossibly complex.

Here is a classical diagram of the autonomic nervous system.

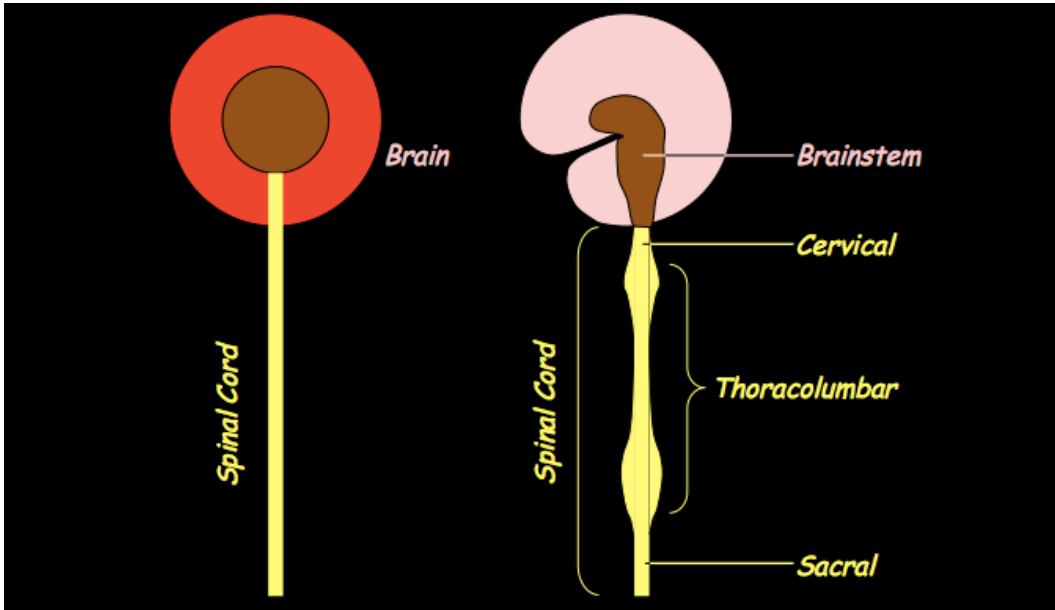
After looking this over for a few seconds, my guess is you would say, "Uh oh."



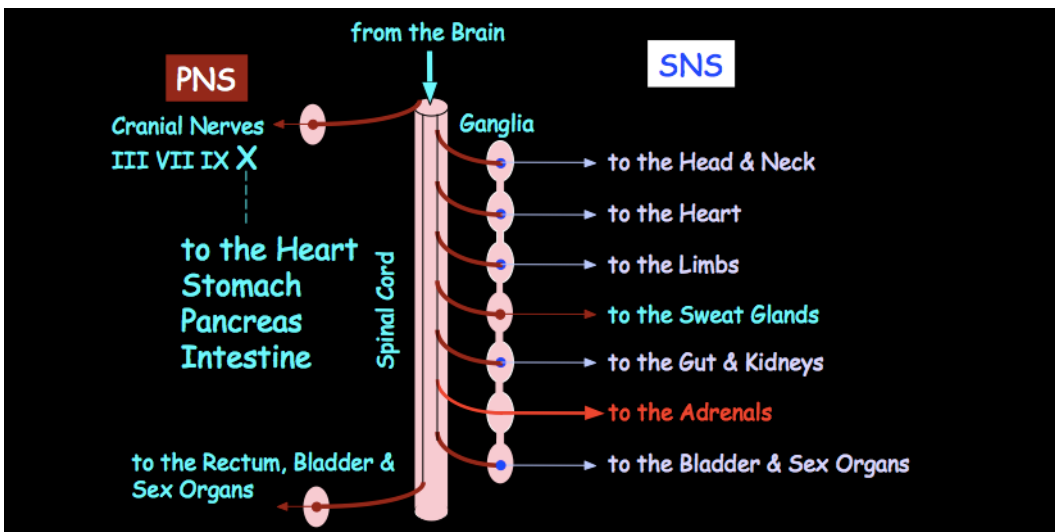
A classical diagram of the autonomic nervous system.

Distribution of the ANS in the Body

The spinal cord is divided into sections. The section in the neck is cervical. Below that is the thoracolumbar spinal cord, and at the bottom is the sacral spinal cord. The autonomic nerves come from the brainstem as cranial nerves and from the thoracolumbar and sacral. The autonomic nerves coming from the thoracolumbar spinal cord are



Sections of the central nervous system.



Autonomic nerves come from the brainstem and spinal cord.

sympathetic nerves. The autonomic nerves coming from the brainstem and sacral spinal cord are parasympathetic nerves.

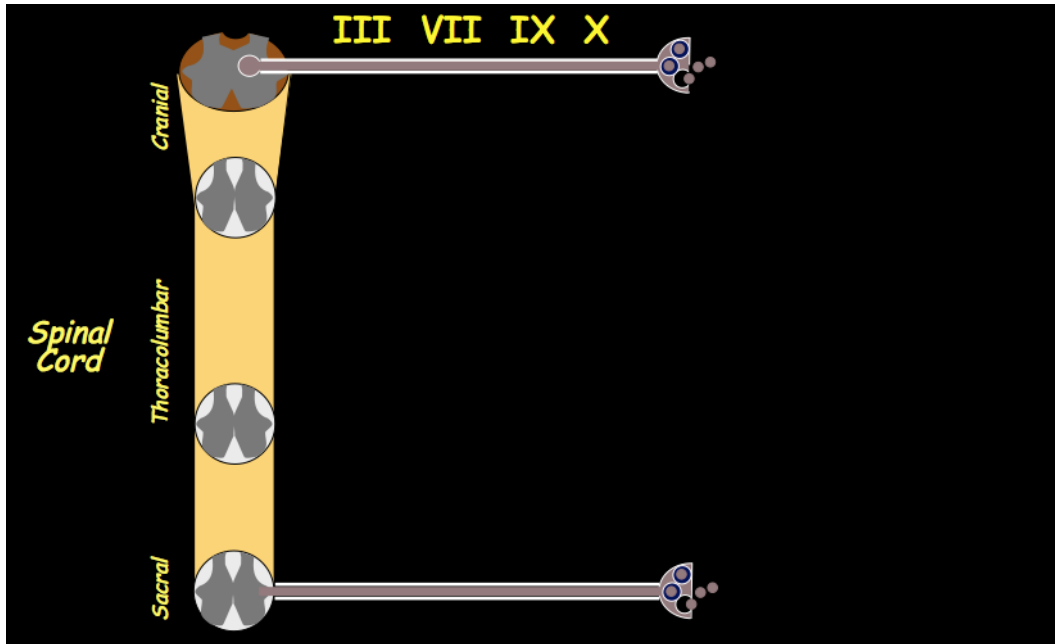
The Parasympathetic Nervous System (PNS)

The parasympathetic nervous system regulates “vegetative” body functions—things you do at night or behind closed doors.

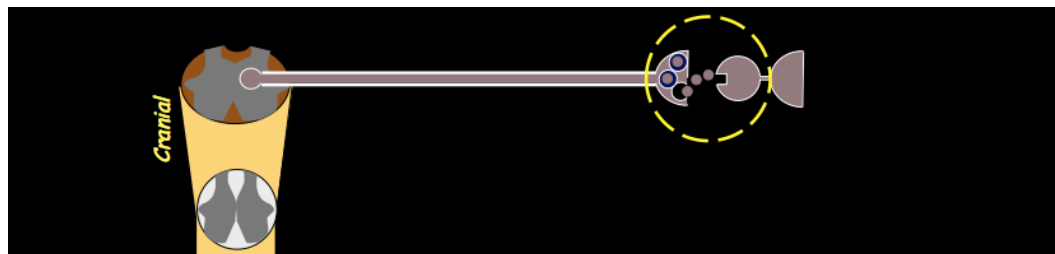
The parasympathetic nervous system (abbreviated as PNS) in many ways acts like the opposite of an emergency system. “Vegetative” behaviors, activities that increase instead of use up energy, are associated with increased activity of this system. Examples are sleeping, eating, salivating, digesting, and excreting waste.

The upper part of the parasympathetic nervous system is the nerves that come from a portion of your brain called the brainstem. The brainstem connects the brain to the spinal cord. Most of the nerves of the parasympathetic nervous system 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.

Parasympathetic nerves come from the brainstem and from the bottom of the spinal cord.

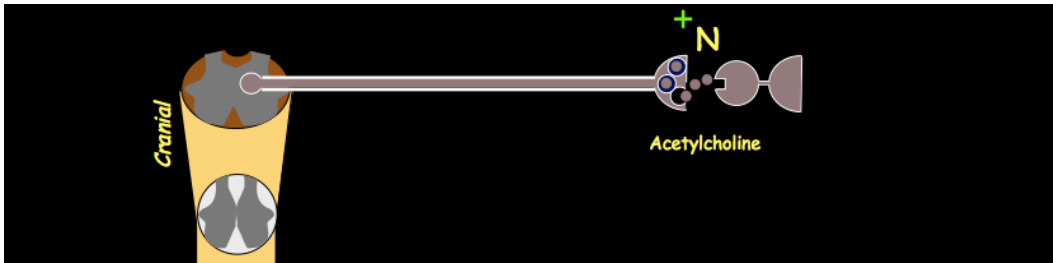


Cranial and sacral parasympathetic nerves



Parasympathetic nerves: Long myelinated pre-ganglionic, short non-myelinated post-ganglionic

The nerves that come from the brainstem are called the cranial nerves

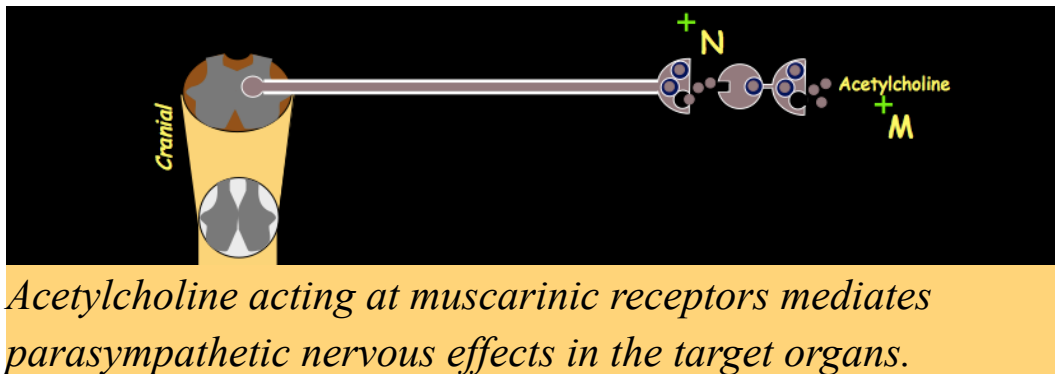
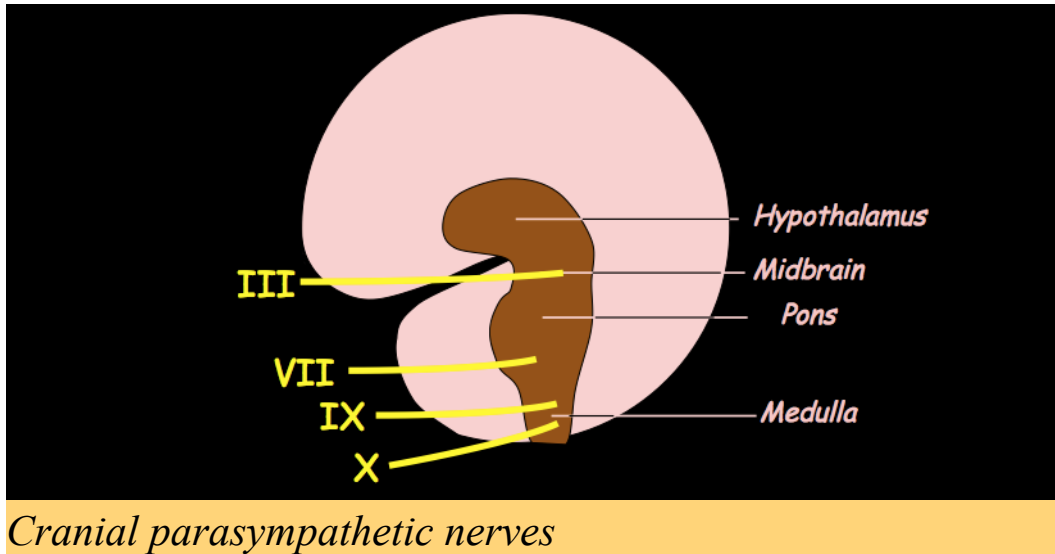


Acetylcholine acting at nicotinic receptors mediates ganglionic neurotransmission.

(the word, “cranial,” refers to the skull). The parasympathetic nerve fibers travel in major cranial nerves that have specific names. The oculomotor nerve connects to the eye, the facial nerve to the face, the glossopharyngeal nerve to the tongue and muscles involved with swallowing and talking, and the vagus nerve to the heart and most of the abdominal organs.

Parasympathetic fibers in the head travel in three cranial nerves, the third (optic nerve), the seventh (facial nerve), and the ninth (glossopharyngeal nerve). The fibers supply the pupils, tear ducts, and salivary glands. Stimulation of the parasympathetic fibers in these nerves causes the pupils to constrict, the lacrimal glands to secrete tears, and the salivary glands to secrete watery saliva. Note that the parasympathetic fibers to the face are peripheral, even though they travel in cranial nerves.

The lower part of your parasympathetic nervous system is the group



of nerves that travel from the bottom level of the spinal cord, which is called the sacral spinal cord. These nerves travel to the genital organs, urinary bladder, and lower gastrointestinal tract.

As for all the parasympathetic nerves, the ganglia are located close to or even inside the target organs, and so the post-ganglionic, non-

myelinated neurons are short.

The neurotransmitter at all the autonomic ganglia is acetylcholine. Acetylcholine binds to nicotinic receptors on the cell bodies of the post-ganglionic nerves.

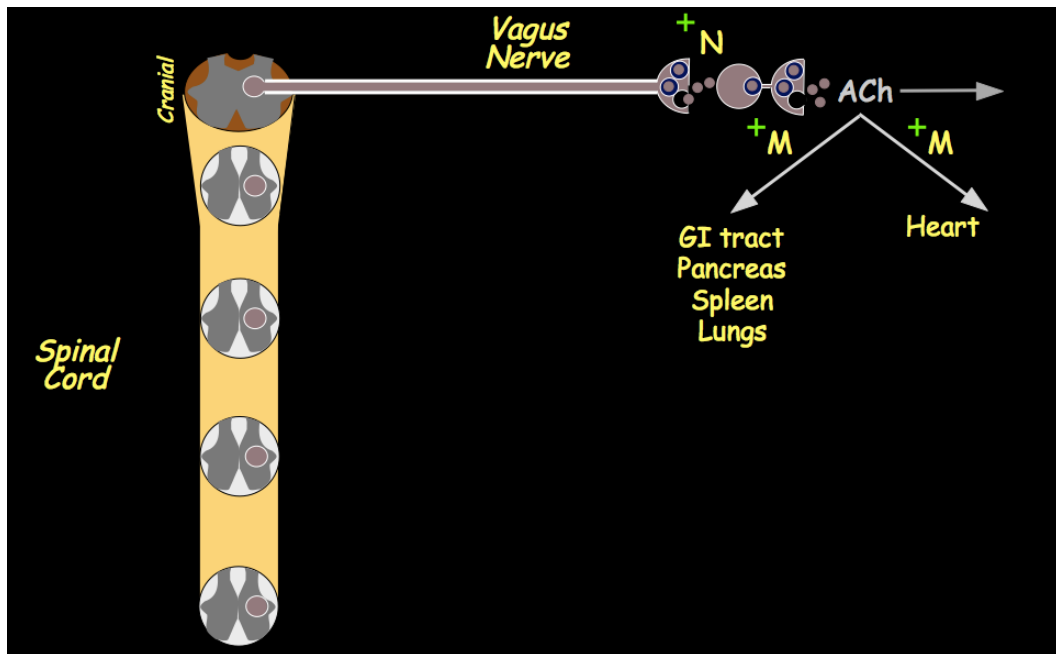
In the parasympathetic nervous system, acetylcholine is also the chemical messenger released from the post-ganglionic nerve terminals in the target organs. The receptors in the target organs are muscarinic.

The vagus nerve is the tenth cranial nerve. 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 gastrointestinal tract. Stimulation of the vagus nerve decreases heart rate, increases smooth muscle tone and mucus secretion in the airways, and increases secretion of stomach acid and digestive hormones.

Parasympathetic nerves from the bottom-most part of the spinal cord, the sacral spinal cord, supply the last segment of the colon, the urinary bladder, and sex organs.

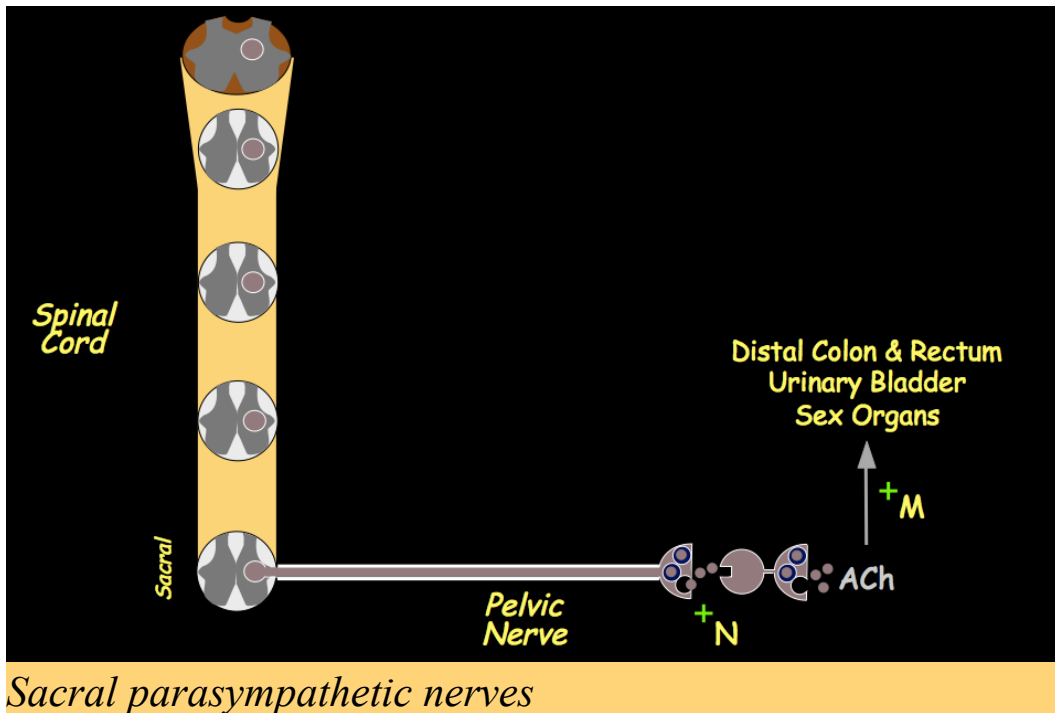
Parasympathetic stimulation increases peristalsis in the colon and



The vagus nerve

contraction of the rectum while relaxing the anal sphincter, so that defecation occurs. Parasympathetic 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. Third, parasympathetic stimulation promotes filling of the corpora cavernosum and corpus spongiosum in the penis and thereby promotes penile erection.

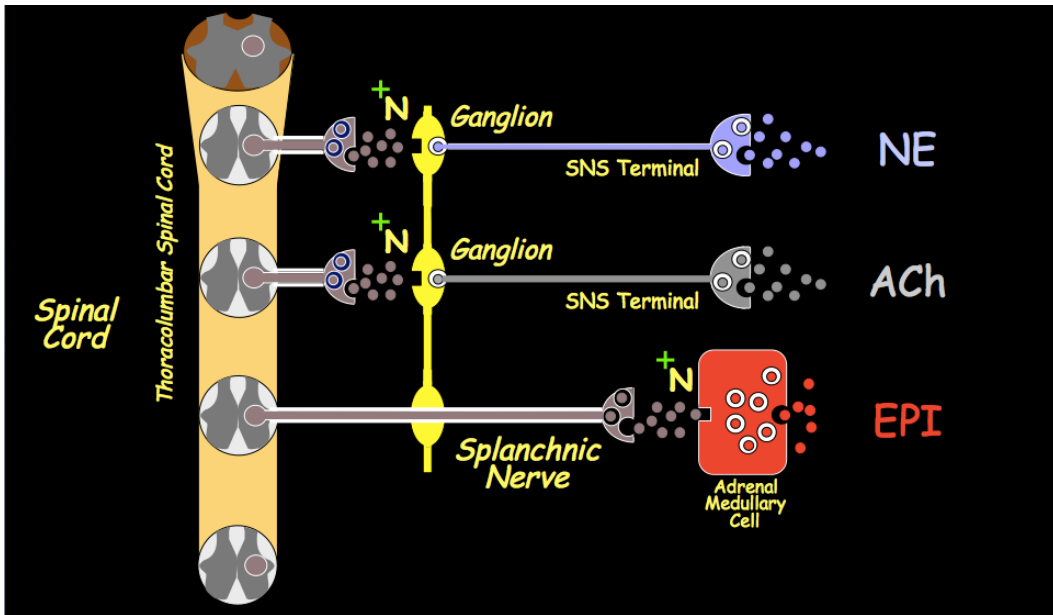
Parasympathetic nervous system failure produces many symptoms, including dry mouth, constipation, urinary



problems, decreased tear production, and (in men) inability to have an erection.

The Sympathetic Nervous System

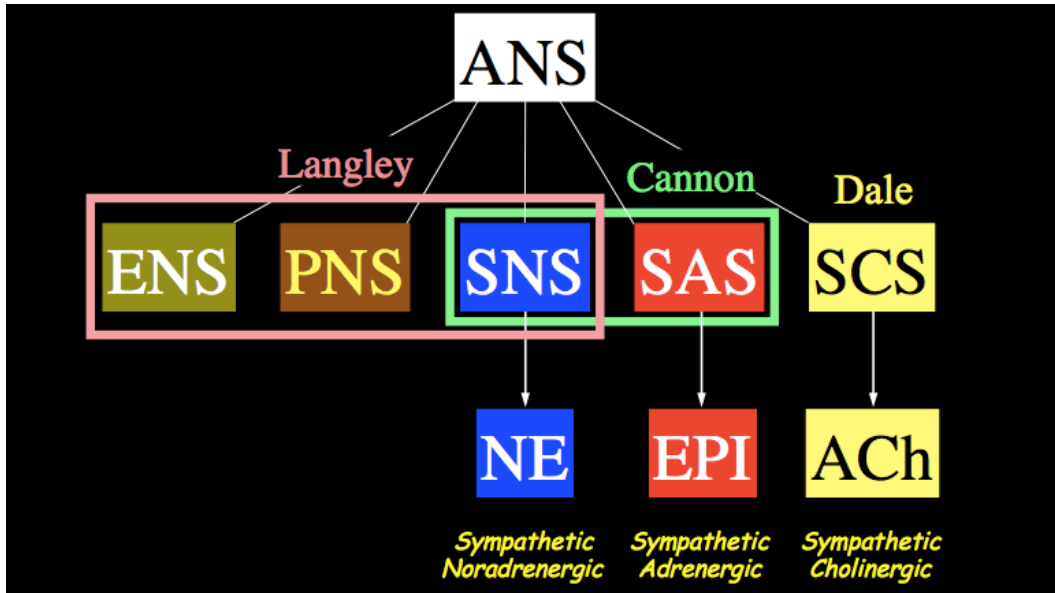
The sympathetic nervous system is involved with processes that happen during the day or out in the open.



The sympathetic nervous system can be divided into 3 parts based on the chemical messenger—norepinephrine (NE), acetylcholine (ACh), or epinephrine (EPI).

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.

Sympathetic nerves come from the middle part of the spinal cord.



The sympathetic nervous system has three components, based on their main chemical messengers.

The sympathetic nervous system can be thought of as being composed of three sub-systems, the sympathetic noradrenergic system (SNS), the sympathetic cholinergic system (SCS), and the sympathetic adrenergic system (SAS), or adrenomedullary hormonal system. These sub-systems use three different chemical messengers, norepinephrine, acetylcholine, and adrenaline.

The sympathetic nervous system has three sub-systems, based on the particular chemical messenger—norepinephrine (NE), acetylcholine (ACh), or epinephrine (EPI, which is adrenaline).

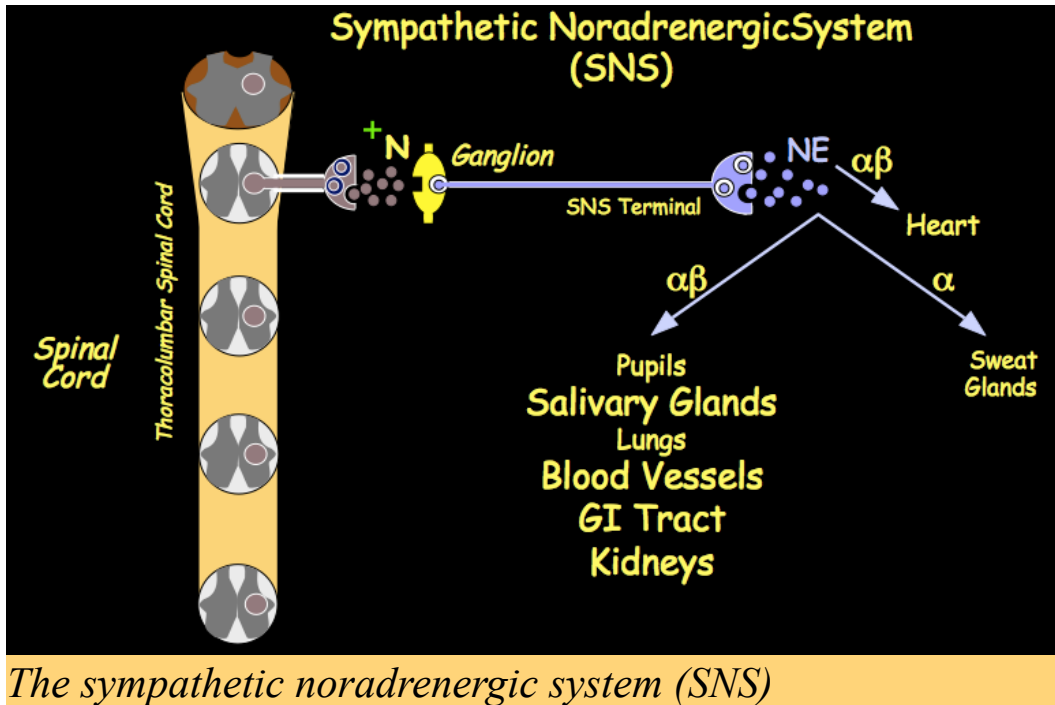
Although it was long thought that the sympathetic nervous system is only an “emergency system” and inactive during day to day life, this system actually is always active and participates in many automatic reactions that occur continually, such as tightening of blood vessels in the muscles when you stand up and in the skin when you are exposed to cold.

The Sympathetic Noradrenergic System (SNS)

The sympathetic noradrenergic system consists mainly of thin, slow-conducting, non-myelinated, post-ganglionic nerves. The neurotransmitter mediating the ganglionic transmission is acetylcholine, acting at nicotinic receptors, and the neurotransmitter released from the post-ganglionic nerve terminals is norepinephrine.

Stimulation of the sympathetic noradrenergic system causes the pupils to dilate and the salivary glands to secrete thick saliva. The force and rate of the heartbeat increase. Smooth muscle cells in the airways relax. The hair stands up, because of stimulation of *arrector pili* muscles in the skin. In the kidneys, norepinephrine promotes tubular reabsorption of sodium.

Probably the most prominent effect of sympathetic noradrenergic stimulation is constriction of blood vessels—especially of arterioles, which 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.

Norepinephrine exerts these 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.

Norepinephrine is a neurotransmitter, not a hormone. Its effects in the

body are determined mainly by it reaching adrenoceptors before it reaches the bloodstream.

The Sympathetic Adrenergic System (SAS)

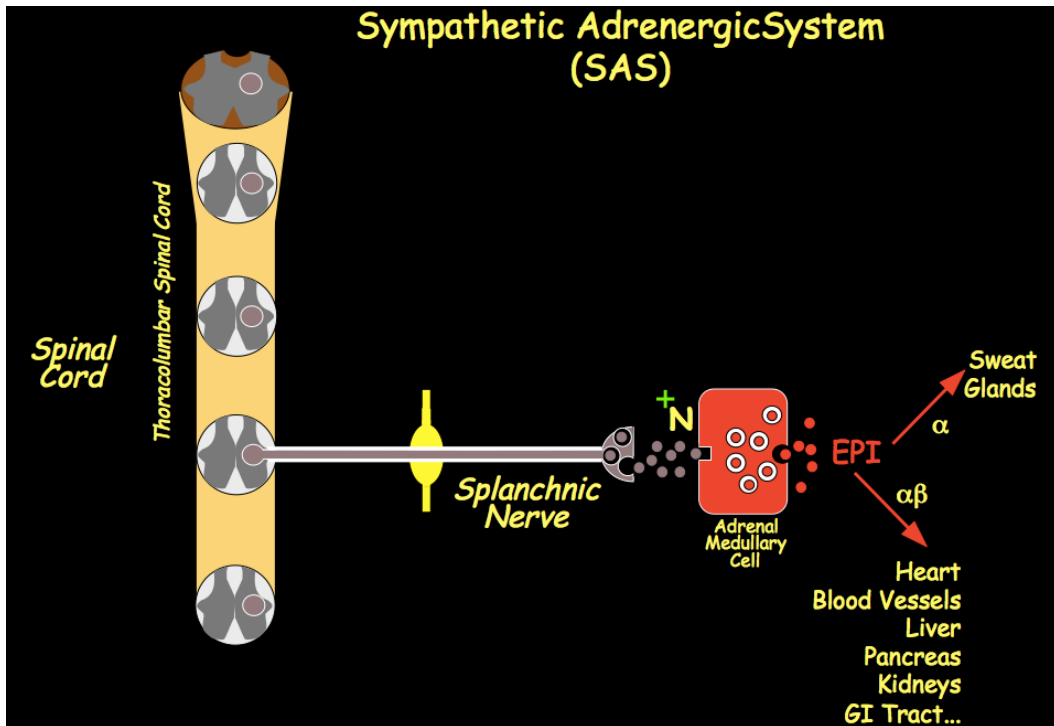
The Sympathetic Adrenergic System (abbreviated as SAS), or Adrenomedullary Hormonal System, is the part of the sympathetic nervous system for which adrenaline is the main chemical messenger.

The sympathetic adrenergic systems reacts 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.

The sympathetic adrenergic system is an emergency system and regulates “emergency” processes such as in distress.

Adrenaline (synonymous with epinephrine, EPI), was discovered about a century ago, at about the time that the autonomic nervous system was named.

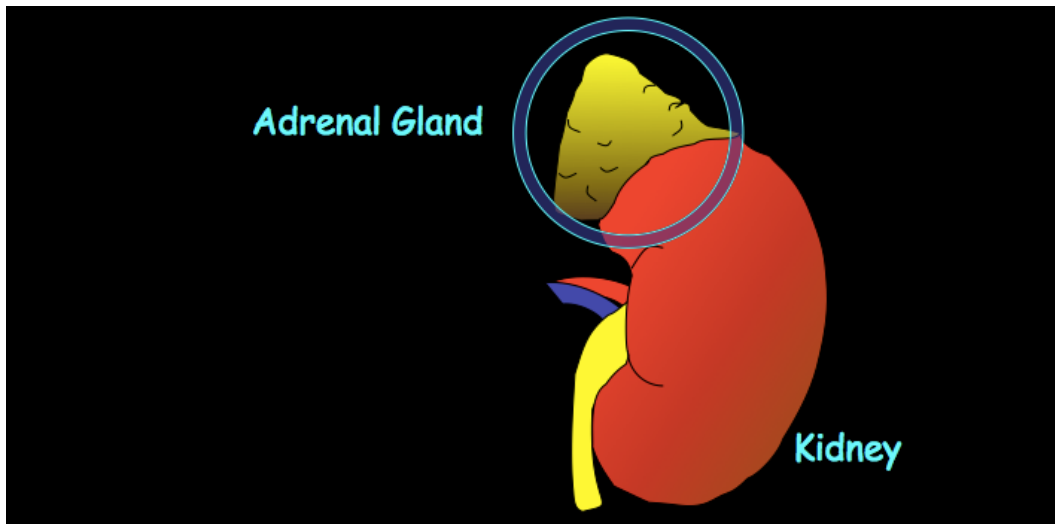
Threats to survival increase adrenaline levels.



In the sympathetic adrenergic system (AHS), the adrenaline-secreting cells of the adrenal medulla receive direct innervation.

The adrenal gland is arranged like a bon bon. The outer shell is the cortex, while the center is the medulla, from the Latin word for marrow. Adrenaline is released into the bloodstream from the medulla of the adrenal glands.

Adrenaline (epinephrine) is released from the adrenal glands,



The adrenal glands are located in the fat above the kidneys.

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 teleologically with the notion of adrenaline being released in sudden emergencies. Adrenaline is secreted into the bloodstream and is distributed widely in the body, so it is a hormone. Norepinephrine and acetylcholine are neurotransmitters, in that they are released from nerve terminals and act locally.

This location explains the origins of the word, adrenaline, which comes from the Latin words for “near the kidney,” and of the word,

epinephrine, which comes from the Greek words for “on the kidney.”

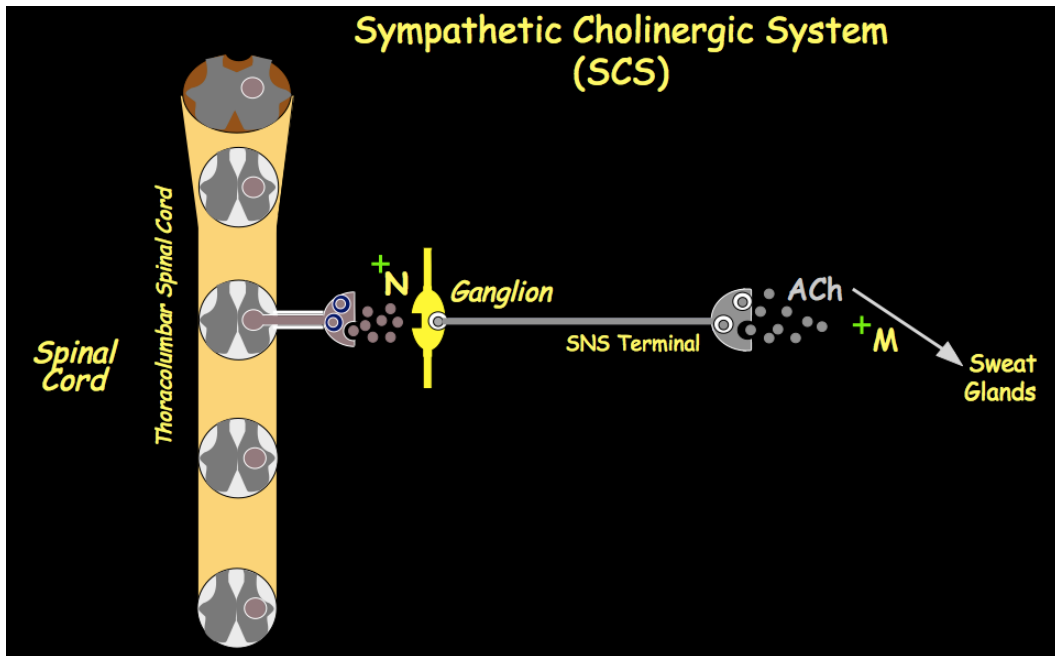
Failure of the sympathetic adrenergic system can cause a tendency to low glucose levels (hypoglycemia).

Adrenaline stimulates all types of adrenoceptors. Because of stimulation of beta-2 adrenoceptors on vascular smooth muscle cells, adrenaline increases blood flow to skeletal muscle, and probably the systemic cardiovascular effect that occurs at the lowest concentration is a fall in total peripheral 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 glucose levels, and increases core temperature.

Because the blood flows from the adrenal cortex through the adrenal medulla, the adrenal medulla is bathed continuously in high concentrations of cortisol, the main steroid of the adrenal cortex. This is important, because cortisol is a trophic factor for PNMT, the enzyme that converts norepinephrine to adrenaline.

The Sympathetic Cholinergic System (SCS)

The sympathetic cholinergic system mediates sweating —



The sympathetic cholinergic system consists mainly of non-myelinated post-ganglionic nerves to sweat glands.

thermoregulatory, gustatory, and emotional.

The sympathetic cholinergic system (abbreviated as SCS) is the component of the sympathetic nervous system that plays a major role in sweating, such as when you perspire upon exposure to hot outdoors, when your forehead breaks out in sweat after you eat spicy foods, and when your palms and armpits get wet during emotional upset.

Acetylcholine, the neurotransmitter of the sympathetic cholinergic

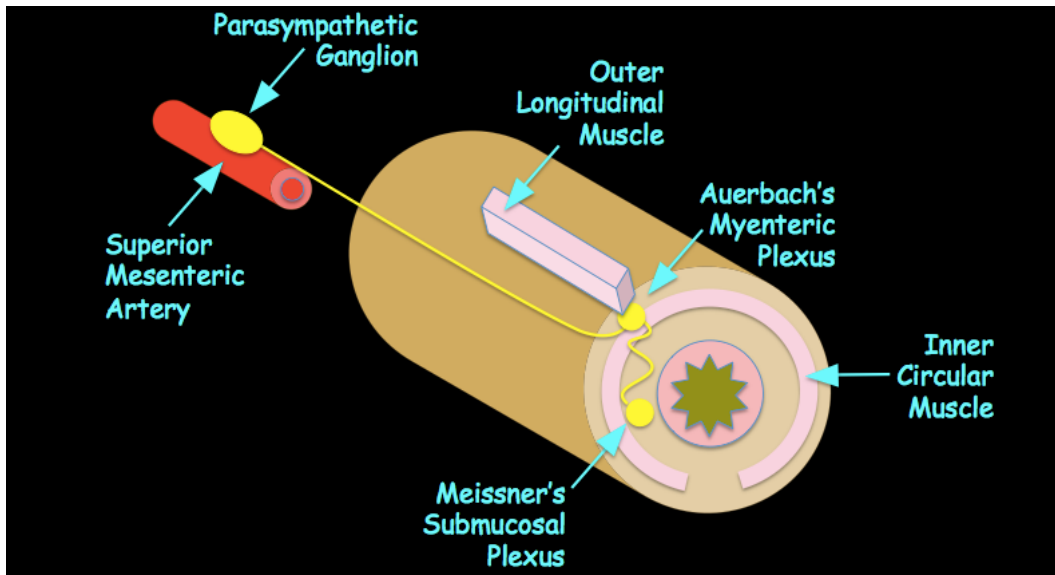
system, stimulates secretion from sweat glands.

The Enteric Nervous System (ENS)

The enteric nervous system is the part of the autonomic nervous system that is within walls of the gastrointestinal tract. Autonomic neurons are found in plexuses (networks) in the walls. Auerbach's plexus (also called the myenteric plexus) is between the longitudinal and circular layers of smooth muscle, and Meissner's plexus, which is derived from fibers coming from Auerbach's plexus, is in the submucosal layer. Auerbach's plexus receives parasympathetic and sympathetic innervation. Meissner's plexus receives purely parasympathetic innervation.

The ENS includes not only autonomic fibers but also intrinsic neuronal cells called ganglion cells. The ganglion cells migrate from the neural crest during fetal development. In Hirschsprung's disease, the migration is incomplete. The ganglion cells are required for movement of intestinal contents. In Hirschsprung's disease 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.

The ENS contains many neurotransmitters. It is a surprising fact that



Arrangement of myenteric and submucosal plexuses of the enteric nervous system

most of the norepinephrine, dopamine, and serotonin made in the body is synthesized in the gut.

Interactions among ANS Components

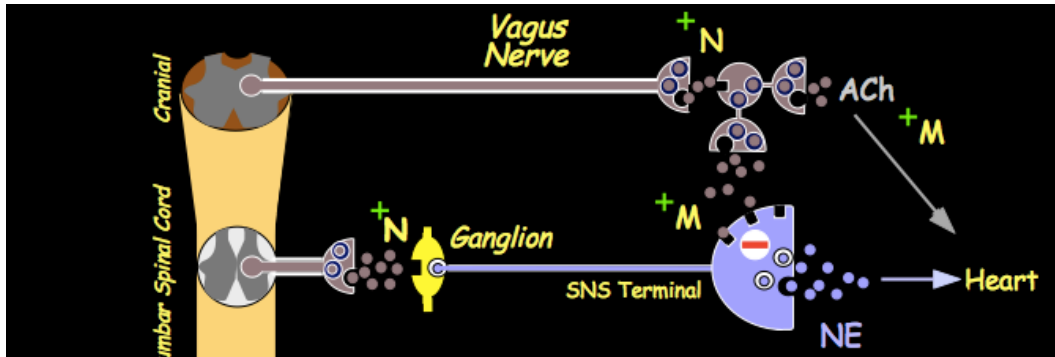
Activation of particular components of the autonomic nervous system can lead to effects on other components. That is, the components interact with each other. For instance, the sympathetic noradrenergic system and the parasympathetic nervous system usually antagonize each other. When sympathetic nerves 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.

There are inhibitory muscarinic receptors on sympathetic post-ganglionic nerves in the heart. Because of this, vagal stimulation decreases the rate and force of cardiac contraction, not only directly by the released acetylcholine acting at muscarinic receptors on the target myocardial cells, but also indirectly by inhibiting norepinephrine release from sympathetic post-ganglionic nerves.

In some forms of dysautonomia, multiple components of the autonomic nervous system are affected similarly. For instance, interference with the transmission of nerve impulses in the ganglia produces symptoms and signs of failure of the sympathetic noradrenergic system, the sympathetic cholinergic system, the sympathetic adrenergic system, and the parasympathetic nervous system.

In other situations, increases in activities of these systems go together. An example is after eating a meal. In this setting, stimulation of the parasympathetic nervous system aids digestion, by increasing gut motions and augmenting secretions of hormones, such as insulin. Meanwhile, stimulation the sympathetic noradrenergic system tightens blood vessels in some body regions, shunting blood toward the gut. After a meal, possibly because of increased levels of glucose in the bloodstream, activity of the sympathetic adrenergic system tends



Components of the autonomic nervous system can interact. For instance, acetylcholine (ACh) released from vagal terminals can inhibit norepinephrine (NE) release from sympathetic noradrenergic system (SNS) terminals.

to decrease.

The sympathetic noradrenergic system and the parasympathetic nervous system usually antagonize each other...but not always.

Fainting involves a complex and unusual pattern of changes in activities of components of the autonomic nervous system. When people faint, activity of the parasympathetic nervous system usually is increased, producing changes such as nausea, churning stomach, and a prominent fall in the heart rate. Activity of the sympathetic noradrenergic system often is decreased, resulting in a fall in blood

Differential SNS vs. SAS Activation		
	SNS	SAS
2-DG	+	++++
Distress	+	+++
Neurocardiogenic syncope	+	++++
Orthostasis	++	+
Mild exercise	++	+
Cool temperature at skin of back	+++	0
Mild core hypothermia	+++	+

Some examples of differential SNS vs. SAS activation

pressure. The sympathetic adrenergic system is stimulated markedly, and high levels of adrenaline in the bloodstream may be responsible for constriction of blood vessels in the skin, resulting in pallor and dilation of the pupils. Finally, when people faint they often have increased sweating, reflecting either increased activity of the sympathetic cholinergic system or effects of adrenaline.

The sympathetic noradrenergic system and the adrenomedullary hormonal system usually work together... but not always.

It has been taught that the sympathetic noradrenergic system and the adrenomedullary hormonal system act together in emergencies such as

“fight-or-flight” situations. Automatic adjustments to stresses of everyday life, such as standing up or going outside on a chilly day, also involve increases in activities of both systems (although mainly of the sympathetic noradrenergic system). As noted above, in fainting activities of some components of the autonomic nervous system change in opposite directions.

Stimulation of the sympathetic noradrenergic system tightens blood vessels and increases the force of the heartbeat (the combination increasing blood pressure), relaxes the gut, evokes goose bumps and the hair standing out, promotes retention of sodium by the kidneys, increases production of thick saliva, and dilates the pupils.

Stimulation of the sympathetic cholinergic system evokes sweating.

Stimulation of the enteric nervous system increases gut motions.

Stimulation of the sympathetic adrenergic system increases the rate and force of the heartbeat, tightens blood vessels in the skin (producing pallor), relaxes blood vessels in skeletal muscle, relaxes the gut, increases blood glucose levels, decreases serum potassium levels, may contribute to emotional sweating, exerts an anti-fatigue effect, and intensifies emotional experiences.

Stimulation of the parasympathetic nervous system decreases the heart rate, increases production of watery saliva, stimulates the gut, stimulates the urinary bladder, promotes erection of the penis, and constricts the pupils of the eyes.

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

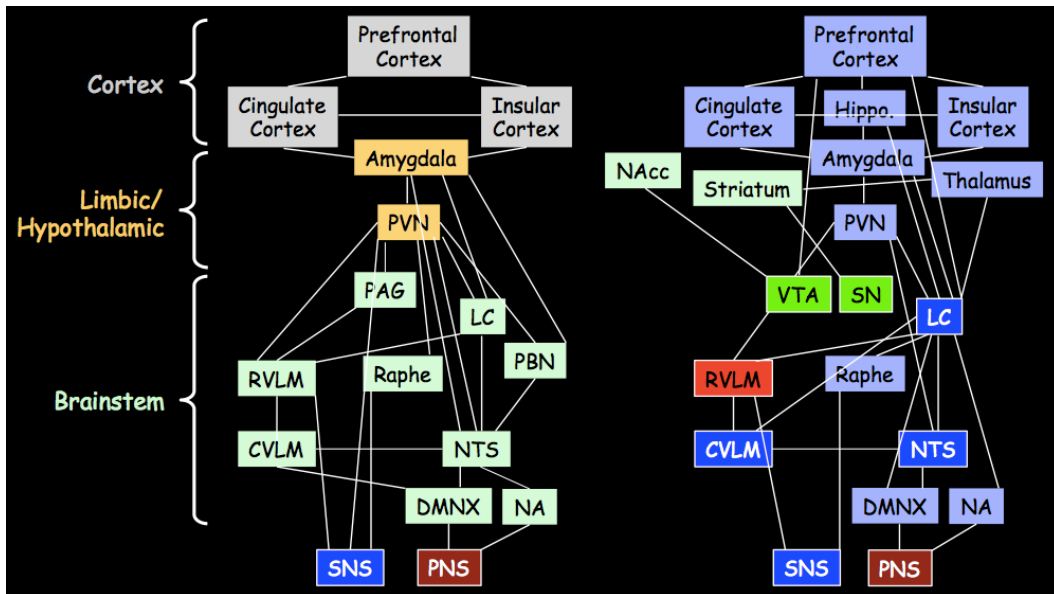
Given the many different effects of stimulation of components of the autonomic nervous system, you may begin to predict what the symptoms and signs would be when those components are overactive or underactive in dysautonomias.

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

The ganglion cells of the ENS contain many putative chemical messengers, including acetylcholine, serotonin, and dopamine. How the ganglion cells with their multiple neurotransmitters interact with the parasympathetic nervous and sympathetic noradrenergic systems remains poorly understood.

The Central Autonomic Network

A network involving several cortical, subcortical, and brainstem centers participate in regulation of outflows to the autonomic nervous system. This has been called the “central autonomic network.” Cortical centers include the prefrontal cortex, anterior cingulate, and insula. Subcortical centers include the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus.



The central autonomic network and the network of central catecholamine systems. Noradrenergic nuclei are in dark blue and projections in light blue, dopaminergic green, and adrenergic red.

Brainstem centers include the peri-aqueductal gray region in the midbrain, the and parabrachial nucleus at the junction of the midbrain and pons, the locus ceruleus in the dorsal pons, and the raphe nuclei, rostral ventrolateral medulla, caudal ventrolateral medulla, dorsal motor nucleus of the vagus, nucleus ambiguus, and nucleus of the solitary tract in the medulla.

The central autonomic network involves not only neuroanatomic but also neurochemical centers and connections, including systems for

each of the body's three catecholamines. 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 and thereby interfere with its own blood-brain barrier.

Summary of the Organization of the ANS

Now is a good time for us to review the information so far. It can be a bit confusing, because of the several “nervous systems” involved.

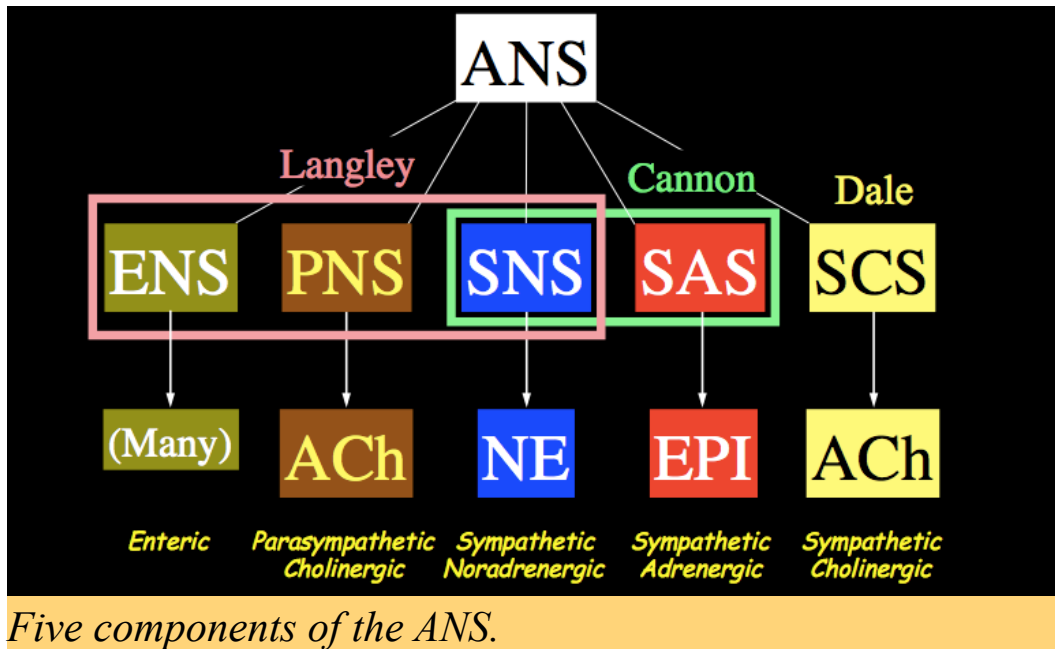
Remember, you have a central nervous system (your brain and spinal cord) and a peripheral nervous system (the rest of your nerves). Your

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 from the ganglia are called 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, and these nerves are called pre-ganglionic.

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

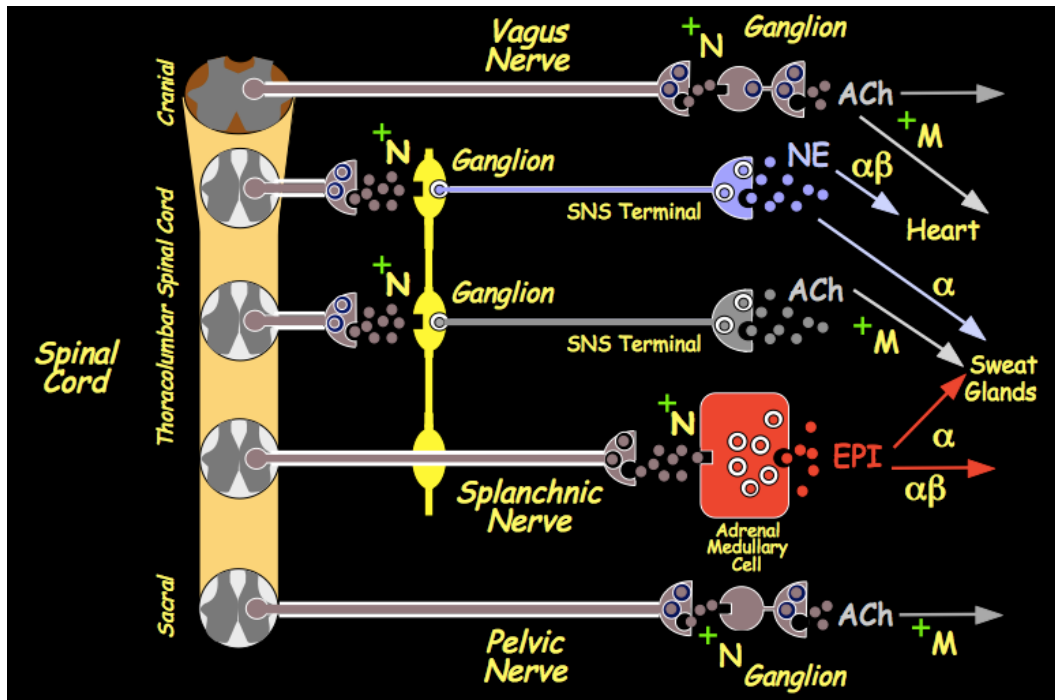
The sympathetic nervous system can in turn be divided into sub-systems based on the chemical messenger use for that component—norepinephrine for the sympathetic noradrenergic system, acetylcholine for the sympathetic cholinergic system, and adrenaline



for the sympathetic adrenergic system.

You have also learned that the autonomic nervous system works by releasing chemical messengers, which act on receptors located in organs throughout the body. Chemical messengers coming from nerves are neurotransmitters, and chemical messengers released into the bloodstream are hormones.

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



Overview of the distribution of autonomic nerves.

“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. Sympathetic nerves (noradrenergic, adrenergic, and cholinergic) from the thoracolumbar spinal cord. Parasympathetic nerves have long, myelinated pre-ganglionic and short, non-myelinated post-ganglionic fibers. Sympathetic noradrenergic and cholinergic 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 cells secrete adrenaline into the bloodstream.