Peripheral neuropathy

What is peripheral neuropathy?
Peripheral neuropathy describes damage to the peripheral nervous system, the vast communications network that transmits information from the brain and spinal cord (the central nervous system) to every other part of the body. Peripheral nerves also send sensory information back to the brain and spinal cord, such as a message that the feet are cold or a finger is burned. Damage to the peripheral nervous system interferes with these vital connections. Like static on a telephone line, peripheral neuropathy distorts and sometimes interrupts messages between the brain and the rest of the body.

Because every peripheral nerve has a highly specialized function in a specific part of the body, a wide array of symptoms can occur when nerves are damaged. Some people may experience temporary numbness, tingling, and pricking sensations (paresthesia), sensitivity to touch, or muscle weakness. Others may suffer more extreme symptoms, including burning pain (especially at night), muscle wasting, paralysis, or organ or gland dysfunction. People may become unable to digest food easily, maintain safe levels of blood pressure, sweat normally, or experience normal sexual function. In the most extreme cases, breathing may become difficult or organ failure may occur.

Some forms of neuropathy involve damage to only one nerve and are called mononeuropathies. More often though, multiple nerves affecting all limbs are affected-called polyneuropathy. Occasionally, two or more isolated nerves in separate areas of the body are affected-called mononeuritis multiplex.

In acute neuropathies, such as Guillain-Barré syndrome, symptoms appear suddenly, progress rapidly, and resolve slowly as damaged nerves heal. In chronic forms, symptoms begin subtly and progress slowly. Some people may have periods of relief followed by relapse. Others may reach a plateau stage where symptoms stay the same for many months or years. Some chronic neuropathies worsen over time, but very few forms prove fatal unless complicated by other diseases. Occasionally the neuropathy is a symptom of another disorder.

In the most common forms of polyneuropathy, the nerve fibers (individual cells that make up the nerve) most distant from the brain and the spinal cord malfunction first. Pain and other symptoms often appear symmetrically, for example, in both feet followed by a gradual progression up both legs. Next, the fingers, hands, and arms may become affected, and symptoms can progress into the central part of the body. Many people with diabetic neuropathy experience this pattern of ascending nerve damage.

How are the peripheral neuropathies classified?
More than 100 types of peripheral neuropathy have been identified, each with its own characteristic set of symptoms, pattern of development, and prognosis. Impaired function and symptoms depend on the type of nerves-motor, sensory, or autonomic-that are damaged. Motor nerves control movements of all muscles under conscious control, such as those used for walking, grasping things, or talking. Sensory nerves transmit information about sensory experiences, such as the feeling of a light touch or the pain resulting from a cut. Autonomic nerves regulate biological activities that people do not control consciously, such as breathing, digesting food, and heart and gland functions. Although some neuropathies may affect all three types of nerves, others primarily affect one or two types. Therefore, doctors may use terms such as predominately motor neuropathy, predominately sensory neuropathy, sensory-motor neuropathy, or autonomic neuropathy to describe a patient's condition.

What are the symptoms of peripheral nerve damage?
Symptoms are related to the type of affected nerve and may be seen over a period of days, weeks, or years. Muscle weakness is the most common symptom of motor nerve damage. Other symptoms may include painful cramps and fasciculations (uncontrolled muscle twitching visible under the skin), muscle loss, bone degeneration, and changes in the skin, hair, and nails. These more general degenerative changes also can result from sensory or autonomic nerve fiber loss.
Sensory nerve damage causes a more complex range of symptoms because sensory nerves have a wider, more highly specialized range of functions. Larger sensory fibers enclosed in myelin (a fatty protein that coats and insulates many nerves) register vibration, light touch, and position sense. Damage to large sensory fibers lessens the ability to feel vibrations and touch, resulting in a general sense of numbness, especially in the hands and feet. People may feel as if they are wearing gloves and stockings even when they are not. Many patients cannot recognize by touch alone the shapes of small objects or distinguish between different shapes. This damage to sensory fibers may contribute to the loss of reflexes (as can motor nerve damage). Loss of position sense often makes people unable to coordinate complex movements like walking or fastening buttons, or to maintain their balance when their eyes are shut. Neuropathic pain is difficult to control and can seriously affect emotional well-being and overall quality of life. Neuropathic pain is often worse at night, seriously disrupting sleep and adding to the emotional burden of sensory nerve damage.

Smaller sensory fibers without myelin sheaths transmit pain and temperature sensations. Damage to these fibers can interfere with the ability to feel pain or changes in temperature. People may fail to sense that they have been injured from a cut or that a wound is becoming infected. Others may not detect pains that warn of impending heart attack or other acute conditions. (Loss of pain sensation is a particularly serious problem for people with diabetes, contributing to the high rate of lower limb amputations among this population.) Pain receptors in the skin can also become oversensitized, so that people may feel severe pain (allodynia) from stimuli that are normally painless (for example, some may experience pain from bed sheets draped lightly over the body).

Symptoms of autonomic nerve damage are diverse and depend upon which organs or glands are affected. Autonomic nerve dysfunction can become life threatening and may require emergency medical care in cases when breathing becomes impaired or when the heart begins beating irregularly. Common symptoms of autonomic nerve damage include an inability to sweat normally, which may lead to heat intolerance; a loss of bladder control, which may cause infection or incontinence; and an inability to control muscles that expand or contract blood vessels to maintain safe blood pressure levels. A loss of control over blood pressure can cause dizziness, lightheadedness, or even fainting when a person moves suddenly from a seated to a standing position (a condition known as postural or orthostatic hypotension).

Gastrointestinal symptoms frequently accompany autonomic neuropathy. Nerves controlling intestinal muscle contractions often malfunction, leading to diarrhea, constipation, or incontinence. Many people also have problems eating or swallowing if certain autonomic nerves are affected.

What causes peripheral neuropathy?
Peripheral neuropathy may be either inherited or acquired. Causes of acquired peripheral neuropathy include physical injury (trauma) to a nerve, tumors, toxins, autoimmune responses, nutritional deficiencies, alcoholism, and vascular and metabolic disorders. Acquired peripheral neuropathies are grouped into three broad categories: those caused by systemic disease, those caused by trauma from external agents, and those caused by infections or autoimmune disorders affecting nerve tissue. One example of an acquired peripheral neuropathy is trigeminal neuralgia (also known as tic douloureux), in which damage to the trigeminal nerve (the large nerve of the head and face) causes episodic attacks of excruciating, lightning-like pain on one side of the face. In some cases, the cause is an earlier viral infection, pressure on the nerve from a tumor or swollen blood vessel, or, infrequently, multiple sclerosis. In many cases, however, a specific cause cannot be identified. Doctors usually refer to neuropathies with no known cause as idiopathic neuropathies.

Physical injury (trauma) is the most common cause of injury to a nerve. Injury or sudden trauma, such as from automobile accidents, falls, and sports-related activities, can cause nerves to be partially or completely severed, crushed, compressed, or stretched, sometimes so forcefully that they are partially or completely detached from the spinal cord. Less dramatic traumas also can cause serious nerve damage. Broken or dislocated bones can exert damaging pressure on neighboring nerves, and slipped disks between vertebrae can compress nerve fibers where they emerge from the spinal cord.

Systemic diseases - disorders that affect the entire body often cause peripheral neuropathy. These disorders may include: Metabolic and endocrine disorders. Nerve tissues are highly vulnerable to damage from diseases that impair the body's ability to transform nutrients into energy, process waste products, or manufacture the substances that make up living tissue. Diabetes mellitus, characterized by chronically high blood glucose levels, is a leading cause of peripheral neuropathy in the United States. About 60 percent to 70 percent of people with diabetes have mild to severe forms of nervous system damage.
Kidney disorders can lead to abnormally high amounts of toxic substances in the blood that can severely damage nerve tissue. A majority of patients who require dialysis because of kidney failure develop polyneuropathy. Some liver diseases also lead to neuropathies as a result of chemical imbalances.

Hormonal imbalances can disturb normal metabolic processes and cause neuropathies. For example, an underproduction of thyroid hormones slows metabolism, leading to fluid retention and swollen tissues that can exert pressure on peripheral nerves. Overproduction of growth hormone can lead to acromegaly, a condition characterized by the abnormal enlargement of many parts of the skeleton, including the joints. Nerves running through these affected joints often become entrapped.

Vitamin deficiencies and alcoholism can cause widespread damage to nerve tissue. Vitamins E, B1, B6, B12, and niacin are essential to healthy nerve function. Thiamine deficiency, in particular, is common among people with alcoholism because they often also have poor dietary habits. Thiamine deficiency can cause a painful neuropathy of the extremities. Some researchers believe that excessive alcohol consumption may, in itself, contribute directly to nerve damage, a condition referred to as alcoholic neuropathy.

Vascular damage and blood diseases can decrease oxygen supply to the peripheral nerves and quickly lead to serious damage to or death of nerve tissues, much as a sudden lack of oxygen to the brain can cause a stroke. Diabetes frequently leads to blood vessel constriction. Various forms of vasculitis (blood vessel inflammation) frequently cause vessel walls to harden, thicken, and develop scar tissue, decreasing their diameter and impeding blood flow. This category of nerve damage, in which isolated nerves in different areas are damaged, is called mononeuropathy multiplex or multifocal mononeuropathy.

Connective tissue disorders and chronic inflammation can cause direct and indirect nerve damage. When the multiple layers of protective tissue surrounding nerves become inflamed, the inflammation can spread directly into nerve fibers. Chronic inflammation also leads to the progressive destruction of connective tissue, making nerve fibers more vulnerable to compression injuries and infections. Joints can become inflamed and swollen and entrap nerves, causing pain.

Cancers and benign tumors can infiltrate or exert damaging pressure on nerve fibers. Tumors also can arise directly from nerve tissue cells. Widespread polyneuropathy is often associated with the neurofibromatoses, genetic diseases in which multiple benign tumors grow on nerve tissue. Neuromas, benign masses of overgrown nerve tissue that can develop after any penetrating injury that severs nerve fibers, generate very intense pain signals and sometimes engulf neighboring nerves, leading to further damage and even greater pain. Neurona formation can be one element of a more widespread neuropathic pain condition called complex regional pain syndrome or reflex sympathetic dystrophy syndrome, which can be caused by traumatic injuries or surgical trauma. Paraneoplastic syndromes, a group of rare degenerative disorders that are triggered by a person's immune system response to a cancerous tumor, also can indirectly cause widespread nerve damage.

Repetitive stress frequently leads to entrapment neuropathies, a special category of compression injury. Cumulative damage can result from repetitive, forceful, awkward activities that require flexing of any group of joints for prolonged periods. The resulting irritation may cause ligaments, tendons, and muscles to become inflamed and swollen, constricting the narrow passageways through which some nerves pass. These injuries become more frequent during pregnancy, probably because weight gain and fluid retention also constrict nerve passageways.

Toxins can also cause peripheral nerve damage. People who are exposed to heavy metals (arsenic, lead, mercury, thallium), industrial drugs, or environmental toxins frequently develop neuropathy. Certain anticancer drugs, anticonvulsants, antiviral agents, and antibiotics have side effects that can include peripheral nerve damage, thus limiting their long-term use.

Infections and autoimmune disorders can cause peripheral neuropathy. Viruses and bacteria that can attack nerve tissues include herpes varicella-zoster (shingles), Epstein-Barr virus, cytomegalovirus, and herpes simplex-members of the large family of human herpes viruses. These viruses severely damage sensory nerves, causing attacks of sharp, lightning-like pain. Postherpetic neuralgia often occurs after an attack of shingles and can be particularly painful.

The human immunodeficiency virus (HIV), which causes AIDS, also causes extensive damage to the central and
peripheral nervous systems. The virus can cause several different forms of neuropathy, each strongly associated with a specific stage of active immunodeficiency disease. A rapidly progressive, painful polyneuropathy affecting the feet and hands is often the first clinically apparent sign of HIV infection.

Lyme disease, diphtheria, and leprosy are bacterial diseases characterized by extensive peripheral nerve damage. Diphtheria and leprosy are now rare in the United States, but Lyme disease is on the rise. It can cause a wide range of neuropathic disorders, including a rapidly developing, painful polyneuropathy, often within a few weeks after initial infection by a tick bite.

Viral and bacterial infections can also cause indirect nerve damage by provoking conditions referred to as autoimmune disorders, in which specialized cells and antibodies of the immune system attack the body's own tissues. These attacks typically cause destruction of the nerve's myelin sheath or axon (the long fiber that extends out from the main nerve cell body).

Some neuropathies are caused by inflammation resulting from immune system activities rather than from direct damage by infectious organisms. Inflammatory neuropathies can develop quickly or slowly, and chronic forms can exhibit a pattern of alternating remission and relapse. Acute inflammatory demyelinating neuropathy, better known as Guillain-Barré syndrome, can damage motor, sensory, and autonomic nerve fibers. Most people recover from this syndrome although severe cases can be life threatening. Chronic inflammatory demyelinating polyneuropathy (CIDP), generally less dangerous, usually damages sensory and motor nerves, leaving autonomic nerves intact. Multifocal motor neuropathy is a form of inflammatory neuropathy that affects motor nerves exclusively; it may be chronic or acute.

**Inherited forms of peripheral neuropathy** are caused by inborn mistakes in the genetic code or by new genetic mutations. Some genetic errors lead to mild neuropathies with symptoms that begin in early adulthood and result in little, if any, significant impairment. More severe hereditary neuropathies often appear in infancy or childhood.

The most common inherited neuropathies are a group of disorders collectively referred to as Charcot-Marie-Tooth disease. These neuropathies result from flaws in genes responsible for manufacturing neurons or the myelin sheath. Hallmarks of typical Charcot-Marie-Tooth disease include extreme weakening and wasting of muscles in the lower legs and feet, gait abnormalities, loss of tendon reflexes, and numbness in the lower limbs.

**How is peripheral neuropathy diagnosed?**

Diagnosing peripheral neuropathy is often difficult because the symptoms are highly variable. A thorough neurological examination is usually required and involves taking an extensive patient history (including the patient's symptoms, work environment, social habits, exposure to any toxins, history of alcoholism, risk of HIV or other infectious disease, and family history of neurological disease), performing tests that may identify the cause of the neuropathic disorder, and conducting tests to determine the extent and type of nerve damage.

A general physical examination and related tests may reveal the presence of a systemic disease causing nerve damage. Blood tests can detect diabetes, vitamin deficiencies, liver or kidney dysfunction, other metabolic disorders, and signs of abnormal immune system activity. An examination of cerebrospinal fluid that surrounds the brain and spinal cord can reveal abnormal antibodies associated with neuropathy. More specialized tests may reveal other blood or cardiovascular diseases, connective tissue disorders, or malignancies. Tests of muscle strength, as well as evidence of cramps or fasciculations, indicate motor fiber involvement. Evaluation of a patient's ability to register vibration, light touch, body position, temperature, and pain reveals sensory nerve damage and may indicate whether small or large sensory nerve fibers are affected.

Based on the results of the neurological exam, physical exam, patient history, and any previous screening or testing, additional testing may be ordered to help determine the nature and extent of the neuropathy.

**Computed tomography, or CT scan**, is a noninvasive, painless process used to produce rapid, clear two-dimensional images of organs, bones, and tissues. X-rays are passed through the body at various angles and are detected by a computerized scanner. The data is processed and displayed as cross-sectional images, or "slices," of the internal structure of the body or organ. Neurological CT scans can detect bone and vascular irregularities, certain brain tumors and cysts, herniated disks, encephalitis, spinal stenosis (narrowing of the spinal canal), and other disorders.

**Magnetic resonance imaging (MRI)** can examine muscle quality and size, detect any fatty replacement of muscle
tissue, and determine whether a nerve fiber has sustained compression damage. The MRI equipment creates a strong magnetic field around the body. Radio waves are then passed through the body to trigger a resonance signal that can be detected at different angles within the body. A computer processes this resonance into either a three-dimensional picture or a two-dimensional "slice" of the scanned area.

**Electromyography (EMG)** involves inserting a fine needle into a muscle to compare the amount of electrical activity present when muscles are at rest and when they contract. EMG tests can help differentiate between muscle and nerve disorders.

**Nerve conduction velocity (NCV)** tests can precisely measure the degree of damage in larger nerve fibers, revealing whether symptoms are being caused by degeneration of the myelin sheath or the axon. During this test, a probe electrically stimulates a nerve fiber, which responds by generating its own electrical impulse. An electrode placed further along the nerve's pathway measures the speed of impulse transmission along the axon. Slow transmission rates and impulse blockage tend to indicate damage to the myelin sheath, while a reduction in the strength of impulses is a sign of axonal degeneration.

**Nerve biopsy** involves removing and examining a sample of nerve tissue, most often from the lower leg. Although this test can provide valuable information about the degree of nerve damage, it is an invasive procedure that is difficult to perform and may itself cause neuropathic side effects. Many experts do not believe that a biopsy is always needed for diagnosis.

**Skin biopsy** is a test in which doctors remove a thin skin sample and examine nerve fiber endings. This test offers some unique advantages over NCV tests and nerve biopsy. Unlike NCV, it can reveal damage present in smaller fibers; in contrast to conventional nerve biopsy, skin biopsy is less invasive, has fewer side effects, and is easier to perform.

**What treatments are available?**

No medical treatments now exist that can cure inherited peripheral neuropathy. However, there are therapies for many other forms. Any underlying condition is treated first, followed by symptomatic treatment. Peripheral nerves have the ability to regenerate, as long as the nerve cell itself has not been killed. Symptoms often can be controlled, and eliminating the causes of specific forms of neuropathy often can prevent new damage.

In general, adopting healthy habits—such as maintaining optimal weight, avoiding exposure to toxins, following a physician-supervised exercise program, eating a balanced diet, correcting vitamin deficiencies, and limiting or avoiding alcohol consumption—can reduce the physical and emotional effects of peripheral neuropathy. Active and passive forms of exercise can reduce cramps, improve muscle strength, and prevent muscle wasting in paralyzed limbs. Various dietary strategies can improve gastrointestinal symptoms. Timely treatment of injury can help prevent permanent damage. Quitting smoking is particularly important because smoking constricts the blood vessels that supply nutrients to the peripheral nerves and can worsen neuropathic symptoms. Self-care skills such as meticulous foot care and careful wound treatment in people with diabetes and others who have an impaired ability to feel pain can alleviate symptoms and improve quality of life. Such changes often create conditions that encourage nerve regeneration.

Systemic diseases frequently require more complex treatments. Strict control of blood glucose levels has been shown to reduce neuropathic symptoms and help people with diabetic neuropathy avoid further nerve damage. Inflammatory and autoimmune conditions leading to neuropathy can be controlled in several ways. Immunosuppressive drugs such as prednisone, cyclosporine, or azathioprine may be beneficial. Plasmapheresis—a procedure in which blood is removed, cleansed of immune system cells and antibodies, and then returned to the body—can limit inflammation or suppress immune system activity. High doses of immunoglobulins, proteins that function as antibodies, also can suppress abnormal immune system activity.

Neuropathic pain is often difficult to control. Mild pain may sometimes be alleviated by analgesics sold over the counter. Several classes of drugs have recently proved helpful to many patients suffering from more severe forms of chronic neuropathic pain. These include mexiletine, a drug developed to correct irregular heart rhythms (sometimes associated with severe side effects); several antiepileptic drugs, including gabapentin, phenytoin, and carbamazepine; and some classes of antidepressants, including tricyclics such as amitriptyline. Injections of local anesthetics such as lidocaine or topical patches containing lidocaine may relieve more intractable pain. In the most severe cases, doctors can surgically destroy nerves; however, the results are often temporary and the procedure can lead to complications.
Mechanical aids can help reduce pain and lessen the impact of physical disability. Hand or foot braces can compensate for muscle weakness or alleviate nerve compression. Orthopedic shoes can improve gait disturbances and help prevent foot injuries in people with a loss of pain sensation. If breathing becomes severely impaired, mechanical ventilation can provide essential life support.

Surgical intervention often can provide immediate relief from mononeuropathies caused by compression or entrapment injuries. Repair of a slipped disk can reduce pressure on nerves where they emerge from the spinal cord; the removal of benign or malignant tumors can also alleviate damaging pressure on nerves. Nerve entrapment often can be corrected by the surgical release of ligaments or tendons.

What research is being done?
The National Institute of Neurological Disorders and Stroke (NINDS), a component of the Federal government's National Institutes of Health (NIH) within the U.S. Department of Health and Human Services, has primary responsibility for research on peripheral neuropathy. Current research projects funded by the NINDS involve investigations of genetic factors associated with hereditary neuropathies, studies of biological mechanisms involved in diabetes-associated neuropathies, efforts to gain greater understanding of how the immune system contributes to peripheral nerve damage, and efforts to develop new therapies for neuropathic symptoms.

Because specific genetic defects have been identified for only a fraction of the known hereditary neuropathies, the Institute sponsors studies to identify other genetic defects that may cause these conditions. Presymptomatic diagnosis may lead to therapies for preventing nerve damage before it occurs, and gene replacement therapies could be developed to prevent or reduce cumulative nerve damage.

Several NINDS-funded studies are investigating some of the possible biological mechanisms responsible for the many forms of neuropathy, including the autonomic neuropathies that affect people with diabetes. The Institute also is funding studies to measure the frequency and progression rates of diabetic neuropathies, examine the effects of these disorders on quality of life, and identify factors that may put certain individuals at greater risk for developing diabetes-associated neuropathies.

Scientists have found that the destructive effects of abnormal immune system activity cause many neuropathies for which a cause could not previously be identified. However, the exact biological mechanisms that lead to this nerve damage are not yet well understood. Many NINDS-sponsored studies are studying inflammatory neuropathies, both in research animals and in humans, to clarify these mechanisms so that therapeutic interventions can be developed.

Neuropathic pain is a primary target of NINDS-sponsored studies aimed at developing more effective therapies for symptoms of peripheral neuropathy. Some scientists hope to identify substances that will block the brain chemicals that generate pain signals, while others are investigating the pathways by which pain signals reach the brain.

Studies of neurotrophic factors represent one of the most promising areas of research aimed at finding new, more effective treatments for peripheral neuropathies. These substances, produced naturally by the body, protect neurons from injury and encourage their survival. Neurotrophic factors also help maintain normal function in mature nerve cells, and some stimulate axon regeneration. Several NINDS-sponsored studies seek to learn more about the effects of these powerful chemicals on the peripheral nervous system and may eventually lead to treatments that can reverse nerve damage and cure peripheral nerve disorders.

Where can I get more information?
For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
(800) 352-9424
https://www.ninds.nih.gov

Information also is available from the following organizations:
American Chronic Pain Association (ACPA)
P.O. Box 850
This information was developed by the National Institute of Neurological Disorders and Stroke, National Institute of Health.


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