

PERIPHERAL

NEUROPATHY

Of the many symptoms associated with HIV/AIDS and its treatment, peripheral neuropathy (PN) can be among the most painful and debilitating. The most common estimate is that about one-third of people with AIDS experience some degree of nerve damage. However, PN usually occurs in the later stages of HIV disease, and many people experience mild or no symptoms. Nerve damage may be caused by HIV itself, by opportunistic infections (OIs) such as cytomegalovirus (CMV), or as a side effect of certain anti-HIV drugs, notably ddI (Videx), ddC (Hivid), and d4T (Zerit). In people with HIV/AIDS, PN most often affects the feet, the lower legs, and later the hands, causing numbness, tingling, and/or pain. Fortunately, there are medical treatments and other measures people with HIV/AIDS can take to ameliorate neuropathy symptoms and improve their quality of life.

WHAT IS PN?

Neuropathy refers broadly to disease or damage to the nerves. The nervous system is divided into two parts: the central nervous system (the brain and spinal cord) and the peripheral nervous system (the nerves that run from the spinal cord to the rest of the body). Peripheral neuropathy is damage to the peripheral nerves. The peripheral nervous system consists of sensory and motor neurons (nerve cells). Sensory neurons carry information about sensations (e.g., touch, pain, vibration, temperature) to the spinal cord and brain, while motor neurons send impulses from the brain and spinal cord to the muscles. Nerve damage impairs the signals sent to and from the brain and spinal cord.

Different types of sensory nerve fibers are responsible for transmitting different sensations. Large fibers are associated with vibration and proprioception (sense of position), while small fibers are associated with pain and temperature. The axons (extensions that conduct electrical impulses) of sensory neurons, which connect the nerve cell bodies near the spinal cord to receptors in the skin, may be quite long. For example, the sensory nerves that extend from the spinal cord to the foot can be three feet long. Axons are insulated with a fatty coating called myelin, which can be compared to the insulating covering of an electrical cord. Loss of the myelin sheath (demyelination) interferes with the ability of neurons to conduct impulses.

People with HIV/AIDS may experience a variety of different types of peripheral neuropathy. The most common is distal sensory polyneuropathy (DSP), a condition also known by various other names including distal symmetrical sensory neuropathy, distal sensory axonal polyneuropathy, distal sensory painful neuropathy, and predominantly sensory neuropathy. “Distal” refers to nerve damage farthest away from the spinal cord, that is, in the feet and hands. “Polyneuropathy” means that many nerves are affected. “Symmetrical” refers to symptoms that occur equally on both sides of the body. This

type of nerve damage is sometimes referred to as a “dying back” neuropathy, since axonal damage starts at the nerve endings in the extremities and progresses upwards toward the spinal cord. The longest nerves are affected first, thus symptoms typically are first noticed in the toes and soles of the feet.

Other types of PN seen in people with HIV/AIDS include acute or chronic inflammatory demyelinating polyneuropathy (AIDP or CIDP, respectively), progressive polyradiculopathy, mononeuropathy (or mononeuritis) multiplex, and diffuse infiltrative lymphocytosis syndrome (DILS).

AIDP (also known as Guillain-Barré Syndrome [GBS]) is sometimes seen in people with primary HIV disease immediately following infection. It is a rapidly progressing, potentially fatal condition characterized by myelin inflammation, mild sensory loss, and severe motor loss or paralysis. GBS usually occurs soon after an infection or immunization; some experts believe it is an autoimmune condition in which the immune system produces antibodies that attack the neurons’ myelin sheaths. Polyradiculopathy (inflammation of nerve roots near the spinal cord) may result from CMV infection in the nerve roots, and can lead to rapidly progressing motor and sensory nerve damage, usually accompanied by pain. Mononeuropathy multiplex affects individual peripheral nerves, sometimes including nerves of the face. DILS is a condition associated with immune cell (typically CD8 cell) infiltration of neurons, which can result in various different types of neuropathy.

Because it is the most common type of HIV/AIDS-related neuropathy, “peripheral neuropathy” and “PN” will be used to refer to DSP or drug-related neuropathy throughout the rest of this article unless otherwise stated.

PN INCIDENCE

Most experts estimate that about 30% of people with HIV/AIDS experience PN at some point during the course of their illness. Of those who do, many experience only mild symptoms. DSP is more common and more severe in people with later-stage HIV disease, but

nerve conduction studies show abnormalities in a majority of people with HIV. At the 5th Conference on Retroviruses and Opportunistic Infections (CROI) held in Chicago in February 1998, Walter G. Bradley, DM, FRCP, of the University of Miami School of Medicine and colleagues presented a stage model of PN in people with HIV/AIDS, noting that HIV/AIDS-related PN is “highly stage-specific” (i.e., different types of PN tend to occur at different stages of HIV disease). Early in HIV disease, people may experience AIDP, CIDP, and various mononeuropathies. DSP is most common in middle and late stages, with incidence increasing as immune system damage progresses. Also in the later stages of HIV, people may develop neuropathies related to OIs, such as CMV-related polyradiculopathy and herpes-related ganglion (a group of nerve cell bodies located outside the central nervous system) inflammation.

Neuropathy expert Justin McArthur, MBBS, MPH, of Johns Hopkins University in Baltimore, gave a presentation on HIV/AIDS-related neuropathy at the 8th CROI in Chicago in February 2001. He stated that the single most important predictive risk factor for developing HIV/AIDS-related sensory neuropathy is viral load “set point,” that is, the viral load level before antiretroviral treatment is started. The higher the “set point,” the greater the chance of developing PN. Lower CD4 cell counts, older age, and the presence of wasting syndrome also are associated with an increased risk of neuropathy in people with HIV/AIDS.

There is evidence that typically reported figures underestimate the true incidence of HIV/AIDS-related neuropathy. Electrophysiological studies and anatomical examination during autopsies reveal high rates of subtle nerve damage. According to Dr. Bradley, “pathologic evidence of peripheral nerve involvement is present in virtually all terminal AIDS cases.” However, this damage is often subclinical, that is, it may not cause any noticeable symptoms.

PN appears to occur at similar rates in men and women with HIV/AIDS. Early in the epidemic, some experts believed neuropathy was uncommon in

HIV-infected children, but this assumption may have resulted from underdiagnosis of the condition in children too young to report symptoms. More recently, Alexandra Prufer de Q.C. Araújo and colleagues from the Federal University of Rio de Janeiro in Brazil have shown, using more careful physiological testing, that approximately 25–30% of children with HIV/AIDS experience PN—about the same rate as adults.

SYMPTOMS OF PN

Because the peripheral nerves relay sensations to the brain, people with PN often experience altered sensations, or paresthesias (described below). Some people experience minor symptoms that are unpleasant but do not interfere with daily life. Others are more seriously disabled, and may have trouble balancing when standing or walking, or difficulty maintaining a grip on objects. Many people with early or mild PN do not experience any symptoms and, again, the worst symptoms generally occur in people with more advanced immunosuppression (lower CD4 cell counts). Symptom progression may be very gradual, or may worsen rapidly over a period of days or weeks.

Paresthesias may include numbness, tickling, tingling, prickling, hypersensitivity, burning, pain, or a “pins and needles” feeling (the sensation of a limb “falling asleep”). Often people experience minor tingling or numbness at first, followed by more painful sensations as nerve damage progresses. Some people describe a loss of sensation, as if they were wearing stockings and gloves. Pain may range from mild to severe; some people describe the pain as feeling like frostbite or like walking on hot coals. Many people (70% in one study) report that their pain is more severe at night, which may lead to difficulty sleeping.

In people with DSP, symptoms are typically symmetrical, that is, experienced equally on both sides of the body.

In most people with HIV/AIDS, altered sensations and pain occur first in the toes and soles of the feet, as noted previously; then, as nerve injury progresses, pain and numbness may extend to the ankles. Sometimes the fingers, hands, and wrists are also involved. Although uncommon, pain above the ankles indicates advanced nerve damage.

Since the peripheral nerves also send motor signals from the spinal cord to the limbs, PN can lead to muscle weakness, although this is much less common than sensory symptoms. Most people with PN have reduced or absent ankle reflexes (involuntary responses to a stimulus).

CAUSES OF PN

Many factors can contribute to nerve damage, including physical injury or trauma, genetic factors, infectious diseases, exposure to toxic substances (e.g., alcohol, drugs, heavy metals, solvents), and metabolic disorders (e.g., thyroid dysfunction, diabetes). But in people with HIV/AIDS, PN is usually due to the effects of the virus itself on nerve cells, immune system activity associated with HIV, nerve damage related to OIs, or drugs used to treat HIV disease and related conditions.

Although studies have produced conflicting data, most experts believe that HIV does not directly infect neurons. However, the virus activates immune system cells (e.g., macrophages, T lymphocytes), which can infiltrate the nerve cells and produce inflammatory substances (cytokines) that damage nerves and/or their myelin sheaths. Dr. McArthur has put forth the hypothesis that inflammation within the dorsal root

ganglia and peripheral nerves leads to axonal degeneration, especially of small, unmyelinated nerve fibers. This then leads to changes in the pain-processing portion of the spinal cord. He suggests that this can result in hyperexcitability (increased sensitivity) of sensory neurons and abnormal nerve fiber maintenance, which can lead to pain and paresthesias.

OI-related neuropathy may be caused by CMV, varicella zoster virus (shingles), or other herpesviruses. Viruses of this family live in the nerves, and can cause inflammation (neuritis, ganglionitis) and permanent nerve damage. This type of PN has become less common as more effective antiretroviral regimens have reduced the incidence of OIs in people with HIV/AIDS.

PN is often seen in people with diseases other than HIV/AIDS. Diabetics commonly experience nerve damage in various parts of the body (especially the feet); this damage is associated with high blood sugar (glucose) levels. HIV/AIDS-related DSP can be distinguished from diabetic sensory neuropathy in that it affects axons of all sizes. Heavy alcohol drinkers and people with certain nutritional deficiencies may also suffer nerve damage. Diabetes and alcoholism are the most common causes of PN in the U.S., while the most common cause worldwide is Hansen’s disease (leprosy). People with HIV/AIDS who have other risk factors for nerve damage (e.g., diabetes, low vitamin B₁₂ levels, thyroid dysfunction, heavy alcohol consumption) are more likely to experience PN. According to Dr. McArthur, about 50% of people with HIV/AIDS who present with sensory neuropathy symptoms have some other contributing factor in addition to HIV itself, most often drug toxicity related to antiretroviral medications.

In people with HIV/AIDS, PN is usually due to the effects of the virus itself on nerve cells, immune system activity associated with HIV, nerve damage related to OIs, or drugs used to treat HIV disease and related conditions.

PN AS A DRUG SIDE EFFECT

As effective antiretroviral therapy has delayed HIV disease progression and reduced the incidence of OIs, drug toxicity may now be the most common cause of PN in people with HIV/AIDS in developed countries. The type of nerve damage and the symptoms seen in drug-related, or neurotoxic, neuropathy are similar to DSP. As mentioned

previously, neurotoxic neuropathy is most often associated with the nucleoside reverse transcriptase inhibitor (NRTI) drugs ddI, ddC, and d4T; these drugs are known as dideoxynucleosides, and are sometimes referred to as the “d-drugs.” 3TC (Epivir), AZT (Retrovir), and abacavir (Ziagen), although also NRTIs, are associated with lower rates of PN. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) are not typically

associated with PN. Several drugs used to treat HIV-related OIs are also known to cause neuropathy, including dapsone, ethambutol (Myambutol), isoniazid, and metronidazole (Flagyl). (See Table 1.) In addition, human growth hormone (used to treat AIDS-related wasting and lipodystrophy) is associated with carpal tunnel syndrome, in which the median nerve is “entrapped” at the wrist and compressed.

Symptoms of drug-related PN may begin immediately after starting one of the offending drugs, but usually occur after taking a drug for several weeks. People who experienced mild neuropathy or who had subclinical nerve damage prior to starting the drug may experience intensified symptoms. Those who have other risk factors for nerve damage should use these drugs cautiously with careful monitoring, or avoid them altogether. Neuropathy symptoms usually improve after the associated drug is stopped, although this may take several weeks or months.

In some early studies the rate of PN in people taking ddI or ddC was as high as 40–50%. The incidence of drug-related PN has decreased since the dideoxynucleoside drugs are now used in lower doses in combination regimens. (Early in the epidemic, the “d-drugs” were used in higher doses, sometimes as monotherapy.) In the December 1998 issue of *Drug Safety*, Graham Moyle, MD, and colleagues estimated that 10% of people taking ddC or d4T and 1–2% of those taking ddI may have to discontinue the drug due to neuropathy. Combining more than one of the “d-drugs” substantially increases the risk of developing PN. According to Dr. McArthur, using a three-drug regimen containing d4T as the only “d-drug” leads to about the same rate of PN as a three-drug regimen that excludes all “d-drugs” (about 8%). But using ddI and d4T together increases the incidence of PN nearly three-fold, and adding hydroxyurea (Hydrea) raises the rate even further. (See Table 2.) While the exact mechanism by which the “d-drugs” cause PN is unknown, most experts believe that drug-induced mitochondrial toxicity may play a role; the drugs may

DRUGS ASSOCIATED WITH PN

- ddC** (zalcitabine; brand name Hivid)
- ddI** (didanosine; brand name Videx)
- d4T** (stavudine; brand name Zerit)
- 3TC** (lamivudine; brand name Epivir)
- dapsone**—used to prevent and treat *Pneumocystis carinii* pneumonia (PCP)
- disulfiram** (Antabuse)—used to prevent alcohol abuse
- ethambutol** (Myambutol)—used to treat *Mycobacterium avium* complex (MAC) and tuberculosis
- isoniazid** (INH)—used to treat tuberculosis
- metronidazole** (Flagyl)—used to treat gastrointestinal parasites and various fungal and bacterial infections
- paclitaxel** (Taxol)—used to treat certain cancers
- thalidomide** (Thalomid)—used to treat wasting, certain cancers, and oral aphthous ulcers
- vincristine** (Oncovin)—used to treat certain cancers, including Kaposi’s sarcoma (KS) and lymphoma

RATES OF PN FOR VARIOUS ANTIRETROVIRAL REGIMENS

ddl/d4T:	21%
ddl/d4T/indinavir (Crixivan):	21%
ddl/d4T/hydroxyurea:	26%
ddl-EC*/d4T:	20%
ddl-EC*/d4T/nelfinavir (Viracept):	20%
d4T/3TC/indinavir:	8%
AZT/3TC/nelfinavir:	8%

*ddl-EC is the newer enteric-coated (buffered) formulation of ddl
(Adapted from Justin McArthur, 8th CROI, 2001)

A *effective antiretroviral therapy has delayed HIV disease progression and reduced the incidence of OIs, drug toxicity may now be the most common cause of PN in people with HIV/AIDS in developed countries.*

interfere with mitochondrial DNA synthesis. (Mitochondria are organelles within cells that produce energy.)

Finally, animal studies of drug-related nerve damage are contradictory. T.D. Anderson and colleagues from Hoffmann-La Roche reported in 1992 that ddC caused both axonal damage and demyelination of rabbit neurons. However, Dr. McArthur found that rats exposed to high concentrations of ddC showed no nerve fiber degeneration.

It can be very difficult to determine whether PN is drug-related or directly related to HIV/AIDS. Experts urge further research to develop tests that distinguish these types of PN, so that effective HIV treatment regimens will not be unnecessarily abandoned in an attempt to ameliorate neuropathy.

DIAGNOSING PN

Peripheral neuropathy is usually diagnosed clinically on the basis of reported symptoms. However, physiological tests may be done to determine the extent of nerve damage and to attempt to pinpoint its cause. Physicians may test responses to pinpricks, temperature, or vibration. They may also test for the loss of ankle reflexes. The same tests may be done periodically to show whether nerve damage is progressing. Tests often reveal evidence of sub-clinical PN before a person experiences symptoms.

More sophisticated tests measure electrical conductance (nerve conduction studies). These tests can reveal nerve damage well before symptoms are present. Some physicians may recommend a biopsy, in which a small sample of tissue is surgically removed, stained, and examined under a microscope. Dr. McArthur and colleagues have

developed a skin-punch biopsy technique that can help ascertain patterns of nerve damage and the types of nerve fibers involved. But, says Dr. McArthur, a biopsy is usually not necessary unless a diagnosis is uncertain. Electrical studies and biopsies are most likely to be done in an effort to determine the specific type of nerve damage (for example, axonal damage vs demyelination) or to rule out other conditions.

Physicians may measure blood glucose levels, vitamin B₁₂ (cobalamin) levels, thyroid function, and other laboratory values to rule out alternative causes of PN. Drug-related PN is generally suspected if a person is taking ddC, ddl, or d4T. If the offending drug is discontinued and neuropathy symptoms persist, the physician may then look for other causes.

Other conditions that may cause similar symptoms and that should be considered in a differential diagnosis include myopathy (muscle damage), vasculitis (blood vessel inflammation), and tarsal tunnel syndrome (the lower extremity equivalent of carpal tunnel syndrome, in which a nerve is “entrapped” and compressed). Syphilis and vitamin B₆ toxicity can also cause symptoms that resemble those of PN. If a person has multiple conditions associated with neuropathy (for example, HIV infection, diabetes, and alcoholism), it can be difficult to tell how much each condition is contributing to nerve damage.

MANAGING PN

A variety of measures can help relieve the symptoms of PN. Which of these are most effective will depend on the cause of the nerve damage and the severity of symptoms. People experiencing PN should tell their health-care

providers about any changes in their symptoms. Sometimes it will take a certain amount of experimentation on the part of a person with PN and his or her health-care provider(s) to determine what strategies work best. Addressing PN early can help avoid long-term—even permanent—nerve damage.

CHANGING DRUGS

As noted previously, neuropathy that occurs as a drug side effect may be relieved by discontinuing or adjusting doses of drugs known to cause nerve damage. Usually PN symptoms improve when the offending drug is stopped, although this may take 4–8 weeks or longer (a phenomenon known as “coasting”). In an estimated 25% of people, PN symptoms worsen immediately after stopping a drug, before they improve. In rare cases, nerve damage may be permanent and symptoms may persist long after a drug is stopped. *Always consult a physician before stopping, changing, or adjusting doses of any drug.* Drugs from the same drug class (i.e., exchanging a nondideoxynucleoside NRTI for a “d-drug”) or a different class (i.e., exchanging an NNRTI for a “d-drug”) can often be substituted in a regimen.

DRUGS FOR PN PAIN

Currently no drugs are approved by the U.S. Food and Drug Administration (FDA) specifically to treat HIV/AIDS-related PN. Because treatment of HIV/AIDS-related neuropathic pain is an “off-label” use for existing drugs (that is, a use other than that for which the drug was approved), insurance companies may deny coverage.

Certainly, if neuropathy is related to an OI such as CMV, treatment of the

OI should be the first consideration. Beyond that, many different treatments are regularly used to relieve pain due to PN.

Various drugs have been shown in studies to provide relief for some people with neuropathy. But study results are often contradictory. Dr. McArthur notes that the subjective pain scales used in many PN clinical trials may not be a good measure of how well a drug works, since they may be too imprecise to measure small treatment effects. Many drug studies have been done in people with diabetic neuropathy, not HIV/AIDS-related PN; drugs that work for one condition do not always work as well for the other. According to Dr. McArthur, there are no consistent patient or symptom characteristics that predict how well a treatment might work. Therefore, physicians may have to try several different medications before finding the one(s) that work best for a specific individual.

For mild cases of PN pain, over-the-counter analgesics (pain relievers) such as acetaminophen (Tylenol) or ibuprofen (Advil) may be helpful. Topical preparations (those applied to the skin surface) include capsaicin cream (Zostrix) derived from hot peppers, topical aspirin preparations, and lidocaine gel.

For moderate neuropathic pain, tricyclic antidepressants (named for their molecular structure that includes three benzene rings) are often used. These include amitriptyline (Elavil), desipramine (Norpramin), imipramine (Tofranil), and nortriptyline (Aventyl, Pamelor). Amitriptyline is used most often, although Dr. McArthur notes that the drug had “no statistically significant effect on neuropathic pain” in two large controlled trials. Antidepressants may take 2–3 weeks to bring relief, and seem to work best in combination with pain relievers. Although tricyclic antidepressants do not appear actually to reduce pain, experts believe they affect how the brain processes pain and people who take them seem to suffer less. Side effects of the tricyclics may include sleepiness, dry mouth, and urinary retention; many find the drugs easier to tolerate if taken at bedtime.

Several anticonvulsant (antiseizure) medications including carbamazepine

(Tegretol), clonazepam (Klonopin), gabapentin (Neurontin), and lamotrigine (Lamictal) have also shown some success in treating PN pain. Side effects may include sedation, gastrointestinal upset, skin rash, and liver dysfunction. David M. Simpson, MD, and colleagues from Mount Sinai Medical Center in New York City and Johns Hopkins University in Baltimore reported in the June 13, 2000 issue of *Neurology* that lamotrigine significantly reduced neuropathic pain in a small, 14-week study of people with HIV/AIDS-related DSP; a larger study is underway.

Another medication that has been used to relieve neuropathic pain is the heart arrhythmia drug mexiletine (Mexitil). Studies in diabetics and people with HIV/AIDS-related neuropathy have yielded mixed results. An electrocardiogram (EKG) heart rhythm test should be done before a person is started on mexiletine.

For severe neuropathic pain, narcotic analgesics (a class of drugs derived from the opium poppy) may be necessary. These include codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and the fentanyl transdermal patch (Duragesic). Of these, Dr. McArthur recommends methadone, sustained-release morphine, and the fentanyl patch. Several weeks may pass before improvement is apparent.

Under-treatment of chronic pain is common in the U.S. due to strict regulations on the use of narcotic drugs and fears that people will become addicted. However, many experts assert that addiction is unlikely when narcotics are used to treat pain. People with severe neuropathic pain may benefit from working with a pain management specialist.

Psychotropic (affecting psychological or mental functioning or behavior) and narcotic drugs may interfere with antiretroviral medications, potentially leading to suboptimal dosing or intensified side effects. People with HIV/AIDS-related PN should work with an experienced medical practitioner and make sure that every provider they see knows about all the drugs they are taking.

REGENERATING DAMAGED NERVES

While analgesics, antidepressants, and anticonvulsants may help relieve PN pain, they do not address the underlying nerve damage. Many experts have expressed hope that treatments can be developed to regenerate damaged nerves. Recombinant human nerve growth factor (rhNGF) is one such drug. It is a genetically engineered form of the body's natural nerve growth factor, which promotes the growth and survival of neurons. RhNGF is manufactured by Genentech of South San Francisco, CA. RhNGF has been tested in several studies of participants with both diabetic and HIV/AIDS-related neuropathy. In a study of 250 diabetic participants, PN symptoms improved in those receiving rhNGF compared with those receiving a placebo, although symptoms returned when participants stopped taking the drug.

Results of the major study of rhNGF in people with HIV/AIDS (ACTG 291) were reported in the March 14, 2000 issue of *Neurology*. Dr. McArthur and colleagues studied 270 participants with HIV/AIDS-related sensory neuropathy. Participants who received 0.1 or 0.3 mcg/kg of rhNGF twice daily for 18 weeks reported a subjective improvement in pain compared with those receiving a placebo. Quantitative tests showed greater pinprick sensitivity, but biopsies did not show an increase in nerve fiber density. The major adverse event was pain at the injection site in half of those receiving the higher dose of rhNGF. The same ACTG 291 research team reported longer-term (48-week) results from an open-label study of 200 people with HIV/AIDS-related DSP in the October 9, 2001 issue of *Neurology*. They found that participants reported a decrease in pain symptoms, but that there was no improvement in terms of neurologic examinations, quantitative sensory testing, or nerve fiber density measurements.

Despite these promising results, rhNGF may not be available to consumers anytime soon. Genentech decided in April 1999 to discontinue development

RESOURCES

of rhNGF, purportedly because of less than expected efficacy in diabetic neuropathy trials. However, according to Giovanni Schifitto, MD, of the University of Rochester, NY, a member of the ACTG 291 team, "The response to NGF in diabetic sensory neuropathy and HIV-associated sensory neuropathy are not necessarily comparable, because the pathological mechanisms involved may differ. Therefore, the negative results of the Phase III diabetic neuropathy study should not be extrapolated to HIV sensory neuropathy."

Dr. McArthur believes that a class of compounds called neurophilins may also ameliorate nerve damage. These drugs are related to immunosuppressive drugs such as cyclosporine, but do not suppress the immune response. In laboratory and animal studies, neurophilins have been shown to stimulate nerve fiber growth and repair; human studies are planned.

NONPHARMACOLOGICAL THERAPIES

Various nonpharmacological therapies also are used to manage neuropathic pain. Acupuncture is recognized in some cultures as an effective pain-relieving therapy. According to San Francisco acupuncturist Mark Denzin, in Chinese medicine nerve pain is caused by "disharmony in the liver." (He says that treatment of neuropathic pain is "directed toward purging the liver fire, protecting the kidney essence and heart Yin, and reducing the pain with appropriate herbs.") Several studies have looked at acupuncture for neuropathic pain. In the largest trial of HIV/AIDS-related PN, Judith Shlay, MD, and colleagues from the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) conducted a randomized, placebo-controlled trial of acupuncture and amitriptyline in 250 people with HIV/AIDS-related neuropathy. The acupuncture component involved several spleen and kidney points. Participants kept pain diaries using the Gracely Pain Scale. The researchers found that neither acupuncture nor the drug was more effective than a placebo in relieving neuropathic pain. Study results were published in the

The Neuropathy Association:

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The Neuropathy Trust (UK): www.neuropathy-trust.org

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November 11, 1998 issue of the *Journal of the American Medical Association*. However, several smaller acupuncture studies have shown more promising results, and positive anecdotal reports from people with HIV/AIDS-related PN suggest that this therapy may be worth trying.

For inflammatory demyelinating neuropathies such as GBS and CIDP, plasmapheresis may be used. In this process, blood plasma is removed, filtered, and returned to the body. Intravenous gamma globulin (IVIG), an injected antibody preparation, is sometimes used with plasmapheresis. Several studies of plasmapheresis and IVIG were conducted in the late 1980s and early 1990s. Plasmapheresis appears to work by filtering out antibodies that attack and damage neurons, but many people relapse soon after treatment. Plasmapheresis and IVIG are not useful for DSP.

Numerous other nonpharmacological methods sometimes are used to relieve neuropathic pain. Among those discussed by John A. Senneff in his recent book *Numb Toes and Aching Soles: Coping with Peripheral Neuropathy* are transcutaneous electrical nerve stimulation (TENS), biofeedback (a technique in which people are trained to control their physiological responses using signals from their own bodies), and physical therapy. In cases of severe, intractable

neuropathic pain, a nerve block may be done; in this procedure, lidocaine or a similar anaesthetic is injected into a nerve "upstream" of the painful area.

NUTRITIONAL STRATEGIES

Although little research has been done on nutritional therapy for people with HIV/AIDS-related neuropathy, some research in diabetics suggests that nutrition may play a role in preventing and treating PN symptoms. However, because HIV/AIDS-related neuropathy differs in some ways from diabetic neuropathy, the effects of nutritional therapies in diabetics and people with HIV/AIDS may not be the same.

In her book *Positively Well: Living with HIV as a Chronic, Manageable, Survivable Disease*, Lark Lands, PhD, discusses nutrition as part of an integrated program of HIV disease management. In addition to being a well-known writer on HIV/AIDS, Dr. Lands (who is herself diabetic) is also well versed in diabetic neuropathy. For people with HIV/AIDS-related PN, she recommends a nutritional program that includes adequate B vitamins, L-acetyl-carnitine, alpha-lipoic acid, gamma-linolenic acid, chromium, and magnesium. Potentially useful B vitamins include biotin, choline, inositol, cobalamin (B₁₂), folic acid (B₉), niacin (B₃), pyridoxine (B₆), and thiamin

(B₁), which promote proper nerve function. Both cobalamin deficiency and vitamin E deficiency are associated with neuropathy. Pyridoxine plays a seemingly contradictory role: deficiency can lead to nerve degeneration, but large doses can have a neurotoxic effect; people should not take more than the recommended dose of this vitamin. Biotin, choline, inositol, and thiamin have been found to be useful in treating diabetic neuropathy. According to Dr. Lands, a study conducted at the University of Alabama showed a statistically significant improvement in nerve function in diabetics who ate a diet high in inositol (including foods such as cantaloupe, peanuts, and whole grains); use of inositol supplements reportedly also has had good results.

Alpha-lipoic acid, also known as thioctic acid, is a coenzyme (an organic molecule required for the function of certain enzymes) that acts as an antioxidant. It has been studied in Europe as a treatment for diabetic peripheral neuropathy, and in Germany it is approved for this indication. Studies suggest that it may protect the nerves from oxidative damage related to HIV infection. Gamma-linolenic acid is an essential fatty acid that has been shown in European studies to improve PN symptoms in diabetics. It is a component of herbal remedies such as grape seed oil and evening primrose oil.

Several studies have been done on L-acetyl-carnitine, an amino acid that may have a neuroprotective effect. Dr. Lands notes that people with HIV/AIDS commonly have a carnitine deficiency. Giuseppe Famularo, MD, and colleagues from the University of L'Aquila in Italy found that study participants who developed PN while taking ddC, ddI, or d4T had low acetyl-carnitine levels. The researchers suggested that "the depletion of acetyl-carnitine, which regulates the metabolism and function of peripheral nerves, could contribute to the neurotoxicity of these compounds." Also, at the 3rd International Workshop on Salvage Therapy for HIV Infection in April 2000, Michael Youle, MD, and colleagues from the Royal Free Center for HIV Medicine in London reported the

results of a very small study of L-acetyl-carnitine supplementation in people with neurotoxic PN. The researchers administered 1,500 mg of L-acetyl-carnitine twice daily for six months to five HIV positive participants with drug-related PN. Participants reported a decrease in neuropathic symptoms, and biopsies showed an increase in the growth of nerve fibers. However, a study by Dr. McArthur and colleagues reported in the November 9, 2001 issue of *AIDS* showed no association between carnitine levels in the blood and severity of HIV/AIDS-related PN. Dr. McArthur's team concluded that their results "do not provide support for a role of carnitine deficiency in the pathogenesis of peripheral neuropathy associated with HIV or [ddI] therapy."

SUPPORTIVE MEASURES

Various supportive measures also can play a role in reducing the severity of PN symptoms. Many experts recommend avoiding tight socks, stockings, shoes, and gloves. It is important to maintain a comfortable temperature in the extremities, so people should wear thick socks, slippers, and warm footwear when it is cold, and sandals when it is warm. People who are bothered by PN pain at night can try keeping their feet uncovered while sleeping or using some sort of prop to make a "tent" over their feet to avoid the pressure caused by direct contact with bedclothes.

As much as possible, people with PN should try not to walk long distances or stand for long periods of time. On the other hand, moderate walking can help improve blood flow to the feet and may improve symptoms. Some people find that soaking their feet in cold water relieves neuropathic pain. Others find warm baths helpful. Some people report that massage of the feet and legs also brings relief.

People with HIV/AIDS who are experiencing neuropathy symptoms should work closely with their medical providers to find the combination of medical treatments and supportive therapies that works best for them.

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