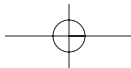
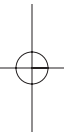
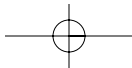
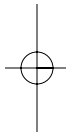
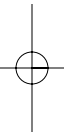
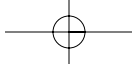


*Part VI*

Symptoms Secondary to  
Cancer and  
Its Treatment





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## Peripheral Neuropathy

ARTHUR FORMAN

Peripheral neuropathy in cancer patients causes significant morbidity and limits dose intensification of drugs such as vincristine, cisplatin, paclitaxel (Taxol), and docetaxel (Taxotere). Considerable advances have been made in understanding the mechanisms of peripheral nerve disorders during the past 25 years, yet clinical oncologists are often frustrated in dealing with neuropathy, perhaps as a result of its protean manifestations, insidious symptomatology, and confusing classification.

### INCIDENCE

Cancer patients are so frequently affected by peripheral nerve disorders that absent deep tendon ankle reflexes are almost considered routine on examination. In a series of lung cancer patients, 48% had clinically evident peripheral neuropathy, most of them before receiving chemotherapy (Teräväinen and Larsen, 1977). In another study of 195 Eastern Indian patients without other known causes of neuropathy and with untreated tumors of diverse types, neuromuscular signs were found in 30%; the highest incidence was in patients with cancers of bronchogenic, ovarian, or testicular origin (Paul et al., 1978). Only alcohol, nutritional deficiencies, and metabolic disturbances such as diabetes are acquired causes of peripheral neuropathy that occurs more frequently than in cancer. Peripheral neuropathies in cancer patients will become even more common as new treatments and longer survivals are achieved.

Confounding evaluation of neuropathy in a cancer patient are the multitude of injuries the peripheral nerves may acquire and the host of potential neuropathy risks to which patients are exposed. These include treatment with multiple cytotoxic drugs, deleterious drug interactions, pre-existing diabetes mellitus, and acquired nutritional and metabolic disturbances caused by the cancer as well as its treatment.

### MORBIDITY

The clinical severity of neuropathy in cancer patients ranges from mild distal paresthesias, to ataxia severe enough to keep patients bed bound, to rare muscle-wasting syndromes sufficient to compromise breathing. It may be that most patients with peripheral neuropathy are not incapacitated enough to have decreased performance status, yet neuropathy remains a frequent reason that oncologists seek neurologic consultation. Peripheral neuropathy's consequences can be devastating; the morbidity associated with toxic treatment-related neuropathies certainly contributes to the suffering associated with cancer and can even be the limiting factor in the amount of therapy that can be given (Legha and Dimery, 1985). More patients suffer some morbidity from neuromuscular disease than are given the benefit of neurologic consultation, perhaps because the manifestations of neuropathy are mistaken for other conditions or because it is thought that little can be done to help.

Any understanding of peripheral nerve disorders in oncology must be grounded in a basic under-

standing of their general principles, a brief review of which follows.

## CLINICAL FEATURES

### Sensory

Peripheral sensory nerves have their cell bodies in the dorsal root ganglion, which lie outside the protective mechanisms of the central nervous system (CNS) and are therefore particularly susceptible to injury. Sensory complaints are often the first symptoms in cancer patients with neuropathy.

Neuropathic pain is a common symptom, more frequently seen in neuropathies predominantly affecting axons. The pain may have an electric or lancinating quality, but more often patients bitterly complain of chronic perversions of sensation such as "burning" or, oxymoronically, "painful numbness." Hyperpathia, increased sensitivity to stimuli so that mild stimuli (e.g., the weight of bed linens on legs) become noxious, is commonly experienced by patients with peripheral neuropathy. Acroparesthesia, or the stocking-glove distribution "tingling" numbness, is often the earliest and most persistent symptom. Great care must be exercised in distinguishing radicular or myelopathic paresthesiae from those due to neuropathy. Focusing on the quality of the symptoms, which unfortunately are not distinctive, yet are often the main concern of the patient, may lead to diagnostic errors. The symptom's distribution for cord or root disease will often have a characteristic anatomic pattern, whereas neuropathic symptoms typically have a stocking-glove and, with rare exception, distal appendicular predominance.

The clinical evaluation of sensation is the most exacting component of the neurologic examination, requiring both patience and skill on the part of the examiner. Complicating the examination is the heterogeneity of nerve fibers, with different-sized fibers having different functions and susceptibility to injury (Table 17-1). Proprioceptive axons and those serving the afferent limb of deep tendon reflex arcs are of similar size so that both functions are often lost concurrently. The clinical signs observed with large fiber dysfunction are reliable and can be quickly assessed so that these axons' physiology can usually be well documented. Romberg's sign, which is considered positive when a patient who is able to stand with feet together and eyes open loses balance when visual cues are taken away, indicates moderate to severe proprioceptive loss. When asked, patients with proprioceptive loss often note difficulty negotiating steps in the dark or shampooing their hair in the shower when closing their eyes.

Paradoxically, motor signs and symptoms are prominent in patients with relatively pure sensory neuropathies, and the degree to which sensory impairment contributes to reflex attenuation, weakness, or incoordination is often underestimated. Difficulty with walking can be the result of the loss of proprioceptive fibers; the loss of spindle afferents in the motor reflex arc causes loss of deep tendon reflexes independently from significant muscle wasting or weakness. Patients complaining of trouble tying shoes or buttoning buttons likely have proprioceptive loss, which causes their decreased fine motor control. The restless leg syndrome, in which patients with neuropathy complain of aching calves relieved by moving the limbs, may be caused by sensory fiber disease. These curiously compelling symptoms

**Table 17-1.** Size and Function Relationships in Peripheral Nerves

<i>Conduction Fiber Size (<math>\mu\text{m}</math>)</i>	<i>Fiber Type</i>	<i>Velocity (m/sec)</i>	<i>Function</i>
10-18	A	70	$\alpha$ -Motor neuron; first-degree spindle afferents
6-12	A	50	Touch and pressure afferents
4-8	A	30	$\gamma$ -Efferents; second-degree spindle afferents
2-6	B	10	Autonomic; preganglionic
0.2-3	C	2	Temperature Nociception Autonomic; postganglionic

can be relieved by treatment with carisoprodol, vitamin E (Walton and Kolb, 1991), benzodiazepines (Horiguchi et al., 1992), carbamazepine, dopa agonists (Walters et al., 1988), gabapentin or opioids (Walters et al., 1993).

### Motor

Neurogenic muscle atrophy is common in axonal neuropathies, often being evident in advance of weakness. As with sensory symptoms, the wasting due to neuropathy affects distal more than proximal musculature, with rare exceptions. Neuropathic disorders are best detected by neurophysiologic testing that can uncover abnormalities well before the appearance of symptomatic motor weakness.

Cramps, while occurring less frequently than muscle wasting, are not uncommon and at times are the source of bitter complaints in cancer patients suffering from neuropathy. Such pain is commonly the presenting symptom. Cramps consist of involuntary, paroxysmal, and painful muscle contraction. Typically, the cramp causes the patient to hold the affected limb in a fixed posture and can often be eased by stretching and massaging the cramped muscle. Patients complain of painful legs, often describing the pain as "spasms." While the physiologic mechanisms underlying cramping are incompletely understood, multiple experimental and clinical clues point to an origin from a lower motor neuron disturbance (Rowland, 1985). Examples can be an early complaint, particularly in vincristine neuropathy, in which cramping may occur acutely following or even during therapy. Besides mechanical therapy, cramps may respond to quinine, carbamazepine, or other agents that serve to raise the threshold of the motor neuron's action potential.

### Small Fibers

Disturbance of small-diameter nerve fibers results in dysautonomia and/or in dysesthetic pain syndromes paradoxically associated with decreased pain and temperature sensation. Loss of small fiber afferent input causes the deafferentation pain syndrome. Such patients may have severe complaints despite having well-preserved reflexes and other negative tests of large fiber function, including nerve conduction studies. Dysautonomia causes complaints of dizziness, delayed gastric emptying, obstipation, impotence, and

incontinence. Those affected may have cool, flushed, dry limbs with distal limb hair loss, easily damaged skin, and trophic nail changes.

Injury to small-diameter axons is the most difficult to clinically assess because of variability in the clinical expression of damage. Standard electrophysiologic studies measure only the fastest conducting fibers. Techniques presently exist to directly assay small fiber function, but these are too painful and laborious for use in routine clinical investigation. The use of thermal discrimination thresholds, in which a patient's ability to perceive changes in temperature is quantified, is one of the few painless and reproducible means of assessing small fiber function (Bertelsmann et al., 1985; Hanson et al., 1992).

Autonomic function can also be assessed by quantifying hemodynamic responses, Valsalva's maneuver, and, even more simply, by checking an electrocardiogram for sinus arrhythmia. A beat-to-beat variation of the heart occurs normally with changes in cardiac return during the respiratory cycle; attenuation of this variability indicates proximal loss of autonomic function. Loss of this beat-to-beat variation can be observed on the electrocardiogram. The galvanic skin response can be measured electrophysiologically, easily, and without undue discomfort. Whereas the thermal discrimination threshold correlates well with the galvanic skin response, it may not predict RR interval abnormality from neuropathy (Wieman et al., 1989), typical of the inhomogeneity of the autonomic nervous system.

Small fiber axon damage affects both autonomic and nociceptive functions; physicians treating patients with neuropathic deafferentation pain must regularly check for orthostatic hypotension. Patients taking tricyclic antidepressants, which ironically are a mainstay of treating neuropathic pain, are at increased risk of developing orthostatic hypotension. Volume depletion from diuresis, bleeding, or vomiting increases susceptibility to symptomatic orthostatic hypotension. The combination of hypotension, lack of proprioceptive function, and deadened reflexes is particularly treacherous, frequently producing subdural hematomas and falls resulting in fractured shoulders and hips.

The autonomic nervous system is very adaptable, and effector receptors become hypersensitive to neurotransmitters following postganglionic denervation (Cannon's rule). As long as the autonomic nervous system is not totally devastated, symptoms may wax

and wane, and clinical improvement often occurs spontaneously. Accurate diagnosis using simple techniques permits rational management, which can lessen morbidity for symptomatic patients (Bannister and Mathias, 1988).

## PATHOPHYSIOLOGY

### Axons

Neural tissue has properties that make it unique in its responses to injury. The cell body, or soma, of peripheral nerves lies either in a ganglion, in sensory or autonomic peripheral nerves, or in the CNS, in motor and other effector neurons. The soma's axon may be as long as 1 m in humans, consequently giving the nerve an enormous surface area relative to the cell body. The distal ends of these cells have specialized structures, such as the synaptic terminal for motor fibers and the pacinian corpuscles for some sensory fibers.

The motor unit consists of the motor neuron soma in the gray matter of the spinal cord or brain stem, its dendrites and long axonal process, the muscle synaptic terminal, and the muscle fibers (extrafusal and intrafusal) themselves. This complex expresses injury as a whole.

Skeletal muscle, like peripheral nerve, is heterogeneous, composed of functionally different fibers most simply classified as type one, or slow-twitch, and type two, or fast-twitch, fibers, each with well-defined biochemical properties. Type one fibers are rich in oxidative metabolism enzymes, and type two fibers utilize anaerobic metabolic pathways. When peripheral nerve is damaged, surviving axons sprout new branches that reinnervate muscle fibers that have lost their nerve supply. The innervation of the individual fiber determines which metabolic type it will be by inducing the appropriate enzyme systems. Under experimental or clinical pathologic conditions producing axonal loss and subsequent reinnervation, the fibers change histochemical type. Determining fiber type grouping is one of the most reliable methods to diagnose an axonal neuropathy.

### Myelin

Perhaps an even more intimate relationship than that between motor neuron and muscle exists between the

peripheral nerve soma's axon and the supporting Schwann cells that accompany it along its lengthy path to its distal terminus. The Schwann cell, ubiquitous in peripheral nerves, envelops normal axons whether they are myelinated or not. The Schwann cell membrane forms the myelin surrounding peripheral nerve axons, but the fact that every unmyelinated axon carries with it an investiture of Schwann cell membrane portends that the Schwann cell plays a critical role in the maintenance of axons. With injury to the axon, the Schwann cells proliferate and play an important, yet presently inadequately understood, role in axonal regeneration. Although the Schwann cell shares with the CNS's oligodendroglia the function of myelinating axons, Schwann cells' rapid proliferation in axonal injury suggests a role analogous to the astrocytes' when axons are damaged in the CNS.

In pure axonal neuropathies, myelin damage occurs regularly and can range from trivial to profound. Myelin breakdown is a hallmark of Wallerian degeneration and occurs in classic axonal trauma, with the proliferating Schwann cells assuming a phagocytic role. In the less frequently seen predominantly demyelinating neuropathies, such as the Landry-Guillain-Barré-Strohl syndrome, the axon survives relatively unscathed, with symptomatology resulting from physiologic alterations in nerve conduction induced by segmental demyelination.

As opposed to axonal loss, which produces denervation, the pathophysiologic hallmark of demyelinating neuropathy is nerve-conduction velocity slowing. The deep tendon reflexes require that a synchronous afferent stimulus volley be generated to the motor neuron pool in the CNS. Because of the disturbance of individual fiber conduction velocity resulting from segmental myelin loss, the deep tendon reflexes are lost early in demyelinating neuropathies. Nerve conduction studies using conventional electrophysiologic technique are affected relatively early compared with the predominantly axonal neuropathies, in which muscle wasting can be profound without significant loss of deep tendon reflexes or decrease in nerve conduction velocity.

A late component of the compound muscle action potential is the F-wave, which is particularly useful in the neurophysiologic evaluation of demyelinating neuropathy. These are formed by an antidromic depolarization volley conducted along motor axons from the distal stimulus site toward the motor neuron pool in the spinal cord. The volley depolarizes a

few motor neurons, which send an orthodromic volley down the same nerve, producing the F-wave, which always has a greater latency than the much larger compound action potential of the muscle caused by the initial orthodromic depolarization volley. Because the F-wave response reflects proximal as well as distal nerve conduction, the study is more sensitive in assessing neuropathies predominantly affecting proximal conduction velocity, such as in the Landry-Guillain-Barré-Strohl syndrome.

### Axonal Transport

Protein synthesis in neurons resides in the perikaryon of the soma. The axon, unlike the soma, is virtually devoid of protein-synthesizing organelles; its volume, however, may be 1000-fold greater than that of its soma (Griffin and Watson, 1988). To what extent the Schwann cell serves to supplement the soma in maintaining the axon is uncertain, but the neuronal cell body's rich endowment of endoplasmic reticulum, as well as overwhelming experimental evidence, demonstrates that the nerve cell body plays the critical role, synthesizing proteins vital for the maintenance of its synaptic terminal or for specialized sensory receptor organs as diverse as the Golgi-Mazzoni corpuscles, involved in tactile sensation, and the muscle spindle axons providing the afferent limb of the stretch reflex.

Since the nineteenth century experiments of Augustus Waller (1852), it has been known that the axonal segment distal to a transection quickly degenerates, whereas the proximal segment, with its connection to the soma intact, survives and proliferates axonal sprouts essential to regeneration. The neuron's cell body synthesizes structural components, enzymes, and trophic factors critical for regenerative sprouting of axons when they are injured.

The soma, removed from the distal axon terminal by as much as 1 m, must have an elaborate transportation mechanism to communicate with its distant end. Multiple transport systems have been identified in the axon, with flow occurring in both the anterograde (away from the soma) and retrograde (toward the soma) directions. The axonal cytoskeleton's neurofilaments and microtubules form an important component of this vehicle for moving proteins, portions of membrane, and transmitters to and from the neuronal perikaryon to the periphery. Retrograde transport plays a critical role in maintaining the dis-

tal axon by continuously returning portions of neural membrane for recycling by the soma's synthetic apparatus, an economizing adaptation. The fast anterograde transport system and retrograde transport are intimately related, and most investigators believe they represent a single looping conveyance. Through retrograde transport from the distal axon terminus, viruses such as herpes simplex and rabies and noxious substances such as tetanus toxin and doxorubicin (Adriamycin) (Yamamoto et al., 1984) can gain access to the cell body.

Peripheral nerves have a limited number of ways of responding to injury, and, without doubt, insults can layer upon the vulnerable neuron, as in the well-known example of diabetics being highly susceptible to compressive neuropathies. Patients already compromised by peripheral neuropathy seem more susceptible to injury from neurotoxic agents. Even agents not commonly associated with causing neuropathic disease can act to potentiate neuropathy, as with the enhancement of vincristine neuropathy by the epipodophyllotoxins (Griffiths et al., 1986). Patients with dietary deficiency or diabetes and chemotherapeutic intoxication almost certainly express more severe neuropathic changes than do patients with any of these single insults alone.

### CLINICAL SYNDROMES

The neuropathies associated with cancer have diverse etiologies and presentations. This section discusses the iatrogenic neuropathies associated with chemotherapy agents and the neuropathies associated with paraproteinemias. The paraneoplastic neuropathies are discussed in Chapter 19. Plexopathy resulting from tumor infiltration and irradiation are discussed in the next section.

#### Neuropathy Associated with Paraproteins

Paraproteinemia such as that occurring in multiple myeloma, Waldenstrom's macroglobulinemia, plasmacytoma, or lymphoproliferative disorders (in particular B-cell lymphoma, Hodgkin's disease, and angiofollicular hyperplasia) causes peripheral neuropathy with at least five distinct patterns (Table 17-2) (Gherardi et al., 1988). As with other paraneoplastic disorders, clinical recognition is critical,

**Table 17-2.** Neuropathic Manifestations of Paraproteins

IgM-associated chronic demyelinating sensorimotor polyneuropathy
IgG- or IgA-associated chronic and predominately demyelinating sensorimotor polyradiculoneuropathy
Amyloidosis neuropathy
Cryoglobulin neuropathy
Motor neuronopathy

as these neuropathies may be the presentation of a malignancy. The paraprotein-associated neuropathies are not uncommon disorders and may accompany the monoclonal gammopathy of uncertain significance syndrome. Monoclonal gammopathy of uncertain significance syndromes usually have a benign course, but in one study (Back et al., 1993) of 35 of these syndromes, 14% of patients evaluated over a 4-year period developed myeloma. In addition to the presence of bone lesions and myeloma protein levels (Dimopoulos et al., 1992), elevated levels of serum  $\alpha_2$ -microglobulins, neopterin, and interleukin-6 (Nachbaur et al., 1991) and circulating CD 38-lymphocyte percentages (Boccardo et al., 1991) all have prognostic value.

The most common clinical pattern is a chronic demyelinating neuropathy, resembling a less severe form of chronic inflammatory demyelinating polyradiculoneuropathy (Simmons et al., 1993). Patients most frequently complain of appendicular ataxia and tremor but may have sensory or autonomic symptoms predominating early. IgM paraproteins with kappa light chains are most commonly expressed in these patients. An antimyelin-associated glycoprotein antibody has been implicated in the pathogenesis in some, but not all, cases (Latov et al., 1988; Nobile-Orazio et al., 1987; Pestronk et al., 1991) and may help make the diagnosis.

A second pattern of paraprotein neuropathy, a sensorimotor polyradiculoneuropathy, may be associated with the polyneuropathy, organomegaly (chiefly hepatic), endocrinopathy, serum myeloma protein, and skin changes (the POEMS, or Crow-Fukase, syndrome). IgG or IgA myeloma proteins with lambda light chains predominate in these patients. The cerebrospinal fluid may show a modest pleocytosis and elevated protein levels. Patients with POEMS syndrome have a demyelinating neuropathy associated with atrophic testes and gynecomastia as well as skin

hyperpigmentation, hypertrichosis, and clubbing of the fingers and toes. For both of these paraprotein neuropathies, the neurophysiologic evaluation may strongly suggest the diagnosis: Nerve conduction velocities are greatly reduced, and there may be evidence of conduction block (Bleasel et al., 1993). Treatment may improve symptoms, particularly when the cause of the gammopathy is a solitary plasmacytoma.

Cryoglobulinemia is associated with an asymmetric, and often painful, axonal neuropathy; with exposure to cold, symptoms generally are increased. The IgM from these patients binds to a sulfated glycosphingolipid, sulfated glucuronic acid paragloboside, with the greatest binding affinity at 4°C (McGinnis et al., 1988), which explains the cold sensitivity of the symptoms. Neuropathy from cryoglobulins arises from two pathogenetic mechanisms. Distal cold-sensitive symptoms are caused by sludging of flow in the vasonervosum, whereas patients may develop mononeuritis multiplex from cryoglobulin-induced vasculitis (Garcia-Bragado et al., 1988). Rapid improvement of symptoms can be achieved with plasmapheresis (Bussel, 1993), but therapy directed at the source of the paraprotein is critical to long-term disease control.

Amyloid neuropathy occurs infrequently in patients with paraproteins. In the characteristic clinical picture, small fiber function bears the brunt of the insult. Presenting symptoms often consist of dysautonomia and dysesthetic pain (Tada et al., 1993; Zanusso et al., 1992) along with those typical of sensorimotor neuropathy. Peripheral nerve entrapments, especially of the median nerve at the carpal tunnel, are common in amyloid neuropathy. Unlike most neuropathic processes, proximal signs and symptoms may dominate the clinical presentation (Li et al., 1992). Unlike other paraprotein neuropathies, plasmapheresis does not reverse symptoms, although aggressive therapy of the primary disease should be undertaken.

A relatively pure motor neuropathy, distinguishable from amyotrophic lateral sclerosis by less prominent upper motor neuron or bulbar signs and a more indolent course, can be seen in rare cases in patients with paraproteinemia. The onset may be asymmetric, with cramping as an early sign. Neurophysiologic testing will demonstrate overt denervation of affected muscles, and, despite a lack of sensory symptoms, there may be slowing of sensory nerve conduction velocity (Bady et al., 1988). Nerve biopsy can help con-



firm the diagnosis, and immunohistochemical and ultrastructural techniques can demonstrate paraproteins deposited within nerve. As has been shown for the other paraprotein-mediated neuropathies, plasma exchange and treatment of the underlying disease may improve symptoms.

Overlap occurs in the paraneoplastic syndromes, and these areas are yet incompletely defined. In a large series of patients from India with cancer who were minimally treated or untreated with chemotherapy, approximately one-third had a neuromuscular syndrome with both neuropathic and myopathic features (Paul et al., 1978). Many patients with advanced (or rapidly advancing) tumors develop a muscle wasting–cachexia syndrome without clear cause. This syndrome likely has multiple etiologies, including malnutrition and circulating factors such as cytokines that affect metabolism.

### Iatrogenic Neuropathies

Many chemotherapy agents can cause peripheral neuropathy. Table 17–3 lists agents used by cancer patients that can cause neuropathy; however, most of

these infrequently cause symptomatic toxicity and are clinically important chiefly as their effects may be additive. The most common iatrogenic neuropathies occurring in cancer patients are those due to vinca and platinum compounds. Neuropathy from paclitaxel (Taxol) and its relatives has already become a concern. These agents offer unique advantages to the modern chemotherapeutic armamentarium, and understanding the natural history, pathogenesis, and therapy of the toxic neuropathies they produce will optimize their clinical use. Animal studies of nerve toxicology have come largely from the agriculture industry (chickens seem particularly susceptible [Moretto et al., 1991; Johnson et al., 1988; Anderson et al., 1988]) or the military (Egan et al., 1980). Only recently have these techniques been widely applied to chemotherapeutic agents (Apfel et al., 1992). Despite the difficulties in the design of animal studies posed by oncologic therapy (Bradley, 1970), consideration of both clinical and experimental studies can be expected to improve patient care.

### Vincristine

Of the Vinca alkaloids, vincristine has greatest use because of its efficacy and relative lack of myelosuppression, cardiac toxicity, or nephrotoxicity, but it is the most neurotoxic. The axonal neuropathy caused by vincristine, while usually recoverable and mild, may produce great morbidity and can limit the drug's use clinically. The earliest symptoms of vincristine neuropathy are usually myalgias, distal paresthesiae, and decreases in ankle jerks (Rosenthal and Kaufman, 1974; Bradley et al., 1970b), although jaw pain and cramps and other muscle cramps (Haim et al., 1991) can occur shortly after its administration. The symptoms typically present insidiously, but patients with cranial neuropathies associated with vincristine intoxication often develop symptoms more rapidly. Ptosis and ophthalmoplegia causing visual disturbance may be of such abrupt onset as to mimic a brain stem stroke, particularly if these symptoms are accompanied by nausea and ataxia. Paralysis of the recurrent laryngeal nerve can occur, causing stridor, which reverses upon drug withdrawal (Annino et al., 1992). Symptomatic recovery of vincristine neuropathy may take as long as 40 months (Postma et al., 1993), but usually patients are not seriously affected if the total dose is kept under 12 mg.

The Vinca alkaloids frequently affect small fiber function, producing both painful paresthesiae due to

**Table 17–3.** Chemotherapy Drugs Associated with Peripheral Neuropathy

Vinca alkaloids (vincristine, vindesine, vinblastine)
Platinum compounds (cisplatin, carboplatin, liproplatin, ormaplatin)
Taxanes (paclitaxel, docetaxel)
Podophyllotoxins (etoposide, teniposide)
Azacytidine
Cytarabine
Bleomycin
Dapsone
Doxorubicin
Ethambutol
Fludarabine
Altretamine (hexamethylmelamine)
Isoniazid
Nitroimidazoles (metronidazole, misonidazole)
Phenytoin
Procarbazine
Pyridoxine
Suramin
Thalidomide

C-fiber dysfunction and dysautonomia. The hemodynamic consequences of autonomic dysfunction appear dose related and consist primarily of orthostatic hypotension (Roca et al., 1985). It is plausible that a component of the syndrome of inappropriate antidiuretic hormone seen with vincristine stems from altered autonomic function. Other phenomena in patients affected by vincristine dysautonomia include reduced gastrointestinal motility, abdominal colic, impotence, and urinary retention (Legha, 1986). Abnormal cardiovascular reflexes are common in patients undergoing vincristine therapy (Hirvonen et al., 1989). Great care must be exercised when prescribing tricyclic antidepressants, neuroleptics, and diuretics, as these may worsen autonomic function.

Older patients are at greatest risk for developing symptomatic vincristine neuropathy, and individual doses higher than 2 mg are less well tolerated (Roca et al., 1985). How much pre-existing neuropathic conditions contribute to the severity of vincristine's neurotoxicity is hard to know with certainty, but evidence exists that severe vincristine neuropathy occurs in patients with the Landry-Guillain-Barré-Strohl syndrome (Norman et al., 1987), Charcot-Marie-Tooth disease (McGuire et al., 1989), or hepatic failure or in those who received concomitant isoniazid (Roca et al., 1985) or teniposide therapy (Yamamoto et al., 1984).

The Vinca alkaloids poison microtubules by interacting with the microtubular protein tubulin (Green et al., 1977), thereby inhibiting the mitotic spindle movements necessary for cellular reproduction. In vivo experiments have clearly demonstrated disruption of both neurofilament and microtubular physiology within hours of nerve exposure to vincristine (Sahenk et al., 1987). Given nature's parsimony, the microtubular system of peripheral nerve, essential to axonal transport, suffers injury from vincristine as an innocent bystander. The pace of the insult suffered by nerve has an important role in the expression of neuropathy. Unfortunately, no experimental studies for vincristine have been designed to determine optimal dose schedules to minimize neuropathic changes.

### *Taxanes*

Recently two taxanes, paclitaxel (Taxol) and docetaxel (Taxotere), have been introduced for cancer chemotherapy. Like the Vinca alkaloids, the taxanes are plant-derived poisons of the mitotic spindle ap-

paratus. In contradistinction to the Vinca drugs, the taxanes cause microtubular aggregation (Pazdur et al., 1993). Paclitaxel at doses of 200 mg/m<sup>2</sup> produces a mild to moderate sensorimotor neuropathy in most patients, but at higher doses the neuropathy can be severe (Rowinsky et al., 1993a,b). Severe orthostatic hypotension from autonomic neuropathy has occurred at this dose range (Jerian et al., 1993). When paclitaxel was combined with cisplatin in a careful study of patients with ovarian cancer, 95% developed dose-related sensorimotor axonal polyneuropathy (Chaudhry et al., 1994). Patients with pre-existing neuropathy were at greatest risk. In our experience, docetaxel may be less neurotoxic than paclitaxel. We, like others (Lipton et al., 1989), have found that sensory symptoms predominate early in taxane neuropathy.

### *Cisplatin*

Cisplatin causes a peripheral neuropathy that was initially reported only in those patients receiving high doses of the drug. The minimal dose found to cause neuropathy progressively decreased as experience with the agent increased. The success of cisplatin in the therapy of certain solid tumors prompted the development of the related compounds iproplatin, ormaplatin, and carboplatin. Although there is less clinical experience with these drugs (van Glabbeke et al., 1988; Schilder et al., 1994), it is clear that carboplatin produces the least degree of neurotoxicity.

Sensory symptoms predominate early in the course of cisplatin neuropathy, with patients most frequently noting distal paresthesiae. Studies including detailed clinical and neurophysiologic testing found that symptoms of neuropathy were common at cumulative doses of approximately 300 mg/m<sup>2</sup> and virtually universal at cumulative doses of greater than 500 mg/m<sup>2</sup> (Roelofs et al., 1984; Thompson, 1984; van der Hoop et al., 1990). In these studies, the earliest clinical sign of cisplatin neuropathy was decreased vibratory sense, with diminished ankle jerks following shortly thereafter. Patients may infrequently experience dysesthetic pain, which may occur late in the course of their peripheral neuropathy or even during recovery. More severe sensory disturbances result in sensory ataxia and can be debilitating. Signs and symptoms of peripheral neuropathy commonly worsen for as long as 6 months following treatment cessation (LoMonaco et al., 1992; Hovestadt et al., 1992). They

significantly improve at 12 months, with continued gradual improvement occurring for as long as 48 months (Ostchega et al., 1988). The theoretical concern that cisplatin neurotoxicity may be irreversible (Krarup-Hansen et al., 1993) has not proved true for the majority of patients despite the fact that platinum concentrates in dorsal root ganglia and its level in neural tissue diminishes little with time (Gregg et al., 1992).

Lhermitte's sign, in which patients complain of electric shock sensations on neck flexion, occurs in patients with platinum neuropathy (Inbar et al., 1992) and is believed to be due to myelin loss in the dorsal columns, similar to that occurring in multiple sclerosis or radiation myelopathy. Scant pathologic evidence exists to support this contention, however. The concomitant marked proprioceptive loss observed in these cases (Dewar et al., 1986) suggests involvement of either posterior columns or large fibers, consistent with the finding that somatosensory evoked potentials are the most sensitive physiologic means of detecting cisplatin changes (Boogerd et al., 1990). Development of Lhermitte's sign may be delayed for as long as 5 months following cisplatin treatment. Cautious therapy may be continued without adverse side effects even after patients demonstrate Lhermitte's sign (Siegal and Haim, 1990). Clinicians should bear in mind, however, that a case has been reported (List and Kummert, 1990) of cervical myelopathy following cisplatin and etoposide chemotherapy of small cell lung cancer. The myelopathy affected cervical dorsal columns and sensory and motor neurons but not pyramidal tracts and was heralded by Lhermitte's sign.

Motor symptoms have been reported far less frequently than for vincristine neuropathy. Weakness with electrophysiologic evidence of denervation may be found later in the clinical course; cramps, however, are not rare (Siegal and Haim, 1990) and may be present early. Even more than with vincristine neuropathy, motor deficits contribute less to the incapacitation of patients than do sensory ataxia. Patients with early objective severe weakness should be evaluated for other causes, such as thiamine and B<sub>12</sub> deficiency, paraprotein neuropathy, and thyroid disorders.

In the early studies of platinum neuropathy, the autonomic nervous system was thought to be spared injury. Autonomic symptoms may be overlooked or may be mistakenly considered due to other causes (Rosenfeld and Broder, 1984). While not as promi-

nently in patients undergoing treatment with the Vinca alkaloids or taxanes, autonomic dysfunction does occur in cisplatin neurotoxicity (Boogerd et al., 1990) and particularly affects cardiovascular reflexes. This is especially important given the marked emetogenic nature of platinum chemotherapy, which increases the risk for orthostatic hypotension because of the synergistic effects of hypovolemia, anticholinergic therapy, and vagal stimulation.

Risk factors for developing platinum neuropathy include pre-existing neuropathy, but it is uncertain whether patient age, history of alcohol use, or diabetes mellitus increases risk (Mollman et al., 1988). Increased age positively correlated with the severity of neuropathy symptoms in one series (Ostchega et al., 1988; Pirovano et al., 1992), and diabetes mellitus has been found to be a risk factor in another (Rowinsky et al., 1993b). The dosage schedule may play a critical role; dosing schemes that use more frequent schedules or continuous infusion cause less neuropathy for a given dose than schedules that use a high-dose bolus of cisplatin (Cavaletti et al., 1992; Sebillé et al., 1990).

Low serum magnesium levels may be a risk factor for cisplatin neuropathy. In a prospective study, 54% of patients developed clinically evident peripheral neuropathy, and a significant association between the development of hypomagnesemia and neuropathy was observed (Ashraf et al., 1983). In this study, 71% of patients given 50 to 100 mg/m<sup>2</sup> of cisplatin with a saline diuresis on an every-4-week basis, alone or in combination with cyclophosphamide, bleomycin, and doxorubicin, developed hypomagnesemia (serum magnesium less than 1.5 mEq/L) during the course of their therapy. Hypomagnesemic patients received significantly higher doses of cisplatin, weighed more, and had greater body surface area than patients who maintained normal serum magnesium levels. In this series, none of the normomagnesemic patients developed peripheral neuropathy, whereas 75% of the patients with hypomagnesemia did. Another study of 12 patients noted hypomagnesemia in 63% of their chemotherapy cycles. Six of these patients developed clinically significant peripheral neuropathy, and five patients had ototoxicity (Trump and Hortvet, 1985). Whether maintaining normal serum magnesium levels in patients during treatment lessens peripheral neuropathy is unknown.

How cisplatin, whose presumed mechanism of action is through impairing DNA synthesis, causes dam-

age to nonmitotic peripheral nerve remains unknown, but damage likely results from cisplatin's deleterious effects on the synthetic mechanisms of the axonal perikaryon. Platinum comes from the same elemental family of the heavy metal neurotoxins arsenic and lead, sharing with them a propensity to concentrate in nervous system tissue. The prominence of sensory signs and symptoms reflects the vulnerability of the dorsal root ganglion, site of the sensory axon's soma, which bears the brunt of injury from cisplatin (Krarup-Hansen et al., 1993). In an important autopsy study (Gregg et al., 1992) of 21 patients who had been treated with cisplatin, elemental platinum was found in highest concentration in the dorsal root ganglion, which lies outside the blood-brain barrier. Platinum concentration directly correlated with cumulative dose and did not appear to diminish over time. This study argues for setting a limit to the amount of cisplatin that can be safely used, much like the therapeutic limits set for doxorubicin and irradiation.

## TREATMENT OF NEUROPATHIES

### Limit Exposure

The best treatment of iatrogenic neuropathy is avoidance. Once the neuropathy has become symptomatic, the clinician must decide whether to continue therapy and risk a debilitating toxicity or switch to a less neuropathic program. Measures to control neuropathic pain with low-dose tricyclic antidepressants (amitriptyline, desipramine, or doxepin) helps many patients. The tricyclics should be used at the lowest possible effective dose; for some patients 10 mg of amitriptyline before sleep will suffice.

Gabapentin, developed as an adjuvant anticonvulsant, has probably found more use as a remedy for neuropathic pain. Although it is significantly more expensive than amitriptyline (Morello et al., 1999), gabapentin has a more favorable toxicity profile (Rosner et al., 1996). The effective dose from most studies is between 900 and 1500 mg per day in three divided doses; significant benefit can be gained with much lower doses. Patients, particularly the elderly, should be started at a dose of 100 mg three times a day with the dose gradually advanced until an acceptable benefit is achieved.

Narcotics are sometimes needed as well. Braces, splints, walkers, household aids, and the benefits of

physical and occupational therapy to neuropathy patients should not be discounted (O'Connell and Levinson, 1991). A healthy and varied diet, rich in the B, C, and E vitamins, should be encouraged whenever possible, as this general health measure will speed recovery.

### Neuroprotection

Efforts to protect peripheral nerves from chemotherapy toxicity may permit use of higher doses of chemotherapy and help to avoid significant treatment-related morbidity. Encouraged by a desire to avoid morbidity and increase the therapeutic margin, particularly for cisplatin, clinicians have attempted many strategies. The hope of application to other neuropathies (particularly diabetic) also motivates interest in neuroprotection from chemotherapeutic agents (de Wied, 1990). Two broad strategies have been adopted: (1) efforts to promote peripheral nerve regeneration and (2) attempts to block the chemotherapy's noxious effects while not effacing its efficacy as an antineoplastic agent.

The pyrimidine isaxonine (2-[isopropylamino]pyrimidine) enhances the rate of regeneration of peripheral nerve following various experimental axonal injuries, and in one double-blind, controlled study it was demonstrated to decrease vincristine-induced neuropathy (Duhamel and Parlier, 1982). Unfortunately, isaxonine has significant hepatic toxicity, and further clinical studies with it have been stopped (Le Quesne et al., 1985).

A mixture of bovine brain gangliosides has been reported to promote peripheral nerve regeneration, and at least one animal study (Favaro et al., 1988) demonstrated a protective effect for vincristine neuropathy without any loss of antineoplastic efficacy. A human clinical trial of gangliosides (DeAngelis et al., 1991) failed to prevent vincristine-induced neuropathy during intensive chemotherapy for lymphoma. European investigations with diabetic neuropathy are still ongoing, but the drug has not gained wide acceptance.

Peptides derived from the melanocyte-stimulating hormone portion of the adrenocorticotrophic hormone (ACTH) polypeptide have generalized neurotrophic effects, serving to both protect and promote regeneration of neurons during a host of injuries, including the noxious effects of cisplatin (Windebank et al., 1994; Hamers et al., 1991, 1993b; Gispén et

al., 1992; de Wied, 1990; Gerritsen van der Hoop et al., 1988), vincristine (Kiburg et al., 1994), and paclitaxel (Hamers et al., 1993c). They may facilitate repair of pre-existing disease as well (Gispén et al., 1992). Early reports of protection with the ACTH-derived peptide ORG 2766 (H-Met[02]-Glu-His-Phe-D-Lys-Phe-OH) (van Kooten et al., 1992) were promising, but wider enthusiasm was tempered by the drug's parenteral delivery requirement. ORG 2766 may act by promoting reinnervation and thus ought not to interfere with chemotherapeutic antitumor effects; however, for at least two lymphoma cell lines, ORG 2766 has been shown to enhance the tumoricidal effects of vincristine (Kiburg et al., 1994).

A number of neurotrophic factors have been identified and manufactured using recombinant DNA technology, which has opened new horizons of therapy for central as well as peripheral nervous system diseases (Cuello, 1989). These factors, which have been characterized in recent years and which are increasing in numbers, selectively stimulate different subsets of neurons, share effector pathways, and overlap in function. Identified factors with neurotrophic activity include nerve growth factor, ciliary neurotrophic factor, brain-derived neurotrophic factor, neurotrophin 3 and neurotrophin 4/5 (Wong et al., 1993), interleukins 6 and 11, oncostatin M (Boulton et al., 1994; Yang, 1993), leukemia inhibitory factor (Thaler et al., 1994), fibroblast growth factor-5, and insulin-like growth factor-1 (Apfel et al., 1993; Hughes et al., 1993). Other trophic factors are being uncovered.

Nerve growth factor selectively promotes growth of sensory neurons and has experimentally protected against the development of cisplatin (Apfel et al., 1992) and paclitaxel (Apfel et al., 1991) neurotoxicity. This benefit has not been observed in all experimental model systems (Windebank et al., 1994). Ciliary neurotrophic factor is critical to sympathetic neuron survival (Burnham et al., 1994) and is one of a host of factors that support motor neurons (Hughes et al., 1993). Clinical trials with ciliary neurotrophic factor have been undertaken for motor neuron disease. Given the complexity of interactions between these growth factors and their functional overlap with cytokines, mixtures of the agents or pharmacologic manipulation of their peptide structures may eventually permit the development of neurologic tonics that can protect peripheral nerves from toxic injury and possibly promote recovery once damage has occurred.

The thiols have well-established neuroprotective qualities due to their ability to stabilize both DNA and proteins and act as antioxidants (Yim et al., 1994). A number of thiol compounds have been considered as antidotes for chemotherapy toxicity, including glutathione, diethylthiocarbamate, metallothionein, alpha lipoic acid, and amifostine (S-2-[3-aminopropylamino]ethyl phosphorothioic acid) (Treskes and van der Vijgh, 1993). Reduced glutathione has been shown to prevent cisplatin toxicity in at least three European clinical trials (Hamers et al., 1993a; Bogliun et al., 1992; Pirovano et al., 1992), but, as with all thiol compounds, concerns have been raised that the tumor may be protected from the effects of the treatment as well.

Amifostine (WR 2721, ethiofos) may preferentially protect healthy tissues (Bergstrom et al., 1999), and clinical investigation with this compound has accelerated. Inactive in its native form, amifostine must be dephosphorylated into an active thiol compound to produce its beneficial effects. Healthy, as opposed to tumor, cells dephosphorylate the drug more efficiently (Treskes et al. 1992a,b), affording a potential therapeutic advantage. An experimental trial (Treskes et al., 1994) of carboplatin toxicity modulation using amifostine demonstrated myeloprotection and actual potentiation of carboplatin's tumoricidal effects.

In an important early study (Mollman et al., 1988) of neuropathy protection, 69 patients received six different chemotherapy programs, including cisplatin, with 28 patients also receiving amifostine. The patients given amifostine developed less neuropathy, but all the patients except two, who were not given the antioxidant, were given regimens consisting of other chemotherapeutic agents. In this study, tumor control was decreased for the amifostine group. Nineteen percent of the patients who did not receive the radioprotector died, whereas more than 54% died in the group that received amifostine. A phase I clinical trial found toxicities to include hypotension, anaphylaxis, and hypocalcemia (Wadler et al., 1993). Numerous subsequent studies have demonstrated that amifostine provided hematologic, renal, and, to a lesser extent, neuroprotection from platinum intoxication.

Alpha lipoic acid (2-dithiolane-3-pentanoic acid; 1,2-dithiolane-3-valeric acid; thioctic acid) is a naturally occurring disulfide catalyst important in pyruvate metabolism (Reed et al., 1951), which has both antioxidant and chelating benefits. It has proved ef-

fective in human diabetic neuropathy trials (Ziegler et al., 1999) and in experimental lead intoxication (Gurer et al., 1999) in doses that should be well tolerated in humans. Because of its chelating effects, it may prove therapeutic for established heavy metal neuropathy such as that caused by cisplatin.

Nimodipine, a calcium channel blocker, was shown to protect rats against peripheral neuropathy from cisplatin (Hamers et al., 1991). The possibility that calcium channel drugs may block the multidrug resistance gene enough to improve chemotherapy efficacy (Pasman and Schouten, 1993; Lum et al., 1993) makes this strategy of neuropathy prevention particularly worthy of pursuit for xenobiotic neurotoxins such as the Vinca alkaloids and the taxanes, which are influenced by this gene. Hypotension limits the use of presently available drugs, but, fortuitously, some calcium channel blocker enantiomers lose blocking ability without any loss of multidrug resistance gene inhibition (Hollt et al., 1992), perhaps permitting development of more specific therapeutic agents.

The ototoxicity and optic neuropathy seen with platinum therapy are not, strictly speaking, peripheral neuropathies, affecting specialized sensory end organ systems. Optic neuropathy or retinopathy is rare unless the platinum is given intra-arterially. In a prospective study of six patients with malignant glioma treated with intra-arterial cisplatin, five patients developed progressive optic neurotoxicity (Maiese et al., 1992). Ototoxicity from platinum is common and can result in severe tinnitus. Risk factors include reduced serum albumin and hemoglobin levels and dark eye color (Barr-Hamilton et al., 1991). Cisplatin, in an experimental model (Delb et al., 1993), was ninefold more ototoxic than carboplatin, paralleling their relative peripheral neurotoxicities. Efforts to abrogate ototoxicity with amifostine have not, however, been encouraging (Markman et al., 1991; Planting et al., 1999).

Study of specialized sensory neurotoxic effects, along with the hypophyseal dysfunction due to cisplatin therapy, may provide clues to the etiology of the more widespread and troubling side effects of peripheral neuropathy. Similarly, careful study of the neuropathies caused by oncologic neurotoxins can yield clues to the pathogenesis and treatment of other neurologic disorders that remain shrouded in mystery.

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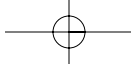
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