PERIPHERAL NERVE LESIONS

Fundamentals

The term “peripheral nerves” in this chapter means the nerve plexuses formed by the junction and regrouping of fibers derived from the spinal nerve roots, as well as to the more distally lying peripheral nerve trunks and branches. The plexuses always contain mixed fiber types and the peripheral nerve trunks nearly always do, i.e., somatic motor, somatosensory, and often also autonomic (particularly sympathetic) fibers. The individual peripheral nerve trunks bear an anatomically invariant relationship to the muscles and cutaneous zones that they innervate. This pattern of innervation is fundamentally different from that of the spinal nerve roots, because, as we recall, the nerve root fibers undergo reassortment in the plexuses. This fact enables the clinical examiner to distinguish a peripheral nerve lesion from a radicular lesion based on the observed pattern of neurological deficits. The main clinical manifestations of peripheral nerve lesions are marked paresis, extensive sensory deficits, and diminished sweating in the zone of innervation of the affected nerve or nerve branch. Pain can be produced by either a radicular lesion or a peripheral nerve lesion and is thus not a distinguishing feature of either.

Causes of peripheral nerve lesions. Most lesions of the nerve plexuses or the peripheral nerve trunks are either traumatic (caused by excessive traction, stab wounds, cuts, bony fractures, etc.), or else due to prolonged compression, which may occur through external influences, at anatomical bottlenecks, or because of space-occupying lesions in the vicinity of the nerve (especially tumors and hematomas). Less commonly, plexus and nerve lesions can be caused by infection and/or inflammation, e. g., neuralgic shoulder amyotrophy, which is probably an autoimmune disorder affecting the brachial plexus. Nearly all lesions affecting a single peripheral nerve trunk or branch (mononeuropathy) are of mechanical origin; in contrast, most polyneuropathies are of toxic, infectious/inflammatory, or paraneoplastic origin.

Non-mechanical causes of peripheral neuropathy are the following: 1) idiopathic inflammatory demyelinating process (Guillain-Barre syndrome); 2) metabolic and nutritional disturbances (diabetes, hypothyroidism, uremia, liver disease, vitamin B_{12} deficiency); 3) infections (AIDS, leprosy, diphtheria, sarcoidosis, sepsis and multiorgan failure); 4) vasculitis (polyarteritis nodosa, rheumatoid arthritis, systemic lupus erythematosus); 5) paraneoplastlc and paraproteinemic syndromes (cancer, paraproteinemias, amyloidosis); 6) drugs (hydralazine, isoniazid, phenytoin, pyridoxine, vincristine) and toxins (alcohol, organophosphates, arsenic, lead, thallium); 7) hereditary diseases (porphyria, Krabbe's disease, Refsum's disease, Fabry's disease).

General clinical manifestations of peripheral nerve lesions. Depending on the particular segment of plexus or peripheral nerve trunk/branch that is affected, there may be a motor, sensory, autonomic, or (usually) mixed neurological deficit:

1) flaccid paresis of the muscle(s) innervated by the affected nerve; 2) usually marked atrophy of the affected muscle(s); 3) the corresponding reflex deficits; 4) diminished sensation and possibly also pain and paresthesia in the cutaneous area innervated by the nerve, though the pain is often felt beyond this area as well; all sensory modalities are affected to a comparable extent; in contrast to a radicular lesion, the affected area of skin is more easily demarcated by testing the sense of touch than by testing nociception; 5) because the sweat secretion fibers travel together with the somatosensory components of the peripheral nerves, diminished sweating is often found in the hypesthetic area of skin and autonomic abnormalities of other kinds may also be present in the distribution of the affected nerve; radicular lesions affecting the limbs, in contrast, generally leave sweating intact (an important criterion for differential diagnosis); 6) fasciculations only in exceptional cases; these are much more common in anterior horn disease.

Bell's palsy

Bell's palsy (idiopathic facial nerve paralysis, IFNP) is, by definition, an acute lower motor neuron facial palsy of unknown cause. It is generally accepted that there is inflammation and edema of the nerve in the facial canal but, not surprisingly, there have been few pathological studies. A viral etiology is suspected. The incidence of Bell's palsy is about 23/100000/annum. It affects both sexes equally and is less frequent in children than adults. It shows relatively weak associations with hypertension and diabetes, particularly in older patients. Recurrence, on the same or opposite side, is relatively common.

A. Clinical features. The entire course of Bell's palsy may be painless, but frequently patients complain of pain behind the ipsilateral ear, in the mastoid region, for a day or two before the onset of weakness, and this may continue for a week or more. Paralysis develops rapidly and may reach maximum severity within a few hours. Continuing progression for 24-48 hours is not uncommon and rarely may be over as long as 5 days.

All of the muscles on the affected side of the face are involved, but the degree of weakness may range in severity from mild to complete (about 70 per cent of patients). The appearance of even an incomplete palsy, is striking and it is not surprising that it causes the patient and sometimes their medical attendant considerable alarm. In elderly patients, presumably due to greater laxity of supporting tissues, the resultant facial deformity is more evident than in younger patients. The eyebrow droops and cannot be elevated, and the brow looses its furrows and becomes smooth. The lower eyelid everts (ectropion) causing impaired drainage of the tears, which overflow onto the cheek. The eye cannot close voluntarily or on blinking but there will be some lowering of the upper lid due to reflex inhibition of levator palpebrae superioris. On attempting to close the eye the eyeball may be diverted upward and inward (Bell's phenomenon). The nasolabial fold becomes shallower, the angle of the mouth droops and cannot be retracted, the cheek billows on respiration, and food tends to accumulate between the cheek and teeth. There is mild dysarthria. If the nerve is involved proximal to the point where it is joined by the chorda tympani, or higher still, affecting the

nerve to stapedius, then the patient may complain of impaired taste sensation or hyperacusis (an unpleasant quality to louder sounds).

Many patients complain of numbness over the affected side of the face and, sometimes, tongue. This may be objective, in the sense that the patient will say that light-touch and pinprick sensation are less on the affected side. The corneal reflex is always preserved. There is no obvious anatomical explanation for such sensory symptoms and they are usually attributed to distorted perception caused by the drooping musculature, skin, and associated tissues.

B. Prognosis. In about 80 per cent of IFNP patients improvement starts early and there is full recovery within a few weeks from the onset. An incomplete palsy is the most favourable prognostic sign. Adverse features may include advanced age, diabetes, hypetension, severe pain, loss of taste, and hyperacusis, but none is a reliable indicator of prognosis. Associated movements (synkinesis) are the result of aberrant re-innervation by regenerating axons. Common patterns include eye closure on lip movement, or elevation of the angle of the mouth on blinking or when the eyebrow is raised. Occasionally the synkinetic movements may be very extensive. There may also be aberrant parasympathetic nerve re-innervation, giving rise to the phenomenon of crocodile tears – profuse watering of the affected eye when eating. The simplest explanation is that regenerating fibres destined to innervate the submandibular salivary glands become misdirected and reach the lacrimal gland.

C. Treatment. Although more than 150 years have passed since Sir Charles Bell established that the facial muscles are under the control of a separate cranial nerve, the treatment of IFNP still remains controversial. Medical treatment should be directed at a causative agent and the inflammatory event. Various treatment modalities have been employed in IFNP – surgical decompression, electrophysiotherapy, physical therapy, biofeedback, injection of the stylomastoid foramen with steroids, intravenous dextran, intravenous steroids, oral nicotinic acid, and acyclovir.

In the absence of contraindications it is very common practice for patients seen within 1 week of onset of the palsy to be given a short course of oral steroids. A typical regimen might start with prednisolone 1 mg/kg body weight/day, with gradually diminishing doses over the next 10-14 days. Acyclovir is used in conjunction with prednisone (2000 mg/day given in divided doses – 400 mg five times daily) in order to minimize gastrointestinal irritation. Patients need to be screened for renal or hepatic dysfunction prior to initiation of treatment.

There is no effective treatment for synkinetic movements. In those few patients with severe residual weakness, various plastic surgery procedures can improve the cosmetic appearance. Because of the slow rate of nerve regeneration, no surgical intervention, except occasionally tarsorrhaphy, should be considered until at least 6, and probably 12, months after the onset of the palsy.

The normal tear film is disturbed in Bell's palsy. Despite anatomical considerations, a dry eye or underproduction of tears due to denervation of the lacrimal gland is very uncommon. Rather, tear drainage is affected due to the ectropion and this, together with reduced blinking, often causes mistiness of vision

and associated patient anxiety. Corneal sensation is normal and corneal damage is rare in Bell's palsy. Tarsorrhaphy is rarely required but the patient may find it more comfortable to tape the eye closed in bed, and to use glasses to protect the eye from dust and wind. If tear production is impaired, methylcellulose eye drops should be used. Crocodile tears may be treated by section of the tympanic nerve which carries the glossopharyngeal salivary fibres.

Trigeminal neuralgia

This is the most frequently encountered disorder of the trigeminal nerve. It may be symptomatic of an underlying structural disorder affecting the nerve, but in the majority of patients no specific cause is identified. It is more common in the second half of life, cases in younger people more often being symptomatic, is slightly more frequent in women, and has an overall prevalence of the order of 3-5 per 100 000 population.

A. Clinical features. These are highly characteristic, but despite this the diagnostic label is frequently applied erroneously to many other causes of facial pain, particularly atypical facial pain and dental disease. In trigeminal neuralgia, pain, typically very severe, occurs in paroxysms, each episode lasting only a few seconds. The frequency of attacks may vary from several in a minute to days between episodes, and in the early stages spontaneous remission for months or years may occur. Unfortunately, permanent remission is rare and with time the bouts of pain become more frequent. Patients often provide graphic descriptions which indicate the severity and quality of the pain-like a dagger, or red hot needle, or poker. Clinicians use the word lancinating. When attacks are frequent, secondary depression is common. Many patients identify one or more triggers to their attacks. These include touching a very specific part of the face, a cold draught, talking, swallowing, chewing, and brushing their teeth. Tactile triggers may prevent the patient washing their face or shaving.

The pain is strictly within the trigeminal distribution, most commonly in the maxillary and mandibular divisions. The ophthalmic division is involved in less than 10 per cent of cases. Typically, pain is felt in only part of the region supplied by the affected division, at least initially, but may then spread to the rest of the divisional area. In later stages both the mandibular and maxillary areas may become involved, but spread to the ophthalmic area is unusual.

Between the paroxysms, particularly if they are frequent, there may be a dull background ache that is not severe. Trigeminal neuralgia never causes continuous discomfort without the characteristic paroxysms. The stabs of pain may be accompanied by involuntary contraction of the facial muscles, giving rise to the synonymous term 'tic douloureux'. Occasional patients develop typical symptoms bilaterally but do not experience bilateral pain at the same time. Physical examination is normal in idiopathic trigeminal neuralgia. Abnormal physical signs suggest symptomatic trigeminal neuralgia.

B. Etiology. It has long been recognized that trigeminal neuralgia may be symptomatic of underlying disease. Thus, about 4 per cent of patients with multiple sclerosis experience it, although it is very rare as a presenting symptom.

Primary tumours of the trigeminal nerve and compression of the nerve (e.g. by a tumour or aneurysm) very rarely produce symptoms identical to those of trigeminal neuralgia, but more commonly produce complaints of continuous pain or numbness, and on examination abnormal physical signs can be detected.

Excluding these rare causes of symptomatic trigeminal neuralgia one is left with a majority of patients in whom no physical cause is readily apparent, and thus the disorder might be considered to be one of altered function rather than structure. However, it has been suggested that in a significant number of these patients (over 90 per cent) the cause is a misdirected or ectatic blood vessel in the posterior fossa compressing the trigeminal sensory roots, and that symptomatic improvement can be gained by surgically separating the root from the aberrant blood vessels. In another series, vascular compression was found in only 11 per cent of patients. Increasingly sensitive MRI techniques may shed further light on this issue-scans may show vessels apparently impinging on the trigeminal nerve, but a cause-effect relationship remains to be proved.

C. Differential diagnosis. Rare symptomatic causes of trigeminal neuralgia have been discussed above and it was noted that they are often accompanied by abnormal physical signs. A substantial number of patients initially diagnosed as having trigeminal neuralgia prove to have other conditions. By far the most common confusion centres around the teeth. Dental disease, such as apical abscess, may cause paroxysmal as well as continuous pain, but the overall features and specific trigger factors should readily distinguish this from trigeminal neuralgia. Conversely, every specialist will have seen patients with trigeminal neuralgia who have had healthy teeth removed. Apart from dental disease, referred facial pain may be caused by sinus disease and eye disease (e.g. glaucoma). Angina may cause lower jaw pain.

Other causes of trigeminal nerve-related pain, which can be distinguished from trigeminal neuralgia on the basis of the history and physical signs, include brainstem lesions, postherpetic neuralgia, and tabes dorsalis. Local irritative lesions and trauma in the regions of exit from the skull of the supraorbital and infraorbital nerves can cause localized neuralgic pain.

Facial pains attributed to temporomandibular joint dysfunction (Costen's syndrome) and maladjustment of the bite are possibly overdiagnosed. Atypical facial pain, despite its name, is a characteristic disorder seen mainly in young and middle-aged women. They complain of a dull, constant ache in the upper jaw/cheek region which may extend to the whole of the side of the head and down into the neck. Often, but not always, there is clear evidence of an anxiety or depressive disorder. There may be a response to antidepressant drugs.

Cluster headache (migrainous neuralgia) is a highly characteristic condition that really should not be confused with trigeminal neuralgia, but sometimes is. The duration, distribution and characteristics of the pain, the different triggering factors, the accompanying symptoms, and the pattern of attacks distinguish the condition from trigeminal neuralgia. Glossopharyngeal neuralgia causes attacks of identical character but in a different distribution.

D. Treatment. Carbamazepine gives good or excellent symptomatic relief in up to 70 per cent of patients. A reasonable starting dose is 100 mg twice daily increasing, as required, over a 1-2 week period to either the lowest effective dose or the maximal tolerable dose. This is a much more rapid increase than would be used for treating epilepsy (and is done because of the frequency and severity of the attacks) and consequently side-effects are more common, although patients may be happy to trade these off against the relief from pain. Common dose-related side-effects include nausea, unsteadiness, and visual disturbance. Up to 10 per cent of patients develop an idiosyncratic drug rash which usually necessitates stopping the drug. If carbamazepine does not work or cannot be tolerated, other drugs that can be tried include sodium valproate, phenytoin, lamotrigine, clonazepam, and baclofen, but success rates are much lower than with carbamazepine.

Spontaneous remission may occur, especially in the early stages. Therefore, if drug treatment leads to resolution of symptoms, it is appropriate to attempt discontinuing treatment when the patient has been pain free for several weeks.

In some patients even very determined attempts with drug treatment prove unsuccessful, whereas in others there may be partial or complete relief but only at the cost of unacceptable side-effects. In such circumstances some form of surgical intervention should be considered. If the pain is localized within the distribution of a single peripheral nerve (e.g. supraorbital or infraorbital), relief for up to 18 months may be obtained by sectioning the nerve or by injecting the nerve or trigeminal ganglion with alcohol or phenol. Such techniques have largely been superseded by radio frequency thermal coagulation of the trigeminal ganglion, in which an electrode is inserted percutaneously, through the foramen ovale, into the ganglion. Pain appreciation may be abolished, while preserving light-touch. Most patients have good initial relief of pain but late recurrence is not uncommon. The procedure can be repeated.

Posterior fossa exploration, looking for neurovascular abnormalities, has been discussed above. Success rates over 90 per cent have been reported, but others have been less impressed and recurrence rates may be high. If a neurovascular abnormality is not identified, an alternative approach during posterior fossa surgery is partial trigeminal nerve root section, which will produce complete numbness in the relevant areas.

A recent review concluded that radio frequency rhizotomy is the treatment of choice for most patients undergoing a first operative procedure for V2 and V3 neuralgia, but that microvascular decompression is more appropriate for V1 neuralgia because there is a lower risk of corneal anaesthesia.

An area of numbness rather than pain might seem to be an acceptable exchange, but up to 10 per cent of patients develop extremely distressing dysaesthesiae in the anaesthetic area and this is very resistant to treatment. A further complication is that of keratitis, if the surgical treatment produces anaesthesia in the ophthalmic nerve territory. These complications are more likely to occur if there is extensive surgically induced sensory loss, but conversely the less sensory impairment there is, the higher the risk of recurrence of trigeminal neuralgia.

Entrapment neuropathies

Certain peripheral nerves are particularly susceptible to mechanical injury at vulnerable sites. The term entrapment (compression) neuropathy is used when the nerve is compressed, stretched, or angulated by adjacent anatomic structures to such an extent that dysfunction occurs. There are numerous entrapment neuropathies, and in many the initial or most conspicuous clinical complaints are of sensory symptoms or pain. Some of the more common syndromes are described below.

A. Radial nerve compression**.** The radial nerve may be compressed in the axilla by pressure from crutches or other causes; this is frequently seen in alcoholics and drug addicts who have fallen asleep with an arm draped over some hard surface. The resulting deficit is primarily motor, with weakness or paralysis occurring in the muscles supplied by the nerve, but sensory changes may also occur, especially in a small region on the back of the hand between the thumb and index finger. Treatment involves preventing further compression of the nerve. Recovery usually occurs spontaneously and completely except when a very severe injury has resulted in axonal degeneration. Physical therapy and a wrist splint may be helpful until recovery occurs.

B. Median nerve compression. Compression of the median nerve can occur in the carpal tunnel at the wrist. Carpal tunnel syndrome is common during pregnancy and can occur as a complication of trauma, degenerative arthritis, tenosynovitis, myxedema, and acromegaly. Early symptoms are pain and paresthesias confined to a median nerve distribution in the hand, ie, involving primarily the thumb, index, and middle fingers and the lateral half of the ring finger. There may be pain in the forearm and, in occasional patients, even in the upper arm, shoulder, and neck. Symptoms are often particularly troublesome at night and may awaken the patient from sleep. As the neuropathy advances, weakness and atrophy may eventually develop in the thenar muscles. Examination reveals impaired cutaneous sensation in the median nerve distribution in the hand and, with motor involvement, weakness and wasting of the abductor pollicis brevis and opponens pollicis muscles. There may be a positive Tinel sign (percussion of the nerve at the wrist causes paresthesias in its distribution) or a positive response to Phalen's maneuver (flexion of the wrist for I minute exacerbates or reproduces symptoms). The diagnosis can generally be confirmed by electrophysiologic studies, showing sensory or motor conduction velocity to be slowed at the wrist; there may be signs of chronic partial denervation in median-supplied muscles of the hand. If the symptoms fail to respond to local corticosteroid injections or simple maneuvers such as wearing a nocturnal wrist splint, surgical decompression of the carpal tunnel may be necessary.

C. Ulnar nerve dysfunction. Ulnar nerve dysfunction at the elbow leads to paresthesias, hypes the paresthesias, and nocturnal pain in the little finger and ulnar border of the hand. Pain may also occur about the elbow. Symptoms are often intensified by elbow flexion or use of the arm. Examination may reveal sensory loss on the ulnar aspect of the hand and weakness of the adductor pollicis, the deep

flexor muscles of the fourth and fifth digits, and the intrinsic hand muscles. The lesion may result from external pressure, from entrapment within the cubital tunnel, or from cubitus valgus deformity causing chronic stretch injury of the nerve. Electrodiagnostic studies may be helpful in localizing the lesion.

Avoiding pressure on or repetitive flexion and extension of the elbow, combined in some instances with splinting the elbow in extension, is sometimes sufficient to arrest progression and alleviate symptoms. Surgical decompression or ulnar nerve transposition to the flexor surface of the arm may also be helpful, depending on the cause and severity of the lesion and the duration of symptoms.

An ulnar nerve lesion may develop in the wrist or palm of the hand in association with repetitive trauma, arthritis, or compression from ganglia or benign tumors. Involvement of the deep terminal branch in the palm leads to a motor deficit in ulnar innervated hand muscles other than the hypothenar group, while a more proximal palmar lesion affects the latter muscles as well; there is no sensory deficit. With lesions at the wrist involving either the ulnar nerve itself or its deep and superficial branches, both sensory and motor changes occur in the hand. Sensation over the dorsal surface of the hand is unaffected, however, because the cutaneous branch to this region arises proximal to the wrist. Surgical treatment is helpful in relieving compression from a ganglion or benign tumor.

D. Peroneal nerve lesions. Peroneal nerve lesions can occur secondary to trauma or to pressure about the knee at the head of the fibula. The resulting weakness or paralysis of foot and toe extension – and foot eversion – is accompanied by impaired sensation over the dorsum of the foot and the lower anterior aspect of the leg. The ankle reflex is preserved, as is foot inversion. Treatment is purely supportive. It is important to protect the nerve from further injury or compression. Patients with foot drop may require a brace until recovery occurs. Recovery occurs spontaneously with time and is usually complete unless the injury was severe enough to cause marked axonal degeneration.

Diseases of the brachial plexus

In the brachial plexus, the axons derived from the nerve roots of C4 to T1 (or T2) are regrouped and distributed to the various nerves that innervate the upper limb. In addition to total paralysis of the entire upper limb, there are two main types of partial lesion: upper and lower brachial plexus lesions.

Upper brachial plexus lesion (Erb–Duchenne palsy). This type of lesion involves the fibers originating in the C5 and C6 nerve roots. The affected muscles are the abductors and external rotators of the shoulder joint, the flexor muscles of the upper arm, the supinator m., and sometimes the elbow extensors and the extensors of the hand. A sensory deficit is not necessarily present; if there is one, it is located in the area of the shoulder, on the outer surface of the upper arm, or on the radial edge of the forearm.

Lower brachial plexus lesion (Dejerine–Klumpke palsy). This type of lesion involves the fibers originating in the C8 and T1 roots. Its prominent findings include weakness of the intrinsic muscles of the hand, sometimes also of the long flexors of the fingers, and rarely of the wrist flexors. The triceps brachii m. usually

remains intact. The mechanism of the precipitating accident, and the anatomical relationships in this area, often lead to an accompanying dysfunction of the cervical sympathetic supply, resulting in Horner syndrome with impaired sweating. On the basis of these findings, a lesion of the T1 root is presumed to be present, proximal to the origin of its branch to the sympathetic chain. There is always a sensory deficit involving the ulnar edge of the forearm, hand, and fingers.

Etiologic classification of brachial plexus lesions. 1) Traumatic lesions of the brachial plexus are usually due to motor vehicle accidents; rarer causes include occupational injury and direct stab or gunshot wounds. The initial clinical finding is not uncommonly a total upper limb paralysis, which may later improve until it resembles one of the types of localized brachial plexus lesion described above. The prognosis is generally better for upper brachial plexus lesions; bloody CSF obtainable by lumbar puncture and, later, clinical evidence of myelopathy are poor prognostic signs indicating probable nerve root avulsion. In such patients, MRI may reveal empty nerve root pouches. The treatment consists of the fitting of an abduction splint and the performance of passive exercises to prevent freezing of the shoulder joint. Brachial plexus surgery is highly complex and demanding and is occasionally resorted to in cases of upper brachial plexus injury.

Brachial plexus palsy caused by trauma during delivery is the result of obstetrical complications, such as breech delivery. When the damaged axons regenerate, they may reconnect to the "wrong" muscles and/or muscle groups, leading to pathological accessory movements and abnormal motor patterns.

2) Compressive lesions of the brachial plexus. External compression can injure the brachial plexus in persons who carry heavy loads on their shoulders or wear heavy backpacks. Lesions of this type usually affect the upper brachial plexus and sometimes only individual branches of it. The long thoracic n. is most frequently involved.

Compression at anatomical bottlenecks. The collective designation "thoracic outlet syndrome" (TOS) is commonly used for these conditions, usually in nonspecific fashion, and often, unfortunately, as a vague term for brachialgia of as yet undetermined origin, or for other unexplained symptoms relating to the brachial plexus. Scalene syndrome is usually due to the anomalous presence of a cervical rib, a fibrous band (which may be visible in a CT scan), or some other type of structural anomaly in the scalene hiatus. The typical manifestations of scalene syndrome include: clinical evidence of a lower brachial plexus lesion, worsening of symptoms on lowering of the arm, and fixed or motion-induced circulatory insufficiency of the subclavian a. (as revealed by a vascular bruit, and/or by disappearance of the radial pulse when certain maneuvers are performed, e. g., the Adson maneuver – turning the chin to the side of the lesion, with simultaneous backward bending of the head).

Costoclavicular syndrome. This syndrome, like the scalene syndrome, should be diagnosed only if a causative anatomical anomaly and specific neurological deficits (usually, a lower brachial plexus palsy) can be found. An arteriogram is occasionally helpful in establishing the diagnosis, as it may demonstrate motion-dependent compression of the subclavian artery or vein.

3) Other causes of brachial plexus lesions. Radiation-induced brachial plexus lesions usually appear with a latency of one or more years after radiotherapy, usually in women who have been treated with surgery and radiotherapy for breast cancer. In 15% of patients, pain is the main symptom; it can increase over the course of several years. The differentiation of radiation-induced brachial plexopathy from a recurrent malignant tumor is not always easy; a short interval between the completion of radiotherapy and the onset of pain (except when a very high radiation dose was given) and very intense pain, both tend to suggest a recurrent tumor rather than radiation injury as the cause. Imaging studies are helpful, but even these cannot always reliably distinguish scarring from new tumor tissue.

Pancoast tumors of the apex of the lung usually cause a lower brachial plexus palsy accompanied by severe pain. The sympathetic chain is usually involved as well; thus, Horner syndrome and diminished sweating in the upper body on the affected side are typical findings.

Polyneuropathy (general features)

This term denotes a disorder in which the function of numerous peripheral nerves is affected at the same time. This leads to a predominantly distal and symmetric deficit with loss of tendon reflexes. Polyneuropathies are sometimes subclassified according to the primary site at which the nerve is affected. In axonopathies, the axon is the principal pathologic target; most polyneuropathies fall into this category. Myelinopathies are conditions that involve the myelin sheath surrounding the axon. These disorders include acute idiopathic polyneuropathy (Guillain-Barre syndrome), chronic inflammatory demyelinating neuropathy, diphtheria, certain paraneoplastic and paraproteinemic states, and some hereditary metabolic conditions (metachromatic leukodystrophy, type III hereditary motor and sensory neuropathy, Krabbe's disease). Finally, certain disorders – termed neuronopathies – principally affect nerve cell bodies in the anterior horn of the spinal cord or dorsal root ganglion. Examples are type II hereditary motor and sensory neuropathy, pyridoxine-induced neuropathy, and some paraneoplastic syndromes.

A. Evaluation of patients. Polyneuropathy that develops acutely over a few days usually relates to an inflammatory process, as in the Guillain-Barre syndrome. It may also relate to an underlying neoplasm, to infections such as diphtheria, to metabolic disorders such as acute intermittent porphyria, or to exposure to such toxic substances as thallium or triorthocresyl phosphate. A chronic course with a gradual evolution over several years is typical of many hereditary or metabolic polyneuropathies but also characterizes chronic inflammatory demyelinating polyneuropathy. Mononeuropathy of acute onset is likely to be traumatic or ischemic in origin, while one evolving gradually is more likely to relate to entrapment (ie, compression by neighboring anatomic structures) or to recurrent minor trauma.

Polyneuropathies that develop during childhood or early adult life often have a hereditary basis, but they may also relate to an underlying inflammatory disorder.

Those developing in later life are more likely to be due to a metabolic, toxic, or inflammatory disorder or to an underlying neoplasm. Mononeuropathy presenting in the neonatal period is likely to be developmental in origin or related to birth injury; one developing in later life may relate to entrapment or injury that is often occupationally determined.

Various industrial substances can lead to peripheral neuropathy, including carbon disulfide, n-hexane, ethylene oxide, methyl bromide, acrylamide, triorthocresyl phosphate and certain other organophosphates, DDT, arsenic, lead, and thallium. A mononeuropathy is sometimes the first clinical manifestation of an occupationally related polyneuropathy, but it may also develop in response to entrapment or recurrent minor occupational trauma.

A peripheral neuropathy may also relate to an underlying malignant neoplasm. The peripheral nerves, spinal nerves, and limb plexuses may be compressed or infiltrated by extension of primary tumors or metastatic lymph nodes. Neoplastic disease can also lead to a nonmetastatic (paraneoplastic) sensory or sensorimotor polyneuropathy or to Lambert-Eaton syndrome.

B. Differential diagnosis. Peripheral neuropathies can lead to a motor or sensory deficit or both. The preservation of sensation and tendon reflexes distinguishes the motor deficit that results from pure pyramidal lesions or is associated with spinal muscular atrophies, myopathies, or disorders of neuromuscular transmission from that caused by peripheral nerve involvement. Myelopathies are characterized by a pyramidal deficit below the level of the lesion as well as by distal sensory loss. In tabes dorsalis, there is often a history of syphilitic infection, and examination reveals other stigmas of syphilis. In addition, tactile sensation is preserved. Radiculopathies are distinguished from peripheral neuropathies by the distribution of motor or sensory deficits. The presence of neck or back pain that radiates to the extremities in a radicular distribution also suggests a root lesion.

C. Investigative Studies. Laboratory studies in patients with peripheral neuropathy are directed at confirming the diagnosis and revealing any underlying cause. Electromyography may reveal evidence of denervation in the affected muscles and can be used to determine whether any motor units remain under voluntary control. Nerve conduction studies permit conduction velocity to be measured in motor and sensory fibers. On the basis of electrodiagnostic or histopathologic studies, peripheral neuropathies can be divided into demyelinating or axonal neuropathies. In the former, electromyography typically reveals little or no evidence of denervation but there is conduction block or marked slowing of maximal conduction velocity in affected nerves. In the axonal neuropathies, electromyography shows that denervation has occurred, especially distally in the extremities, but maximal nerve conduction velocity is normal or slowed only slightly.

In patients with electrophysiologically confirmed peripheral neuropathy, laboratory studies should include a complete blood count; erythrocyte sedimentation rate; serum urea nitrogen and creatinine, fasting blood glucose, and serum vitamin B_{12}; serum protein, protein electrophoresis, and

immunoelectrophoresis; liver and thyroid function blood tests; serologic tests for syphilis (FTA or MHA-TP), rheumatoid factor, and antinuclear antibody; and chest x-ray. If toxic causes are suspected, a 24-hour urine collection followed by analysis for heavy metals may be necessary, and hair and fingernail clippings can be analyzed for arsenic. Examination of a fresh specimen of urine for porphobilinogen and δ-aminolevulinic acid is necessary if porphyria is suspected.

Acute inflammatory polyneuropathy (Guillain-Barre syndrome)

Guillain-Barre syndrome (GBS) is an acute or subacute polyneuropathy that can follow nonspecific infection. GBS has an annual incidence of 1-2/100,000 worldwide and occurs at all ages. An upper respiratory tract or gastrointestinal infection precedes the onset of neurological symptoms by 1-3 weeks in 70% of patients. A considerable number of viruses or bacteria have been reported to trigger GBS. Of these the most frequent is *Campylobacter jejuni,* which is reported to precede GBS in 15%-46% of cases.

The exact pathogenesis of GBS is not fully understood. It is now recognized to be a clinical syndrome encompassing a number of pathological entities. About 75% of cases of GBS are demyelinating, with multifocal demyelination with mononuclear inflammatory cell infiltrates in the peripheral nerves. Cases of primarily axonal neuropathy involving either motor (acute motor axonal neuropathy) or motor and sensory (acute motor and sensory neuropathy) make up the remaining 25% of cases. An autoimmune origin is generally assumed on the basis of the close association with infection and the histological similarities with experimental autoimmune neuritis, an animal model of GBS. It is suggested that activation of T cells against peripheral nerve antigens initiates the auto-destructive process, and subsequently macrophages, cytokines, and antibodies lead to the full-blown inflammatory picture with demyelination.

Patients generally present with weakness that is symmetric, usually begins in the legs, is often more marked proximally than distally, and is sometimes so severe that it is life-threatening, especially if the muscles of respiration or swallowing are involved. Muscle wasting develops if axonal degeneration has occurred. Sensory complaints, while usually less marked than motor symptoms, are also frequent. The deep tendon reflexes are typically absent. There may be marked autonomic dysfunction, with tachycardia, cardiac irregularities, labile blood pressure, disturbed sweating, impaired pulmonary function, sphincter disturbances, paralytic ileus, and other abnormalities.

Investigative studies. The CSF often shows a characteristic abnormality, with increased protein concentration but a normal cell count; abnormalities may not be found in the first week, however. Electrophysiologic studies may reveal marked slowing of motor and sensory conduction velocity, or evidence of denervation and axonal loss. The time course of the electrophysiologic changes does not necessarily parallel any clinical developments.

Diagnostic criteria for Guillain-Barre syndrome (based on Asbury and Cornblath, 1990).

Required for diagnosis

Progressive weakness of more than one limb Distal areflexia with proximal areflexia or hyporeflexia
Supportive of diagnosis Progression for up to 4 weeks Relatively symmetric deficits Mild sensory involvement Cranial nerve (especially VII) involvement Recovery beginning within 4 weeks after progression stops Autonomic dysfunction No fever at onset Increased CSF protein after 1 week CSF white blood cell count ≤ 10/µl Nerve conduction slowing or block by several weeks
Against diagnosis Markedly asymmetric weakness Bowel or bladder dysfunction (at onset or persistent) CSF white blood cell count >50/µl CSF polymorphonuclear count >0/µl Well-demarcated sensory level
Excluding diagnosis Isolated sensory involvement Another polyneuropathy that explains clinical picture

Note. These criteria do not include up to 15% of variant syndromes.

Treatment. Plasmapheresis appears to reduce the time required for recovery and may decrease the likelihood of residual neurologic deficits. It is best instituted early, and it is indicated especially in patients with a severe or rapidly progressive deficit or respiratory compromise. Intravenous immunoglobulin (400 mg/kg/d for 5 days) appears to be equally effective and should be used in preference to plasmapheresis in adults with cardiovascular instability and in children; the two therapies are not additive.

In the past, corticosteroids were often prescribed for patients with a progressive downhill course, but recent studies have shown that these agents may affect the outcome adversely and even increase the time necessary for recovery. Therapy is otherwise symptomatic, the aim being to prevent such complications as respiratory failure or vascular collapse. For this reason, patients who are severely affected are best managed in intensive care units, where facilities are available for monitoring and assisted respiration if necessary (eg, if the vital capacity falls below about 1 L, the patient is short of breath, or the blood oxygen saturation declines). Volume replacement or treatment with pressor agents is sometimes required to counter hypotension, and low-dose heparin may help to prevent pulmonary embolism.

Symptoms and signs cease to progress by about 4 weeks into the illness. The disorder is self-limiting, and improvement occurs over the weeks or months following onset. About 70-75% of patients recover completely, 25% are left with

mild neurologic deficits, and 5% die, usually as a result of respiratory failure. The prognosis is poorer when there is evidence of preceding Campylobacter jejuni infection, and a more protracted course and less complete recovery are also likely when axonal degeneration rather than demyelination is the primary pathology. Advanced age, the need for ventilatory support, or more rapid onset of symptoms may also predict a poorer prognosis.

Chronic inflammatory demyelinating polyneuropathy is clinically similar to Guillain-Barre syndrome, but differs in the following ways: 1) chronic or relapsing-remitting course (more than four weeks); 2) possibly subacute course; 3) pain is common; 4) asymmetrical distribution of neurological deficits; 5) recurrent cranial nerve involvement 6) marked elevation of CSF protein concentration, often combined with an elevated IgG index and pleocytosis; 7) central nervous manifestations are more common than in Guillain-Barre syndrome; 8) electroneurography reveals evidence of focal demyelination or axonal damage. The disorder is often responsive to treatment with corticosteroids (prednisone, 60-100 mg/d for 2-4 weeks, then gradually tapered to 5-20 mg every other day), which may have to be continued on a long-term basis. In nonresponsive patients, treatment with azathioprine or cyclophosphamide may be helpful. In other instances, plasmapheresis or intravenous immunoglobulin therapy (400 mg/kg/d) is beneficial, although the response is usually short-lived; treatment therefore has to be continued intermittently to maintain benefit.

Metabolic & nutritional polyneuropathies

A. Diabetes Mellitus. Peripheral nerve involvement in diabetes is common and may be characterized by polyneuropathy, which is of mixed (sensory, motor, and autonomic;) character in about 70% of cases and predominantly sensory in about 30%; mononeuropathy multiplex; or mononeuropathy simplex. Such clinical manifestations can occur in isolation or in any combination. The incidence of peripheral nerve involvement may be influenced by the adequacy of diabetes control, which should, in any event, be optimal.

The most common manifestation is a distal sensory or mixed polyneuropathy, which is sometimes diagnosed, before it becomes symptomatic, from the presence of depressed tendon reflexes and impaired appreciation of vibration in the legs. Symptoms are generally more common in the legs than in the arms and consist of numbness, pain, or paresthesias. In severe cases, there is distal sensory loss in all limbs and some accompanying motor disturbance. Diabetic dysautonomia leads to many symptoms, including postural hypotension, disturbances of cardiac rhythm, impaired thermoregulatory sweating, and disturbances of bladder, bowel, gastric, and sexual function. Diabetic mononeuropathy multiplex is usually characterized by pain and weakness and often has a vascular basis. The clinical deficit will depend on the nerves that are affected. Diabetic amyotrophy is due to radiculoplexopathy, polyradiculopathy, or polyradiculoneuropathy. Pain, weakness, and atrophy of pelvic girdle and thigh muscles are typical, with absent quadriceps reflexes and little sensory loss. Diabetic mononeuropathy simplex is typically abrupt in onset and often painful.

CSF protein is typically increased in diabetic polyneuropathy and mononeuropathy multiplex.

Treatment and Prognosis. No specific treatment exists for the peripheral nerve complications of diabetes except when the patient has an entrapment neuropathy and may benefit from a decompressive procedure. Phenytoin (200-400 mg/d orally), mexiletine (600-900 mg/d), or carbamazepine (100-600 mg orally twice daily) may help to relieve shooting or stabbing neuropathic pain, while amitriptyline (75-150 mg orally at bedtime) or a combination of amitriptyline and fluphenazine may be useful for treating deep, constant, aching pain.

Postural hypotension may respond to treatment with salt supplementation; sleeping in an upright position; wearing waist-high elastic hosiery; fludrocortisone, 0.1-1 mg/d; and midodrine (an α-agonist), 10 mg three times daily. Treatment is otherwise symptomatic. Diabetic amyotrophy and mononeuropathy simplex usually improve or resolve spontaneously.

B. Other endocrinopathies. Hypothyroidism is a rare cause of polyneuropathy. More commonly, hypothyroidism is associated with entrapment neuropathy, especially carpal tunnel syndrome. Polyneuropathy may be mistakenly diagnosed in patients with proximal limb weakness caused by hypothyroid myopathy or in patients with delayed relaxation of tendon reflexes, a classic manifestation of hypothyroidism that is independent of neuropathy. Other neurologic manifestations of hypothyroidism such as acute confusional state, dementia, and cerebellar degeneration are discussed elsewhere.

Acromegaly also frequently produces carpal tunnel syndrome and, less often, polyneuropathy. Since many acromegalic patients are also diabetic, it may be difficult to determine which disorder is primarily responsible for polyneuropathy in a given patient.

C. Metabolic disorders. 1) Uremia. A symmetric sensorimotor polyneuropathy, predominantly axonal in type, may occur in uremia. It tends to affect the legs more than the arms and is more marked distally than proximally. Restless legs, muscle cramps, and burning feet have been associated with it. The extent of any disturbance in peripheral nerve function appears to relate to the severity of impaired renal function. The neuropathy itself may improve markedly with renal transplantation. Carpal tunnel syndrome (see below) has also been described in patients with renal disease and may develop distal to the arteriovenous fistulas placed in the forearm for access during hemodialysis. In patients on chronic hemodialysis, it often relates to amyloidosis and the accumulation of β_2-microglobulin. 2) Liver disease. Primary biliary cirrhosis may lead to a sensory neuropathy that is probably of the axonal type. A predominantly demyelinative polyneuropathy can occur in patients with chronic liver disease. There does not appear to be any correlation between the neurologic findings and the severity of the hepatic dysfunction. 3) Vitamin B_{12} deficiency. Vitamin B_{12} deficiency is associated with many features that are characteristic of polyneuropathy, including symmetric distal sensory and motor impairment and loss of tendon reflexes.

Infective polyneuropathies

A. Diphtheria. Corynebacterium diphtheriae infects tissues of the upper respiratory tract and produces a toxin that causes demyelination of peripheral nerves. Within about 1 month after infection, patients may develop a cranial motor neuropathy with prominent impairment of ocular accommodation. Blurred vision is the usual presenting complaint. Extraocular muscles and the face, palate, pharynx, and diaphragm may also be affected, but the pupillary light reflex is preserved. Recovery typically occurs after several weeks. A more delayed syndrome that commonly has its onset 2-3 months following the primary infection takes the form of a symmetric distal sensorimotor polyneuropathy. Most patients recover completely.

B. Sarcoidosis. Sarcoidosis can produce mononeuropathy or, rarely, polyneuropathy. The mononeuropathy commonly involves cranial nerves, especially the facial nerve, in which case the resulting syndrome may be indistinguishable from idiopathic facial paralysis (Bell's palsy). X-rays of the lungs and bones and determination of serum levels of angiotensin-converting enzyme are helpful in establishing the diagnosis. Treatment with prednisone, 60 mg/d orally followed by tapering doses, may speed recovery.

C. AIDS. Neuropathy is a common complication of HIV-l infection; involvement of peripheral nerves is seen at autopsy in about 40% of patients with AIDS. Distal symmetric sensorimotor polyneuropathy is the most common neuropathy associated with HIV-1 infection. Axons, rather than myelin, are primarily affected. The cause is unknown, but in some patients vitamin B_{12} deficiency or exposure to neurotoxic drugs may be responsible in part. HIV-1 is rarely identified in the affected nerves. Sensory symptoms predominate and include pain and paresthesias that affect the feet especially. Weakness is a minor or late feature. Ankle and sometimes knee reflexes are absent. The course is typically progressive and no treatment is available, but pain may be controlled pharmacologically, as described above for diabetic neuropathy. Plasmapheresis is of no benefit.

Inflammatory demyelinating polyneuropathy may occur early in HIV-1 infection and may follow an acute or chronic course. The neuropathy may be immune-mediated, but sometimes results from direct, secondary viral infection, as from cytomegalovirus. It is characterized by proximal, and sometimes distal, weakness with less-pronounced sensory disturbances and areflexia or hyporeflexia. The CSF is abnormal, with an elevated protein concentration and often a lymphocytic pleocytosis (unlike the findings in Guillain-Barre syndrome or chronic inflammatory demyelinating polyneuropathy in patients without HIV-1 infection). Some patients improve spontaneously or stabilize, and others may respond to corticosteroids, plasmapheresis, or intravenous immunoglobulins.

Lumbosacral polyradiculopathy occurs late in the course of HIV-1 infection, usually in patients with prior opportunistic infections. Cytomegalovirus infection is thought to be the cause, at least in some instances. Clinical features usually develop over several weeks and include diffuse, progressive leg weakness, back pain, painful paresthesias of the feet and perineum, lower extremity areflexia, and early urinary retention. The course may be fulminant, with ascending paralysis

leading to respiratory failure. The course is more benign in some patients, however, especially when the etiology is unclear. CSF findings include mononuclear or polymorphonuclear pleocytosis, elevated protein, and decreased glucose. It is always important to exclude meningeal lymphomatosis, cord compression, or syphilis as the underlying cause, as these require specific treatment and affect the prognosis. Patients with cytomegalovirus infection may respond to ganciclovir, 2.5 mg/kg intravenously every 8 hours for 10 days, then 7.5 mg/kg/d 5 days per week.

Mononeuropathy multiplex affects multiple cranial and peripheral nerves, resulting in focal weakness and sensory loss. Some cases may have an autoimmune basis, whereas others result from neoplastic or infectious causes (eg, cytomegalovirus infection) or from vasculopathy. In early HIV-1 infection, mononeuropathy multiplex may be a self-limited disorder restricted to a single limb, with spontaneous stabilization or improvement. Late in AIDS, multiple limbs may be affected in a progressive fashion.

Autonomic neuropathy tends to occur late in the course of HIV-1 infections and may lead to syncopal episodes, orthostatic hypotension, disturbances of sphincter or sexual function, impaired thermoregulatory sweating, and diarrhea. The dysautonomia may relate to central or peripheral pathology. Treatment is symptomatic (as discussed earlier under diabetic neuropathy).

Polyneuropathy due to arterial and connective tissue disease

Systemic vasculitides and collagen vascular diseases can produce polyneuropathy, mononeuropathy simplex, mononeuropathy multiplex, or entrapment neuropathy.

Systemic necrotizing vasculitis includes polyarteritis nodosa and allergic angiitis and granulomatosis (Churg-Strauss syndrome). Neuropathy occurs in about 50% of patients, most often as mononeuropathy multiplex, which may manifest itself with the acute onset of pain in one or more cranial or peripheral nerves. Distal symmetric sensorimotor polyneuropathy is less common. Treatment should begin as soon as the diagnosis is made; it includes prednisone, 60-100 mg/d orally, and cyclophosphamide, 2-3 mg/d orally. Plasmapheresis may also be helpful.

Wegener's granulomatosis is associated with mononeuropathy multiplex or polyneuropathy in up to 30% of cases. Treatment is the same as for systemic necrotizing vasculitis.

Giant cell arteritis. Mononeuropathy affecting cranial nerves innervating the extraocular muscles can occur.

Rheumatoid arthritis produces entrapment neuropathy (most commonly involving the median nerve) in about 45% of patients and distal symmetric sensorimotor polyneuropathy in about 30%. Mononeuropathy multiplex is a frequent feature in cases complicated by necrotizing vasculitis.

Systemic lupus erythematosus. Neuropathy occurs in up to 20% of patients. The most common pattern is a distal, symmetric sensorimotor polyneuropathy. An ascending, predominantly motor polyneuropathy (Guillain-Barre syndrome, see

above) can also occur, as may mononeuropathy simplex or multiplex, which often affects the ulnar, radial, sciatic, or peroneal nerve.

Sjogren's syndrome involves the peripheral nerves in about 20% of cases. Distal symmetric sensorimotor polyneuropathy is most common, entrapment neuropathy (affecting especially the median nerve) is also frequent, and mononeuropathy multiplex can occur.

Progressive systemic sclerosis (scleroderma) and mixed connective tissue disease may produce cranial mononeuropathy, which most often involves the trigeminal (V) nerve.

Neoplastic & paraproteinemic neuropathies

Nerve compression is a common complication of multiple myeloma, lymphoma, and carcinoma. Tumorous invasion of the epineurium may occur with leukemia, lymphoma, and carcinoma of the breast or pancreas.

Paraneoplastic syndromes. Carcinoma (especially oat-cell carcinoma of the lung) and lymphoma may be associated with neuropathies that are thought to be immunologically mediated, based on the detection of autoantibodies to neuronal antigens in several cases. Sensory or sensorimotor polyneuropathy occurs with both carcinoma and lymphoma. This can be either an acute or chronic disorder; it is sometimes asymmetric and may be accompanied by prominent pain.

Carcinoma can also cause sensory neuronopathy, a polyneuropathy that primarily affects the cell bodies of sensory neurons in the dorsal root ganglion. This rare condition may be the presenting manifestation of cancer. Initial symptoms of pain and numbness usually begin distally but sometimes begin proximally or in the face. The disorders often progress over days or several weeks, leading to marked sensory ataxia and impairment of all sensory modalities. Motor involvement is late, and autonomic dysfunction is uncommon. The CSF may have an inflammatory formulation. Treatment, even of the underlying tumor, is usually unrewarding.

Lymphoma may be complicated by motor neuronopathy, a disorder of anterior horn cells. Hodgkin's disease and angioimmunoblastic lymphadenopathy are sometimes associated with Guillain-Barre syndrome.

Paraproteinemias. Polyneuropathy is a common complication of multiple myeloma. Patients affected by lytic myeloma are usually men. The clinical picture is of a distal symmetric sensorimotor polyneuropathy. All sensory modalities are affected, pain is a frequent feature, and the reflexes are depressed. The disorder is usually progressive and leads to death within 2 years. Sclerotic myeloma may be accompanied by a chronic demyelinating polyneuropathy. Motor involvement predominates, but vibration and position sense may also be impaired, and the reflexes are depressed. Pain is less common than in the neuropathy of lytic myeloma, and symptoms may improve with treatment of the underlying cancer or by plasmapheresis. The POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) may complicate plasma cell dyscrasias, especially osteosclerotic myeloma. The sensorimotor polyneuropathy

may respond to treatment with corticosteroids or cyclophosphamide; irradiation of solitary osteosclerotic lesions may also be worthwhile.

A sensorimotor polyneuropathy similar to that observed with lytic myeloma may also occur in Waldenstrom's macroglobulinemia or benign monoclonal gammopathy. Treatment with immunosuppressant drugs and plasmapheresis is sometimes helpful.

Amyloidosis. Nonhereditary amyloidosis occurs as an isolated disorder (primary generalized amyloidosis) or in patients with multiple myeloma and may be associated with polyneuropathy. Polyneuropathy is also a feature of hereditary amyloidosis. Amyloid neuropathies are considered below in the section on hereditary neuropathies.

Drud-induced & toxic neuropathies

A. Alcohol. Polyneuropathy is one of the most common neurologic complications of chronic alcoholism; it can occur alone or in combination with other alcohol-related neurologic disorders, such as Wernicke's encephalopathy or the Korsakoff amnestic syndrome. Controversy exists concerning the relative contributions of direct neurotoxicity of alcohol and associated nutritional (especially thiamine) deficiency in producing polyneuropathy.

Alcoholic polyneuropathy is typically a symmetric distal sensorimotor neuropathy. The legs are particularly likely to be affected, resulting in defective perception of vibration and touch and depressed or absent ankle reflexes. In some cases, distal weakness is also pronounced and autonomic dysfunction may occur. When pain is a prominent feature, it may respond to the same treatment described above for painful diabetic neuropathy. Abstinence from alcohol and thiamine repletion can halt the progression of symptoms.

B. Drugs. A large number of drugs have been reported to cause neuropathies. Hydralazine, an antihypertensive drug, is associated on rare occasions with a predominantly sensory polyneuropathy that has been attributed to drug-induced pyridoxine deficiency and that resolves after the drug is discontinued. Isoniazid is a widely used antituberculous agent that interferes with pyridoxine metabolism and produces a polyneuropathy that principally affects the sensory neurons. High doses, hereditary variations in drug metabolism, and malnutrition predispose to this complication. Spontaneous recovery is the rule when administration of the drug is halted. Isoniazid-induced neuropathy can be prevented by concurrent administration of pyridoxine, 100 mg/d orally.

Pyridoxine (vitamin B_6) toxicity has been implicated as the cause of a sensory neuronopathy that disproportionately impairs vibration and position sense. This disorder occurs in patients taking at least 200 mg of pyridoxine daily – about 100 times the minimum daily requirement. Sensory ataxia, Romberg's sign, Lhermitte's sign, and ankle areflexia are common findings. Pain is less common, and motor involvement is unusual. Symptoms are usually reversible over months to years if the abuse ceases, but an irreversible syndrome has also been reported following intravenous administration of high doses of pyridoxine.

Vincristine produces a polyneuropathy in most patients who receive the drug for treatment of (usually hematologic) cancer. The earliest manifestations are distal sensory symptoms and loss of reflexes. Motor deficits may predominate later in the course, however. Constipation is a common finding and may be due to autonomic involvement. Discontinuing the drug or administering it at a reduced dosage often leads to improvement.

C. Toxins. Organic compounds implicated as causes of polyneuropathy include hexacarbons present in solvents and glues (eg, n-hexane, methyl n-butyl ketone) and organophosphates used as plasticizers or insecticides (eg, triorthocresylphosphate). Sensory involvement is most striking in n-hexane neuropathy, whereas neuropathy caused by triorthocresyl phosphate primarily affects motor nerves.

Heavy metals may also be responsible for polyneuropathy. Neuropathy caused by lead, arsenic, and thallium. Gold, which is used to treat rheumatoid arthritis, may cause a symmetric polyneuropathy, and cisplatin (a platinum analogue with anticancer activity) may produce a sensory neuropathy.

Eosinophilia-myalgia syndrome was first identified in 1989 in patients taking L-tryptophan who developed disabling myalgias with blood eosinophil counts above 1,000/μL. About 85% of patients are women. The cause appears to be 1,1'-ethylidenebis [tryptophan], a contaminant in certain commercial preparations of L-tryptophan, which have since been withdrawn. Symptoms include myalgia, arthralgia, dyspnea, cough, rash, fever, and sclerodermiform skin changes. Neurologic findings include weakness of distal and proximal limb and bulbar muscles, distal sensory loss, and areflexia. Eosinophilia, leukocytosis, and elevated liver enzymes are typical. Nerve conduction studies and electromyography may show evidence of polyneuropathy, myopathy, or both. Inflammation is prominent in skin biopsy specimens, but less so in nerve and muscle, which show primarily axonal degeneration and muscle fiber atrophy. Treatment is discontinuation of L-tryptophan and administration of corticosteroids, nonsteroidal antiinflammatory drugs, and analgesics. Most patients improve or recover fully, but deaths have been reported.

Hereditary neuropathies

A. Idiopathic. Hereditary motor and sensory neuropathies (HMSN) include the hypertrophic (HMSN type I) and neuronal (HMSN type II) forms of Charcot-Marie-Tooth disease as well as Dejerine-Sottas disease (HMSN type III). HMSN type I is a slowly progressive demyelinating neuropathy that occurs either sporadically or with a dominant, X-linked, or recessive mode of inheritance. Dominant inheritance is the most common pattern, and genetic studies have shown linkage to the short arm of chromosome 17, the long arm of chromosome 1, or the X chromosome. When chromosome 17 is involved (as occurs in most cases), there is duplication of the PMP-22 gene that can be detected in single affected individuals and therefore forms the basis of a useful diagnostic test. On chromosome 1, the myelin protein zero (P0) gene has been implicated, whereas point mutations of the connexin 32 gene have been incriminated in the X-linked

form. The nerves may be palpably enlarged. HMSN type II, which is less common, affects the anterior horn cells and thus resembles progressive spinal muscular atrophy. Genetic studies of the autosomal dominant form have shown linkage to chromosome 1p in some cases. HMSN type III is a slowly progressive demyelinating disorder that usually has a recessive mode of inheritance and progresses from its onset in infancy or childhood to cause severe disability by the third decade of life. The nerves are typically enlarged.

Hereditary sensory and autonomic neuropathies (HSAN) also take a variety of forms. In HSAN type I, there is a dominant inheritance, a gradually progressive course from onset in early adulthood, and symmetric loss of distal pain and temperature perception, with relative preservation of light touch. Perforating ulcers over pressure points and painless infections of the extremities are common. The tendon reflexes are depressed, but there is little, if any, motor disturbance. In HSAN type II, inheritance is recessive, onset is in infancy or early childhood, all sensory modalities are affected, and tendon reflexes are lost. HSAN type III (Riley-Day syndrome, familial dysautonomia) is a recessive disorder that commences in infancy and is characterized by conspicuous autonomic dysfunction (absent tearing, labile temperature and blood pressure), accompanied by absent taste sensation, impaired pain and temperature sensation, and areflexia. HSAN type IV is associated with congenital insensitivity to pain and absent sweating.

Polyneuropathy can occur in both the hereditary and nonhereditary forms of amyloidosis. Because small-diameter sensory and autonomic nerve fibers are especially likely to be involved, pain and temperature sensation and autonomic functions are prominently affected. Clinical presentation is commonly with distal paresthesias, dysesthesias, and numbness; postural hypotension; impaired thermoregulatory sweating; and disturbances of bladder, bowel, or sexual function. Distal weakness and wasting eventually occur. The tendon reflexes are often preserved until a relatively late stage. Entrapment neuropathy – especially carpal tunnel syndrome – may develop as a consequence of amyloid deposits. There is no specific treatment.

Friedreich's ataxia usually has a recessive mode of inheritance but occasionally occurs with dominant inheritance. It is caused in many cases by a triplet repeat expansion in a noncoding region of the frataxin gene (X25) on chromosome 9q13-q21.l, but there is some heterogeneity of phenotype and variation in age of onset among patients with this expansion. This expansion has not been found in all cases, suggesting that other genetic or environmental factors are sometimes responsible. An ataxic gait develops, followed by clumsiness of the hands and other signs of cerebellar dysfunction. Involvement of peripheral sensory fibers leads to sensory deficits of the limbs, with depressed or absent tendon reflexes. There may also be leg weakness and extensor plantar responses from central motor involvement.

Hereditary neuropathy with liability to pressure palsies is a genetically heterogeneous disorder that relates most commonly to deletion of the PMP-22 gene on chromosome 17. Inheritance is as an autosomal dominant trait with variable expression. Patients present with simple or multiple mononeuropathies that occur

after mild pressure or stretch of nerves, and electrophysiologic studies reveal that abnormalities are more widespread than is evident clinically.

B. Metabolic. In acute intermittent porphyria, which is transmitted by recessive inheritance, the initial neurologic manifestation is often a polyneuropathy that (usually) involves motor more than sensory fibers. Sensory symptoms and signs may be predominantly proximal or distal. The peripheral nerves may also be affected in variegate porphyria.

Two recessive lipidoses are associated with polyneuropathy with a typical onset in infancy or childhood. These are metachromatic leukodystrophy, which results from deficiency of the enzyme arylsulfatase A, and Krabbe's disease, which is due to galactocerebroside β-galactosidase deficiency. Both are inherited in an autosomal recessive fashion.

Lipoprotein deficiencies that cause polyneuropathy include abetalipoproteinemia, which is associated with acanthocytosis, malabsorption, retinitis pigmentosa, and cerebellar ataxia; and Tangier disease, which produces cataract, orange discoloration of the tonsils, and hepatosplenomegaly. These are autosomal recessive conditions.

Refsum's disease is an autosomal recessive disorder related to impaired metabolism of phytanic acid. It produces polyneuropathy, cerebellar ataxia, retinitis pigmentosa, and ichthyosis. It can be treated by restricting dietary intake of phytol. Plasmapheresis to reduce body stores of phytanic acid may also be helpful at the initiation of treatment.

Fabry's disease is an X-linked recessive deficiency of the enzyme a-galactosidase-A. It results in a painful sensory and autonomic neuropathy, angiokeratomas, renal disease, and an increased incidence of stroke. The responsible gene has been localized to the long arm of the X chromosome; mutations causing the disease have been recognized and include gene rearrangements, an RNA-splicing defect, and various exotic lesions. Phenytoin or carbamazepine may be helpful in treating the pain that characterizes the disorder. Enzyme replacement therapy is under investigation.

BACK & NECK PAIN

Spinal disease occurs most commonly in the neck or low back and can cause local or root pain or both. It can also lead to pain that is referred to other parts of the involved dermatomes. Pain from the lower lumbar spine, for example, is often referred to the buttocks. Conversely, pain may be referred to the back from the viscera, especially the pelvic organs. Local pain may lead to protective reflex muscle spasm, which in turn causes further pain and may result in abnormal posture, limitation of movement, and local spinal tenderness.

Experimental studies suggest that neck or back pain may originate from many spinal structures, including ligaments, facet joints, the vertebral periosteum, the paravertebral musculature and fascia, blood vessels, the anulus fibrosus, and spinal nerve roots. Perhaps most common are musculoligamentous injuries and

age-related degenerative processes in the intervertebral disks and facet joints. Other common problems include spinal stenosis and disk herniation.

The history may provide clues to the underlying cause, and physical examination will define any neurologic involvement. Diagnostic studies that can help in evaluating patients include x-rays of the affected region and a complete blood count and erythrocyte sedimentation rate (especially if infective or inflammatory disorders or myeloma is suspected); determination of serum protein and protein electrophoresis; and measurement of serum calcium, phosphorus, alkaline and acid phosphatase, and uric acid. Electromyography may be helpful in determining the extent and severity of root involvement; it also provides a guide to prognosis. A CT scan, MRI of the spine, or a myelogram may be necessary, especially if neoplasm is suspected, neurologic deficits are progressive, pain persists despite conservative treatment measures, or there is evidence of cord involvement. At myelography, CSF can be obtained for laboratory examination.

Low back pain

Low back pain is a common cause of time lost from work. It has many causes.

Trauma. Unaccustomed exertion or activity – or lifting heavy objects without adequate bracing of the spine – can cause musculoskeletal pain that improves with rest. Clinical examination commonly reveals spasm of the lumbar muscles and restricted spinal movements. Management includes local heat, bed rest on a firm mattress, nonsteroidal anti-inflammatory drugs or other analgesics, and muscle-relaxant drugs, eg, diazepam, tolperizon. Vertebral fractures that follow more severe injury and lead to local pain and tenderness can be visualized at radiography. If cord involvement is suspected – eg, because of leg weakness following injury – the patient must be immobilized until radiographed to determine whether fracture – dislocation of the vertebral column has occurred.

Prolapsed lumbar intervertebral disk. This most commonly affects the L5-S1 or the L4-5 disk. The prolapse may relate to injury, but in many patients it commonly follows minor strain or normal activity. Protruded disk material may press on one or more nerve roots and thus produce radicular pain, a segmental motor or sensory deficit, or a sphincter disturbance in addition to a painful stiff back.

Lumbar osteoarthropathy. This tends to occur in later life and may cause low back pain that is increased by activity. Radiologic abnormalities vary in severity. In patients with mild symptoms, a surgical corset is helpful, while in more severe cases operative treatment may be necessary. Even minor changes may cause root or cord dysfunction in patients with a congenitally narrowed spinal canal (spinal stenosis), leading to the syndrome of intermittent claudication of the cord or cauda equina. This is characterized by pain – sometimes accompanied by weakness or radicular sensory disturbances in the legs – that occurs with activity or with certain postures and is relieved by rest. In such circumstances, spinal decompression is indicated.

Ankylosing spondylitis. Backache and stiffness, followed by progressive limitation of movement, characterize this disorder, which occurs predominantly in young men. Characteristic early radiologic findings consist of sclerosis and narrowing of the sacroiliac joints. Treatment is with nonsteroidal anti-inflammatory agents, especially indomethacin or aspirin. Physical therapy, including postural exercises, is also important.

Neoplastic disease. Extradural malignant tumors are an important cause of back pain and should be suspected if there is persistent pain that worsens despite bed rest. They may eventually lead to cord compression or a cauda equina syndrome, depending upon the level of involvement. There may initially be no change on plain radiographs of the spine, but a bone scan is sometimes revealing. Benign osteogenic tumors also produce back pain, and plain x-rays then show a lytic lesion; treatment is by excision.

Infections. Tuberculous and pyogenic infections of the vertebrae or intervertebral disks can cause progressive low back pain and local tenderness. While there are sometimes no systemic signs of infection, the peripheral white cell count and erythrocyte sedimentation rate are raised. X-rays may show disk space narrowing and a soft tissue mass, but they are frequently normal initially.

The osteomyelitis requires long-term antimicrobial therapy; surgical debridement and drainage may also be needed. Spinal epidural abscess similarly presents with localized pain and tenderness, sometimes associated with osteomyelitis. Cord compression may occur with the onset of a rapidly progressive flaccid paraplegia. MRI, CT scanning, or myelography and operative treatment are undertaken urgently if there is evidence of cord compression. In early cases without neurologic involvement, treatment with antibiotics alone may be sufficient.

Osteoporosis. Low back pain is a common complaint in patients with osteoporosis, and vertebral fractures may occur spontaneously or after trivial trauma. Pain may be helped by a brace to support the back. It is important that patients keep active and take a diet containing adequate amounts of calcium, vitamin D, and protein. Estrogen therapy may be helpful in postmenopausal women. In special circumstances, calcitonin, sodium fluoride, or phosphate supplements are helpful.

Referred pain. Disease of the hip joints may cause pain in the back and thighs that is enhanced by activity; examination reveals limitation of movement at the joint with a positive Patrick sign (hip pain on external rotation of the hip), and x-rays show degenerative changes. Aortic aneurysms, cardiac ischemia, visceral and genitourinary disease (especially pelvic disorders in women), and retroperitoneal masses also cause back pain. There are often other symptoms and signs that suggest the underlying disorder. Moreover, there is no localized spinal tenderness or restriction of motility. Treatment is of the underlying cause.

Nonspecific chronic back pain. In many patients whose chronic back pain poses a difficult management problem, there are no objective clinical signs or obvious causes of pain despite detailed investigations. In some cases, the pain may have a postural basis; in others, it may be a somatic manifestation of a psychiatric

disorder. Pain that initially had an organic basis is often enhanced or perpetuated by nonorganic factors and leads to disability out of proportion to the symptoms.

Nonsteroidal anti-inflammatory drugs may provide short-term symptomatic relief. There is some controversy about the chronic use of narcotic analgesics in patients with persisting low back pain, but such agents are generally best avoided. Treatment with tricyclic antidepressant drugs is sometimes helpful, and psychiatric evaluation may be worthwhile. Unnecessary surgical procedures must be avoided.

Neck pain

Neck pain is a common problem in the general population; surveys indicate that approximately one-third of the adult population have experienced it over the previous year and in many instances it lasts for more than 6 months.

Congenital abnormalities of the cervical spine, such as hemivertebrae or fused vertebrae, basilar impression, and instability of the atlantoaxial joint, can cause neck pain. The traumatic, infective, and neoplastic disorders mentioned above as causes of low back pain can also affect the cervical spine and then produce pain in the neck. Rheumatoid arthritis may involve the spine, especially in the cervical region, leading to pain, stiffness, and reduced mobility; cord compression may result from displacement of vertebrae or atlantoaxial subluxation and can be life-threatening if not treated by fixation.

Cervical injuries are an important cause of neck pain. Whiplash flexion-extension injuries have become especially common as a result of automobile accidents. Other occult cervical injuries such as disk clefts and fissures may be responsible for symptoms in some instances, but are difficult to recognize. Management of persistent symptoms following whiplash injuries is controversial. Conservative therapeutic measures are appropriate. Other approaches sometimes advocated include block of cervical facet joints with bupivacaine and injection into the joints of depot corticosteroids, but the response is variable and often short-lived. Subluxed cervical facet joints are another well-recognized complication of automobile accidents. Even minor trauma may lead to cervical fractures in an apparently ankylosed region in patients with diffuse idiopathic skeletal hyperostosis, but major neurologic deficits are common in such circumstances.

Acute cervical disk protrusion. Patients may present with neck and radicular arm pain that is exacerbated by head movement. The mechanism responsible for the pain is unclear; pressure on nerve roots is unlikely to be the sole cause because pain may resolve with time and conservative measures despite persisting compression. With lateral herniation of the disk, there may also be segmental motor, sensory, or reflex changes, usually at the C6 or C7 level, on the affected side. With more centrally directed herniations, spastic paraparesis and a sensory disturbance in the legs, sometimes accompanied by impaired sphincter function, can occur as a result of cord involvement. The diagnosis is confirmed by CT scan, MRI, or myelography. However, these imaging studies may show abnormalities in asymptomatic subjects in middle or later life, so that any disk protrusion may be incidental and unrelated to patients' symptoms. Electromyography may help to establish that anatomic abnormalities are of functional relevance.

In mild cases, bed rest or intermittent neck traction, followed by immobilization of the neck in a collar for several weeks, often helps. If these measures fail or if there is a significant neurologic deficit, surgical treatment may be necessary.

Cervical spondylosis is an important cause of pain in the neck and arms, sometimes accompanied by a segmental motor or sensory deficit in the arms or by spastic paraparesis.

Herpes zoster (shingles)

This viral disorder becomes increasingly common with advancing age, causing an inflammatory reaction in one or more of the dorsal root or cranial nerve ganglia, in the affected root or nerve itself, and in the CSF. There seems to be spontaneous reactivation of varicella virus that remained latent in sensory ganglia after previous infection. Herpes zoster is common in patients with lymphoma, especially following regional radiotherapy. The initial complaint is of a burning or shooting pain in the involved dermatome, followed within 2-5 days by the development of a vesicular erythematous rash. The pain may diminish in intensity as the rash develops. The rash becomes crusted and scaly after a few days and then fades, leaving small anesthetic scars. Secondary infection is common. The pain and dysesthesias may last for several weeks or, in some instances, may persist for many months (postherpetic neuralgia) before subsiding, especially in the elderly. The increased incidence and severity of postherpetic neuralgia with age may reflect an age-related reduction in virus-specific cell-mediated immunity. It is not clear whether immunocompromise secondary to HIV infection or connective tissue disease predisposes to postherpetic neuralgia. Pain is exacerbated by touching the involved area. Superficial sensation is often impaired in the affected dermatome, and focal weakness and atrophy can also occur. Signs are usually limited to one dermatome, but more are occasionally involved. Mild pleocytosis and an increased protein concentration sometimes occur in the CSF. The most commonly involved sites are the thoracic dermatomes, but involvement of the first division of the fifth cranial nerve, also common, is especially distressing and may lead to corneal scarring and anesthesia, as well as to a variety of other ocular complications. Facial (VII) nerve palsy occurring in association with a herpetic eruption that involves the ear, palate, pharynx, or neck is called Ramsay Hunt syndrome. Other rare complications of herpes zoster include other motor neuropathies, meningitis, encephalitis, myelopathy, and cerebral angiopathy.

There is no specific treatment. Analgesics provide symptomatic relief. Corticosteroids or acyclovir may reduce the duration and severity of the acute eruption, but neither reduces the likelihood that postherpetic neuralgia will occur. Although postherpetic neuralgia can be very distressing, it sometimes responds to treatment with carbamazepine, up to 1200 mg/d; phenytoin, 300 mg/d; or amitriptyline, 10-100 mg at bedtime. Attempts at relieving postherpetic neuralgia by peripheral nerve section are generally unrewarding, but treatment with topically applied local anesthetics is sometimes helpful.