

24.16 Diseases of the peripheral nerves 6176

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Robert D.M. Hadden

ESSENTIALS Disorders of peripheral nerve function can be categorized in terms of the site of the primary disturbance. (1) **Neuronopathies** (sensory or autonomic neuronopathies are also known as ganglionopathies)—conditions causing death of the neuron cell bodies which then leads to degeneration of axons; (2) **Axonal neuropathies**—conditions that affect axons; (3) **Demyelinating neuropathies**—conditions in which the myelin sheaths or supporting Schwann cells are damaged and the axons are relatively preserved. Combinations of axonal and demyelinating pathology are common. (4) **Interstitial neuropathies**—conditions in which there is infiltration of the endoneurium; for instance, by granuloma or amyloid. **Clinical pattern** Peripheral neuropathy characteristically causes predominantly distal weakness (with or without atrophy), sensory changes and/or autonomic malfunction, either alone or in combination. These occur in an anatomical distribution appropriate to the nerve or nerves affected, with three broad categories recognized: (1) **mononeuropathy**—a lesion of an isolated peripheral nerve; (2) **multifocal neuropathy** (multiple mononeuropathies or ‘mononeuritis multiplex’); and (3) **polyneuropathy**—diffuse and bilaterally symmetrical disturbance of function, typically length dependent (affecting nerves in proportion to their length). **Investigation** The diagnosis can usually be made from the history and examination. Presence of both localized and generalized neuropathies may be confirmed by nerve conduction studies. Simple blood tests for diabetes mellitus, B12 deficiency, and common medical causes are sufficient for the diagnosis of many cases. Cerebrospinal fluid examination may be useful—especially in suspected inflammatory demyelinating polyradiculopathy. When the diagnosis is not revealed by simple tests an extensive range of investigations for rare causes may be needed. Causes of

peripheral neuropathies Mononeuropathies—common conditions include median nerve entrapment due to carpal tunnel syndrome, and compression of the ulnar nerve at the elbow and the common peroneal nerve at the fibular head. Generalized neuropathies—causes include (1) diabetes mellitus—most commonly producing a symmetrical sensory polyneuropathy; autonomic neuropathy may be debilitating; (2) alcohol—usually in association with thiamine deficiency; (3) other metabolic/ endocrine disorders (e.g. amyloidosis, uraemia, hypothyroidism, acromegaly, critical illness polyneuropathy); (4) toxic—including industrial/environmental substances (e.g. acrylamide, lead, thallium) and drugs (e.g. phenytoin, cisplatin, isoniazid, vincristine, thalidomide); (5) deficiencies (e.g. thiamine, vitamin B12); (6) inflammatory (e.g. Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy), multifocal motor neuropathy, paraprotein-associated neuropathy; (7) infection related—leprosy, Lyme disease, HIV infection; (8) granulomatous—sarcoidosis; (9) vasculitic disorders; (10) neoplastic and paraneoplastic—most often with bronchial or ovarian malignancy; (11) genetic conditions (e.g. Charcot-Marie-Tooth disease; hereditary motor and sensory neuropathy), hereditary neuropathy with liability to pressure palsies, and multisystem conditions including familial amyloid polyneuropathy; and (12) chronic idiopathic axonal polyneuropathy—the cause of about 25% of cases

of late-onset symmetrical polyneuropathy remains unknown despite extensive investigation.

General principles Structure of peripheral nerves The peripheral nerves consist of bundles (fascicles) of unmyelinated and myelinated axons that have their cell bodies in the anterior horns of the spinal cord (motor), dorsal root ganglia (sensory), or autonomic ganglia. Each fascicle is surrounded by a lamellated cellular sheath, the perineurium, which provides a diffusion barrier that separates the endoneurial compartment from the extracellular 24.16 Diseases of the peripheral nerves Robert D.M. Hadden¹ 1 This chapter is adapted from earlier editions written by Professors P. K. Thomas and Richard Hughes.

24.16 Diseases of the peripheral nerves 6177 tissues. Peripheral nerve trunks usually consist of several fascicles bound together by the mainly collagenous epineurial connective tissue. The nutrient vessels connect with a longitudinal anastomotic network of arterioles and venules in the epineurium. This, in turn, communicates through perforating vessels with a longitudinal, intrafascicular, capillary anastomotic network. This anastomotic system is extremely efficient: experimentally it is very difficult to produce ischaemia of nerve trunks by ligation of nutrient vessels. The occurrence of an ischaemic neuropathy therefore implies widespread vascular insufficiency. A blood-nerve barrier, comparable to the blood-brain barrier, exists in peripheral nerves (except in the sensory and autonomic ganglia and at motor nerve terminals). This, together with the diffusion barrier provided by the perineurium, regulates the composition of the endoneurial connective tissue fluid and thus the ionic environment of the nerve fibres. Normal physiology All peripheral nerve fibres, whether myelinated or unmyelinated, are located closely adjacent to Schwann cells. These may provide metabolic support for the axons, which often extend for very considerable distances from their perikarya. In myelinated fibres, the myelin segments are derived by the spiralling of the surface membrane of Schwann cells around the axons. The axon is exposed at the nodes of Ranvier, which represent the gaps between adjacent myelin segments. Conduction in unmyelinated axons takes place by the spread of a continuous wave of depolarization, the action potential, which migrates along the axolemma. In myelinated fibres, because of the high electrical resistance of the lipid in the myelin lamellae, the generation of the action potential is restricted to the nodes of Ranvier. Conduction is therefore saltatory, jumping

from one node to the next by local currents that traverse the axon and the extra-cellular tissue fluid. By this means, conduction velocity is increased from about 1 m/s in unmyelinated axons to 60 to 70 m/s in the largest myelinated fibres. Most of the synthetic mechanisms in neurons are sited in the cell bodies. Synthesized materials are then transported down the axons to the termination of the fibres by an active transport system. This involves a fast system with a rate of about 400 mm/day, and a slow system, in which the structural proteins travel at 1 to 2 mm/day. The system is bidirectional: there is also a retrograde system transporting materials, including neurotrophic factors, back from the periphery to the cell body. The retrograde system may be involved in the regulation of protein synthesis in the cell body and probably carries the signal for chromatolysis, which follows transection.

Peripheral nerve pathology

Disorders of peripheral nerve function can be categorized in terms of the site of the primary disturbance. Conditions that lead to the death of the neuron as a whole, with the loss of the cell body and the axon, are categorized as neuronopathies. Conditions that have a selective effect on axons are termed 'axonal neuropathies'. Focal axonal lesions occur as a result of insults such as trauma or ischaemia. Axonal interruption leads to wallerian-type degeneration below the site of injury. Recovery must take place by axonal regeneration which is a slow process: the rate of axonal regeneration is about 1–2 mm/day. A selective block of axonal conduction, without degeneration, may be caused by blockage of sodium channels at the nodes, by antibodies (e.g. some patients with axonal Guillain-Barré syndrome) or toxins (e.g. tetrodotoxin). Generalized axonal neuropathies often lead to a selective degeneration of the distal portion of the fibres, which then extends proximally. The axons are said to 'die back' towards the cell bodies. This pattern is seen in many toxic neuropathies and neuropathies due to nutritional deficiency. In these conditions, the axonal breakdown may result either from interference with enzymes involved in glycolysis which provide the metabolic energy for axonal transport mechanisms, or from cofactor deficiency or inactivation. As the enzymes are synthesized in the cell bodies and then transported down the axons, the further the distance from the cell body the greater the likelihood of metabolic insufficiency occurring. This probably accounts for the length-dependent (distal) distribution of many such neuropathies, because longer axons will be more vulnerable. Again, recovery must take place by axonal regeneration. In many distal axonal neuropathies that involve the peripheral nervous system, not only does the degeneration affect the distal parts of the motor and sensory axons in the periphery, but also the terminal parts of the centrally directed axons derived from the dorsal root ganglion cells. Thus, degeneration may be found in the rostral portions of the posterior columns in the spinal cord. This process has been referred to as central-peripheral distal axonopathy. Neuropathy from iminodipropionitrile blocks the slow axonal transport system and leads to large swellings in the proximal parts of the axons that contain aggregations of neurofilaments (proximal axonopathy). Other neuropathies primarily affect the myelin, either directly, or through interference with Schwann cell function. The consequence is a selective demyelination with relative preservation of axonal integrity. This may be restricted to the region of the nodes of Ranvier (paranodal demyelination) or involve whole internodal segments (segmental demyelination), with consequent conduction block. Selective myelin damage may occur, for example, as the result of a cell-mediated attack on myelin by sensitized mononuclear cells, which is a possible explanation for the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) form of Guillain-Barré syndrome. Another instance is in diphtheritic neuropathy where the demyelination is secondary to an interference with Schwann cell protein metabolism. Local compression by a tourniquet also gives rise to selective damage to myelin through mechanical effects, although more severe pressure causes axonal interruption. In diffuse demyelinating neuropathies, the distribution of the clinical effects, as for distal axonal

neuropathies, is often maximal peripherally. Presumably, this is a statistical effect: the longer the nerve fibre, the more likely it is to include a region of demyelinating conduction block. Recovery after paranodal or segmental demyelination occurs by remyelination. Initially, the newly formed myelin segments are short and thin, which results in an abnormally slow conduction velocity. Such reductions in conduction velocity may be focal (e.g. in relation to localized myelin damage in entrapment neuropathies), or widespread as in most inherited demyelinating neuropathies. In the latter, motor nerve conduction velocity is sometimes reduced to 10 m/s or less. Finally, in other neuropathies the nerve fibres may be secondarily damaged by processes that primarily affect the connective tissues of

section 24 Neurological disorders 6178 nerves or of the vessels (vasa nervorum). Usually a combination of demyelination and axonal loss occurs. Symptomatology Weakness or sensory loss may be due to either conduction block or axonal degeneration, but isolated conduction slowing is generally asymptomatic. Conduction block is related to demyelination with preservation of axonal continuity (neurapraxia). Recovery may occur by remyelination and may be rapid and complete. This can be the situation in localized nerve lesions (e.g. 'Saturday night' palsy of the radial nerve), or in more widespread polyneuropathies, such as in the AIDP form of Guillain-Barré syndrome (see next). If axonal interruption takes place, axonal degeneration occurs below the site of interruption. The muscle weakness is accompanied by atrophy and electromyographic signs of denervation. If the interruption is reversible, recovery has to take place by axonal regeneration which is often slow and incomplete. An important recovery mechanism in conditions in which muscles become partially denervated is reinnervation of denervated muscle fibres by collateral sprouting from the remaining intact axons. Motor symptoms. In generalized symmetrical polyneuropathies, the muscle weakness and wasting are usually distal so begin in the lower limbs. This results in bilateral foot drop and a high stepping gait to avoid catching the toes on the ground. Involvement of the upper limbs begins with weakness and wasting of the small hand muscles, and usually weakness of the finger and wrist extensors, before the forearm flexor muscles. Proximal limb weakness suggests root involvement, especially inflammatory demyelinating polyradiculoneuropathy. Fasciculation due to spontaneous contraction of isolated motor units is a feature of anterior horn cell (motor neuron) disease but may be encountered in peripheral neuropathies, as may muscle cramps. However, benign fasciculations are very common and distinguished by the lack of weakness and typically greater prominence in the history than the examination. Neuropathic postural tremor, mainly affecting the upper limbs and resembling essential tremor, may be seen in patients with chronic demyelinating polyneuropathies, either genetic, inflammatory, or associated with IgM paraprotein. A rare manifestation of peripheral neuropathy is the occurrence of continuous repetitive discharges in motor nerve fibres, leading to generalized muscular rigidity or 'neuromyotonia' (Isaacs' syndrome, continuous motor unit activity syndrome). Loss of the tendon reflexes is a frequent accompaniment of a peripheral neuropathy, and usually first affects the ankle jerks; absence of all tendon reflexes suggests a demyelinating neuropathy. Sensory symptoms and sensory loss in symmetrical polyneuropathies are usually distal ('length dependent') in distribution, giving rise to the 'glove-and-stocking' pattern of involvement. Only rarely is a proximal pattern encountered, suggestive of radiculoplexus neuropathy or ganglionopathy. The sensory loss typically affects all modalities, but sometimes is restricted to one of two broad patterns. In the first, the impairment predominantly affects the sensations of joint position, vibration, and light touch, corresponding to a predominant loss of function in the larger myelinated nerve fibres. Loss of joint position sensation may cause sensory ataxia of gait or

limbs, which can resemble that in cerebellar disease. When very severe it may also cause 'pseudoathetosis', involuntary movements of the fingers and hands with arms outstretched and the eyes closed. In the second pattern of selective sensory loss, known as small fibre neuropathy, pain and temperature sensibility are predominantly affected, often with loss of autonomic function, corresponding to a predominant loss of small myelinated and unmyelinated axons. Typically, there is spontaneous 'burning' pain; in more severe cases the loss of the protective effect of pain sensation may lead to persistent ulceration or more extensive tissue loss, most commonly in the feet, and neuropathic joint degeneration (Charcot's joints). Positive sensory symptoms are frequent in peripheral neuropathy, due to excessive spontaneous action potentials. They are usually of a tingling nature ('pins and needles'), but in small fibre neuropathies cause burning hot or cold sensations and pain. These may be aggravated by touching or stroking the skin. The International Association for the Study of Pain (2012 online update) defines the following terms, all of which may be caused by neuropathy. An abnormal sensation, whether spontaneous or evoked, is termed dysesthesia if unpleasant or paraesthesia if not. Neuropathic pain is pain caused by a lesion or disease of the somatosensory nervous system. Hyperalgesia is increased pain from a stimulus that normally provokes pain. Allodynia is pain due to a stimulus that does not normally provoke pain. Hyperpathia is a syndrome of pain characterized by an abnormally (increased) painful reaction to a stimulus (whether normally painful or not), especially a repetitive stimulus, as well as (paradoxically) an increased threshold; there may be faulty identification and localization of the stimulus, delay, explosive character, radiating sensation, and aftersensation. Sensitization is increased responsiveness of nociceptive (peripheral or central) neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs. Spontaneous pains of an aching or lancinating character may complicate several generalized polyneuropathies. Severe paroxysms of lancinating pain occur in trigeminal neuralgia in which the lesion is at or close to the point of entry of the sensory roots into the pons. Following a traumatic lesion of peripheral nerve or plexus, sometimes complex regional pain syndrome type 2 (causalgia) develops, characterized by sustained burning pain, allodynia, and hyperpathia, often with vasomotor and sudomotor dysfunction and later trophic changes. Sympathectomy relieves some cases. Restless legs syndrome (involuntary movements of the legs to relieve unpleasant sensations, usually when resting or in bed) may be idiopathic or secondary to neuropathy, often a painful small fibre neuropathy, for example, due to renal failure. Dopamine agonists or pregabalin may help. Intermittent sensory symptoms without evidence of organic neuropathy are common but not well understood. They may arise in the peripheral nerves (from causes including compression, ectopic action potentials, or hyperexcitability), cutaneous sensory receptors, or central nervous system disturbances including anxiety, migraine sensory aura, and central sensitization. Disturbances of autonomic function are occasionally the predominant abnormality in a peripheral neuropathy, as in rare syndromes of primary autoimmune autonomic neuropathy/ganglionopathy and familial dysautonomia. More commonly they accompany other manifestations, either with localized peripheral nerve lesions and/or with generalized neuropathies, such as AIDP, diabetic or amyloid polyneuropathy.

24.16 Diseases of the peripheral nerves 6179 Clinical phenotypes of neuropathy Neuropathies may be classified in several dimensions, firstly by distribution. Lesions of isolated peripheral nerves or nerve roots are termed 'mononeuropathy' or 'radiculopathy'; multiple isolated lesions are termed multiple mononeuropathies, mononeuritis multiplex, or multifocal neuropathy. The lesions in a widespread multifocal neuropathy may summate to produce a symmetrical disturbance, but the

history or a careful examination may indicate asymmetry or involvement of individual nerves. Isolated or multi-focal peripheral nerve lesions arise from conditions that produce localized damage, such as mechanical injury, nerve entrapment, vascular causes especially vasculitis, thermal, electrical, or radiation injury, granulomatous, neoplastic, or other infiltrations, and nerve tumours. Alternatively, there may be a diffuse, length-dependent, and bilaterally symmetrical disturbance of function termed polyneuropathy. When this affects the spinal roots as well as the peripheral nerves, the term 'polyradiculoneuropathy' is more appropriate. In general terms, polyneuropathies result from conditions that act diffusely on the peripheral nervous system, such as metabolic disturbances, toxic agents, deficiency states, and some autoimmune disorders. Isolated nerve lesions may sometimes be superimposed on a symmetrical polyneuropathy, as a consequence, for example, of pressure lesions in a patient confined to bed. In certain peripheral nerve disorders, there is an abnormal susceptibility to pressure lesions. Further dimensions include the timing which may be acute, sub-acute or chronic; and axonal or demyelinating neuropathy may be suggested by nerve conduction studies. The symptomatology (see earlier) suggests whether the predominant type of fibres involved are motor, sensory, or autonomic, and if the predominant sensory involvement is large fibre (touch and movement) or small fibre (pain and temperature), with positive (tingling/pain) or negative (numbness) sensory symptoms. In practice this gives several typical clinical phenotypes:

- Distal sensory polyneuropathy, the most common type, also known as length dependent. The increased vulnerability of the longer axons gives the typical stocking and glove distribution.
- Painful small fibre sensory neuropathy (often with autonomic neuropathy).
- Mononeuropathy (usually due to local compression or trauma).
- Multifocal/asymmetric neuropathy (suggesting an inflammatory cause).
- Sensory ataxic neuropathy (sometimes coexists with pathology of the dorsal columns of the spinal cord).
- Motor and sensory neuropathy.
- Demyelinating neuropathy (clinical clues are proximal weakness and absence of all tendon reflexes).

Formulation of the clinical phenotype is an important first step towards narrowing the differential diagnosis and selecting appropriate investigations. The Washington University neuromuscular website is a useful advanced reference tool (<http://neuromuscular.wustl.edu>). Diagnosis and investigation A screen of blood tests should be done for the most common causes. The American Academy of Neurology practice parameter recommended the most useful blood tests to be glucose, vitamin B12 with B12-metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis. Glucose tolerance testing and HbA1c should be considered, particularly in overweight patients. Most neurologists would also test renal, liver, and thyroid function, folic acid, FBC, ESR, and HIV. A careful history assessing risk factors for neuropathy may guide further investigation. The history and physical examination are usually sufficient to indicate that the patient has a peripheral neuropathy. If confirmation is required, this may usually be obtained by nerve conduction studies. Conduction may be examined in motor and sensory nerve fibres, and can give evidence of both localized and generalized neuropathies. Although axonal and demyelinating neuropathy can usually be distinguished, mildly reduced conduction velocity may also occur in regenerating axons following axonal degeneration. Somatosensory evoked potentials are most useful if the patient has sensory deficit with areflexia yet paradoxically normal sensory nerve conduction, to show preganglionic disease, such as chronic immune sensory polyradiculopathy. Cerebrospinal fluid examination may be helpful, particularly where there is proximal involvement of nerve roots (polyradiculoneuropathy). In symmetrical axonal neuropathy, the cerebrospinal fluid protein is usually normal or only slightly increased. In chronic inflammatory demyelinating polyradiculoneuropathy, the protein concentration is usually markedly increased, often to more

than 1000 mg/litre. The protein concentration is also usually increased in Guillain-Barré syndrome, especially after the first week, whereas the cell count remains normal or only shows a few lymphocytes. The cell count is usually increased in neuropathies associated with Lyme disease and some other infections. Imaging of peripheral nerves by magnetic resonance neurography or ultrasound has improved technically in recent years, allowing diagnostic utility in conditions with enlargement, compression, or inflammation of nerves, such as demyelinating neuropathies (inflammatory or genetic), nerve tumours, or leprosy. This requires specialist expertise and equipment. Ultrasound is useful in diagnosis of entrapment/compression where the nerve is close to the skin, for example, in carpal tunnel syndrome; paradoxically a chronically compressed nerve actually becomes thickened not thinned. MRI is also useful for excluding lumbar spinal canal stenosis and central nervous system disease. Nerve biopsy is useful in only a few situations, especially multi-focal neuropathy to show vasculitis or other inflammatory disorders, and in amyloidosis. It is best performed in centres with expertise in nerve biopsy to minimize the high risk of artefact from suboptimal surgical or laboratory technique. Treatment of neuropathies in general The following may benefit even neuropathies lacking a specific treatment. Patients with significant sensory loss should be advised on foot care: to inspect their feet regularly for early signs of injury or blistering that may lead to ulceration, to take extra care with new shoes, to limit walking barefoot to avoid injury, and to see a podiatrist early for any problems. Neuropathic pain may be helped by tricyclic antidepressants, gabapentin (standard or extended release), pregabalin, duloxetine, or venlafaxine as first-line treatment; further treatment may

section 24 Neurological disorders 6180 include carbamazepine, tramadol or strong opioids (including sustained-release oxycodone, transdermal buprenorphine, or tapentadol). Fewer than one in three patients gets acceptable benefit from any drug, but the most common avoidable cause of failure is inadequate titration of the dose to the maximum tolerated. Those with pain localized to a small area (including the feet), especially with allodynia or touch-sensitive dysaesthesia, may benefit from 5% lidocaine plasters, capsaicin (either 0.075% cream, or the much more effective 8% patch which must be applied by trained specialists every three months), or botulinum toxin. Rehabilitation. Patients with foot drop may benefit from one of many different types of ankle-foot orthosis, which must fit well. Patients with abnormal foot posture or deformity (especially those with Charcot-Marie-Tooth disease) should see an orthotist or biomechanical podiatrist. Physiotherapy may benefit those with weakness or abnormal gait, but excessive strength training may be detrimental to severely weak muscles. Weight loss eases the burden on weak legs, but the best form of aerobic exercise is usually not walking or running which overstrains weak ankles. Mononeuropathies Phrenic nerve (C2–4) This nerve innervates the diaphragm. When the diaphragm is totally paralysed, breathlessness is worse when lying flat or swimming. Examination shows loss of the normal protrusion of the upper abdomen during inspiration (especially during rapid sniff), or replacement by retraction (paradoxical movement). Radiographically, paralysis may be detected by unilateral or bilateral elevation of the diaphragm in a chest radiograph and its failure to descend on inspiration. The phrenic nerve may be involved in its course through the neck or thorax by wounds or tumours such as bronchial carcinoma, and it is sometimes affected in idiopathic brachial plexus neuropathy (neuralgic amyotrophy) and in some rare forms of Charcot-Marie-Tooth disease. Nerve to serratus anterior (C5–7) The serratus anterior acts as a fixator of the scapula, holding the scapula against the chest wall when forwards pressure is exerted by the arm. It is involved in forwards movement of the shoulder, as in a rapier thrust, and in elevation of the arm, when it rotates the scapula. When serratus anterior is paralysed in

isolation, the position of the scapula is almost normal at rest but, if the extended arm is pushed forwards against resistance, 'winging' of the scapula becomes more evident. The vertebral border, particularly in its lower portion, stands away from the chest wall. The nerve to serratus anterior may be involved in penetrating wounds, but usually in association with damage to the brachial plexus. It may be injured by forcible depression of the shoulder. Serratus anterior weakness is a common component of idiopathic brachial plexus neuropathy (neuralgic amyotrophy) and it is frequently encountered as an isolated and unexplained lesion. Brachial plexus The brachial plexus may be affected by intrinsic lesions, neoplastic infiltration, penetrating wounds of the neck, in fractures and dislocations of the shoulder and clavicle, as a result of traction on the arm, or by pressure from an aneurysm or a cervical rib or fibrous band. Idiopathic brachial plexus neuropathy This condition is also known as 'neuralgic amyotrophy' and 'brachial neuritis'. It is likely an immune-mediated disorder, with a probable underlying genetic predisposition (unidentified in sporadic cases) and susceptibility to mechanical injury of the brachial plexus. It may follow immunization, surgery, or infections (including hepatitis E), or occur without a recognizable antecedent event. Some cases occur as an autosomal dominant disorder, hereditary neuralgic amyotrophy, with variable penetrance, which is genetically heterogeneous but often caused by mutations in the SEPT9 gene. It develops acutely with intense pain in the shoulder region which lasts days or weeks. Paralysis of the muscles of the shoulder girdle becomes evident within a day or two of the onset of the pain, sometimes also of the arms or of the diaphragm. It may be unilateral or bilateral, usually without much sensory loss. More distal upper limb muscles may be affected (such as variants affecting predominantly the anterior or posterior interosseous nerves), as may the phrenic nerve and, occasionally, the recurrent laryngeal nerve. The cerebrospinal fluid is consistently normal. There is often prominent wasting of scapular muscles with electromyographic evidence of denervation. Recovery is variable over 1 to 2 years but may ultimately be satisfactory. Not all cases recover fully and recurrences can occur. A comparable disorder can affect the lumbosacral plexus (idiopathic lumbosacral plexopathy). The pattern of muscle involvement suggests a patchy process, allowing distinction from a root lesion because of selective involvement of some but not all muscles innervated by the same root. An immune reaction is assumed but not established. In a retrospective observational study oral prednisone given in the first month after onset shortened the duration of the initial pain and led to earlier recovery in some patients, but there are no randomized trials. Postirradiation brachial plexopathy Brachial plexus damage may occur as a sequel to radiotherapy for breast carcinoma or tumours in the neck. The onset of symptoms is usually several years after treatment, but may be within months. It can be difficult to distinguish from tumour recurrence but is less likely to be painful. MRI, and especially positron emission tomography, may be helpful in diagnosis. It does not improve and treatment is supportive only. Traction lesions of the brachial plexus Traction on the arm may result in damage to the plexus itself or may lead to avulsion of the spinal roots from the cord. If the roots are avulsed, sensory nerve action potentials from affected fingers will be preserved despite total anaesthesia, and the histamine flare response will be preserved in anaesthetized skin. This follows from the fact that the nerve fibres are interrupted proximal to the dorsal root ganglia and therefore the peripheral sensory axons do not degenerate. In severe traction lesions, commonly encountered in current medical practice as a result of motorcycle accidents, the whole of the plexus may be damaged. With forcible downward displacement of the shoulder, as when someone is thrown forwards and the shoulder strikes against an obstacle, only the upper part of the plexus, involving

24.16 Diseases of the peripheral nerves 6181 the contribution from the fifth and sixth cervical nerve roots, may be damaged. This may also be encountered as a birth injury from traction on the head, or on the trunk in a breech presentation (Erb's palsy), and rarely in anaesthetized patients during surgery or in individuals carrying heavy rucksacks. Selective injury to the lower part of the plexus involving the contributions from the eighth cervical and first thoracic nerve roots occurs as a result of traction with the arm extended, as when an individual falls from a height and tries to save himself by hanging on to a ledge. It may also occur as a birth injury following traction with the arm extended (Klumpke's paralysis), but is less common than upper plexus damage. Selective damage to the upper portion of the plexus (C5 and C6 roots or upper trunk) results in paralysis of deltoid, biceps, brachialis, brachioradialis, and sometimes supraspinatus, infraspinatus, and subscapularis. If the roots are avulsed from the cord, the rhomboids, serratus anterior, levator scapulae, and the scalene muscles will be affected. The arm hangs at the side, internally rotated at the shoulder, with the elbow extended and the forearm pronated in the 'waiter's tip' position. Abduction at the shoulder and flexion at the elbow are not possible. The biceps and brachioradialis jerks are lost. Sensory loss affects the lateral aspect of the shoulder and upper arm and the radial border of the forearm. Selective paralysis of the lower brachial plexus (C8, T1) results in paralysis of all the intrinsic hand muscles and a consequent claw-hand deformity, weakness of the medial finger and wrist flexors, and sensory loss along the medial border of the forearm and hand and over the medial two fingers. Cervical sympathetic paralysis, giving rise to Horner's syndrome, is frequently associated. When the spinal roots are avulsed from the cord, regeneration is impossible and intractable spontaneous pain may be a highly troublesome sequel. Where the injury is distal to the dorsal root ganglia, lesions of the upper portion of the brachial plexus recover more satisfactorily than lower plexus lesions. The value of surgical repair is still a controversial issue. In Erb's form of birth injury, weakness of abduction at the shoulder and flexion at the elbow often persist, although there may be little residual sensory loss. Full recovery takes place in about a third of cases. It is less likely to occur with lower plexus injuries or if the whole plexus is involved. Early recognition and the application of measures to reduce the risk of joint contractures are important. Surgical treatment may be considered soon after the injury in cases where the nerve roots have been avulsed. Thoracic outlet syndromes The contribution of the eighth cervical and first thoracic roots to the brachial plexus may be damaged by angulation over a cervical rib or, more usually, a fibrous band arising from the seventh cervical vertebra and attached to the first rib. Numbness, pain, and paraesthesiae occur along the medial (ulnar) border of the forearm and hand, extending into the medial two fingers. The pain tends to be provoked by carrying heavy articles with the hand on the affected side. Damage to the lower part of the brachial plexus leads to weakness and wasting of the small hand muscles, and of the medial forearm wrist and finger flexors. Occasionally, there is selective wasting of the thenar muscles in the hand, mimicking median nerve involvement. Horner's syndrome may be a feature. Nerve conduction studies are helpful for distinguishing from a lesion of the ulnar or median nerves. Standard MRI may miss a small lesion. Surgical removal of the rib or fibrous band often leads to abolition of the pain and paraesthesiae, but may not improve wasted muscles. The subclavian artery may be affected by cervical ribs, giving rise to aneurysmal dilatation and vascular symptoms such as Raynaud's phenomenon and embolic phenomena, but the simultaneous occurrence of both neural and vascular phenomena is rare. Neoplastic involvement Tumours may arise locally in the brachial plexus, such as a nerve sheath tumour in neurofibromatosis type I, or the plexus may be invaded by tumours arising in other structures. The most common are invasion of the lower part of the plexus by an apical carcinoma of the lung (Pancoast's tumour) or by breast carcinoma, which give

rise to wasting and weakness of the small hand muscles and of the medial forearm wrist and finger flexors, with prominent pain and sensory loss affecting the medial border of the forearm and hand, and cervical sympathetic paralysis. Radial nerve (C5–8) The long course of the radial nerve and its position in relation to the humerus make this nerve unusually susceptible to external compression. It is a continuation of the posterior cord of the brachial plexus. In the upper arm, it supplies triceps and anconeus, and the posterior cutaneous nerve of the arm, and more distally the lower lateral brachial cutaneous branch and the posterior cutaneous nerve of the forearm. Muscular branches of the radial nerve innervate brachioradialis and extensor carpi radialis longus and brevis. The superficial radial nerve descends along the radial border of the forearm and supplies the skin over the dorsum of the hand and the thumb, index, and middle fingers. The deep branch forms the posterior interosseous nerve which winds around the lateral aspect of the radius, passes through supinator, which it supplies, and innervates extensor digitorum, extensor digiti minimi, extensor carpi ulnaris, and often extensor carpi radialis brevis, abductor pollicis longus, extensor pollicis longus and brevis, and extensor indicis. The nerve may be injured in wounds of the axilla so that the paralysis includes triceps, resulting in loss of extension at the elbow. The most frequent type of injury is compression of the nerve in the middle third of the arm against the humerus, as in 'Saturday night palsy' in which an individual falls asleep when intoxicated with the upper arm over the arm of a chair. Triceps is spared, but brachioradialis, supinator, and all the forearm extensor muscles are paralysed including weakness of finger and wrist extension. Sensory impairment is limited to the dorsum of the hand. Commonly the lesion consists of a localized conduction block so that muscle wasting does not occur and a muscle response can be obtained on electrical stimulation of the nerve below the level of the lesion. Recovery may be complete within a matter of weeks. At times, there is some associated axonal degeneration so that electromyographic evidence of denervation is detectable and full recovery is correspondingly delayed. Many muscles not supplied by the radial nerve work at a disadvantage when the wrist and finger extensors are paralysed. These defects must not be mistaken for signs of injury to other nerves. Owing to the flexed position of the wrist, gripping is impaired, but, if the power of the wrist and finger flexors is tested with the wrist extended, it can be shown to be normal. The action of the interossei in abducting and adducting the fingers is also feeble when the fingers are flexed, but full power is demonstrable if these muscles are tested with the hand resting flat on a table so that the fingers are

section 24 Neurological disorders 6182 maintained in extension. This explains the benefit of a wrist extension splint while recovery is awaited. A lesion of the posterior interosseous nerve gives rise to weakness confined to extension of the fingers and wrist (extensor carpi ulnaris), and extension and the long abductor of the thumb. Supinator is spared, together with brachioradialis and the radial wrist extensors, and there is no sensory loss. The nerve may be compressed, usually under the arcade of Frohse (a sharp band of fibrous tissue, which binds together the superficial and deep heads of the supinator muscle as they arise from the lateral epicondyle of the humerus and lateral border of the radius). A similar pattern of weakness may be caused by multifocal motor neuropathy (typically with differing weakness in different fingers) or idiopathic brachial plexus neuropathy, so NCS/EMG and MRI or ultrasound are needed before considering surgical exploration and decompression. Axillary nerve (C5, C6) This is a branch of the posterior cord of the brachial plexus. It supplies deltoid and teres minor and the skin over deltoid through the upper lateral brachial cutaneous nerve. It may be damaged in injuries to the shoulder and the chief symptom is an almost complete inability to abduct the arm at the shoulder. Musculocutaneous nerve (C5, C6)

This nerve is rarely damaged alone, but may be involved in injuries to the brachial plexus. It supplies coracobrachialis, biceps, and brachialis, and the lateral cutaneous nerve of the forearm. Flexion at the elbow is still possible by brachioradialis, but is weak. Median nerve (C6–8, T1) The median nerve arises from the medial and lateral cords of the brachial plexus and descends with the brachial artery through the upper arm, entering the forearm deep to the bicipital aponeurosis. It has no muscular branches above the elbow. It supplies all the muscles in the anterior aspect of the forearm except flexor carpi ulnaris and the medial half of flexor digitorum profundus. The main trunk of the nerve supplies pronator teres, flexor carpi radialis, palmaris longus, and flexor digitorum superficialis. Through the anterior interosseous branch, it also supplies the lateral aspect of flexor digitorum profundus, flexor pollicis longus, and pronator quadratus. The main trunk passes deep to the flexor retinaculum of the wrist and its recurrent muscular branch supplies abductor pollicis brevis and opponens pollicis, and contributes to the innervation of flexor pollicis brevis. It also supplies the lateral two lumbrical muscles, the skin of the lateral aspect of the palm, and the lateral three and a half digits over their palmar aspects and terminal parts of their dorsal aspects. Median nerve lesions in the forearm The median nerve may be injured in the region of the elbow or compressed at the level of the pronator teres muscle. Entrapment neuropathies in the upper forearm are, however, uncommon. Occasionally the anterior interosseous branch is involved in isolation. Complete lesions of the median nerve at the elbow give rise to paralysis of pronator teres, the radial flexor of the wrist, the long finger flexors except the ulnar half of the deep flexor, most of the muscles of the thenar eminence, and the two radial lumbricals. In brief, there is an inability to flex the index finger and the distal phalanx of the thumb, flexion of the middle finger is weak, and opposition of the thumb is defective. The appearance of the hand has been described as simian; it shows ulnar deviation, the index and middle fingers are more extended than normal, and the thumb lies in the same plane as the fingers. In more detail, pronation is incomplete and defective. The patient attempts to overcome this by rotating the whole limb at the shoulder. Paralysis of the wrist flexors is evident when attempts are made to flex against resistance. The tendon of flexor carpi ulnaris stands out alone and the hand goes into ulnar deviation. Flexion of the fingers is good in the ulnar two fingers, although weaker than normal. The index finger cannot be flexed and the middle finger only incompletely. Flexion at the metacarpophalangeal joints is possible in all fingers, including the index, and flexion at these joints with extension at the interphalangeal joints is accomplished by interossei and the lumbricals. If the proximal phalanx of the thumb is immobilized, it will be found that flexion of the terminal phalanx is abolished because of paralysis of flexor pollicis longus. Paralysis of the thenar muscles gives rise to defective abduction and opposition of the thumb. By means of the adductor, the thumb can be drawn into the palm, but, as the radial fingers cannot be flexed or the thumb opposed, it is impossible to place the tip of the thumb on the fingers. Sensory loss is evident over the lateral three and a half digits and the lateral aspect of the palm, although individual variations occur. There is anaesthesia over the two terminal phalanges of the index and middle fingers. This degree of sensory loss, combined with the motor deficit, renders the thumb and index fingers almost useless and makes paralysis of the median the most serious single nerve lesion in the upper limb. Vasomotor and trophic changes often ensue: the skin, nails, and finger pulp tend to become atrophic. After a total transection of the nerve in the region of the elbow, even with a satisfactory surgical repair, recovery is slow and rarely complete, particularly with respect to the innervation of the hand. With partial lesions of the median nerve in the arm or forearm, complex regional pain syndrome (causalgia) may be a troublesome consequence. The pain develops hours to weeks after the injury. The pain is severe and unremitting, and frequently has a burning or smarting quality. Upon this may be superimposed

severe paroxysms of pain (allodynia) provoked by touching the limb or emotional distress. The skin usually becomes dry and scaly, but excessive sweating may be a feature. Immobility may lead to contractures of the joints. Treatment is difficult but sympathectomy may help. Carpal tunnel syndrome Much the most common median nerve lesion is the carpal tunnel syndrome, in which the median nerve is compressed at the wrist as it passes deep to the flexor retinaculum. The usual presentation is with intermittent acroparaesthesiae, which consist of numbness, tingling, and burning sensations felt in the hand and fingers; the pain sometimes extends up the forearm as far as the elbow or even as high as the shoulder or root of the neck. The paraesthesiae are sometimes restricted to the radial $3\frac{1}{2}$ digits, but may affect all the digits because some fibres from the median nerve are distributed to the little finger through communication with the ulnar nerve in the palm. The attacks of pain and paraesthesiae are most common at night and often wake the patient from sleep. The hand tends to feel numb and useless on waking. Symptoms are then relieved within minutes by shaking the hand. The symptoms may recur during the day when the hand is used, gripping a steering wheel, or immobile

24.16 Diseases of the peripheral nerves 6183 in certain positions. Intermittent acroparaesthesiae may persist for years without the appearance of constant sensory loss or weakness. Examination is usually normal, but a minority develop weakness and wasting of the thenar muscles, particularly of abduction of the thumb (Fig. 24.16.1), or sensory loss over the tips of the median-innervated fingers. Occasionally patients present with symptoms or signs of median nerve deficit in the hand without attacks of acroparaesthesiae having occurred, particularly in older individuals. The symptoms are usually characteristic, with abnormal signs not being found except in advanced cases. At times percussion over the carpal tunnel may elicit Tinel's sign, or symptoms may be provoked by hyperextension of the wrist or sustained flexion (Phalen's sign). Neither sign is very specific or sensitive. Confirmation can usually be obtained by nerve conduction studies (except these are normal in 5% of cases). Carpal tunnel syndrome is more common in women than men and its lifetime prevalence is 10%. It is commonly associated with excessive use of the hands. It may develop as a consequence of wrist joint abnormality from rheumatoid arthritis, osteoarthritis, or an old fracture. Predisposing causes include pregnancy, obesity, myxoedema, acromegaly, and amyloidosis, but most cases are idiopathic so screening for underlying causes is not recommended. A twin study has shown a strong genetic component. The superficial situation of the median nerve at the wrist also renders it liable to injury as a result of lacerations or suicide attempts. Fluctuation of symptoms is common and spontaneous recovery occurs in about 20% of patients. A conservative approach to treatment is appropriate initially, with weight loss and avoidance of provoking activities. Splinting of the wrist in a neutral position during the day and/or night may also be useful. The preferred treatment for milder cases is local corticosteroid injection at the wrist, shown in short-term randomized trials as more efficacious than placebo or oral corticosteroids. About half of patients obtain satisfactory relief from corticosteroid injection alone but symptoms may recur, so injection can be repeated if necessary. Oral steroids, splinting, ultrasound, yoga, and carpal bone mobilization are also efficacious. Surgical carpal tunnel release (dividing the flexor retinaculum) is recommended for more severe cases, or those with persistent weakness or numbness, or refractory to steroid injection or splinting. Surgery and steroid injection have not been directly compared in a randomized trial. The average success rate from surgery is about 75%, but it is more inconvenient and may be complicated by a painful scar. About 7% of patients report that their hands are worse after the operation than before. Symptoms that were previously intermittent usually recover completely but permanent symptoms may not. Ulnar nerve

(C7, C8, T1) The ulnar nerve arises from the medial cord of the plexus, usually with a contribution from the lateral cord. It descends in the medial side of the upper arm, passes around the elbow in the ulnar groove between the olecranon process of the ulna and the medial epicondyle of the humerus, and enters the forearm under an aponeurotic band between the humeral and ulnar heads of flexor carpi ulnaris. It then runs superficial to flexor digitorum profundus to the wrist and enters the hand between the pisiform bone and the hook of the hamate, superficial to flexor retinaculum. After penetrating the hypothenar muscles, its deep branch crosses the palm and ends in flexor pollicis brevis. In the upper arm, branches arise that supply flexor carpi ulnaris and the medial part of flexor digitorum profundus. In the forearm, the dorsal branch arises, winds around the ulna and supplies the skin over the dorsal aspect of the hand and the medial one and a half fingers. In the hand, a superficial branch supplies palmaris brevis and the skin over the medial aspect of the palm and the medial one and half fingers. The deep branch, after supplying the hypothenar muscles, innervates interossei, the third and fourth lumbricals, adductor pollicis, and part of flexor pollicis brevis. Ulnar nerve lesions at the elbow Total paralysis from lesions at this level, including the branches to flexor carpi ulnaris and flexor digitorum profundus, gives rise to wasting along the medial side of the forearm flexor muscles. There is weakness of flexion of the fourth and fifth fingers. If the proximal portions of these fingers are held immobilized, flexion of the terminal phalanges is not possible. When the hand is flexed to the ulnar side against resistance, the tendon of flexor carpi ulnaris is not palpable. Paralysis of the hypothenar muscles abolishes abduction of the fifth finger. Paralysis of interossei and the medial two lumbricals gives rise to the 'claw-hand' deformity (Fig. 24.16.2). The action of these muscles is to flex the fingers at the metacarpophalangeal joints with the fingers extended at the interphalangeal joints. In a claw hand, the posture of the fingers is opposite to this, namely extension of the metacarpophalangeal joints with flexion at the interphalangeal joints. Although all the interossei are paralysed, the defect is seen mainly in the ulnar fingers because the lumbricals supplied by the median nerve are still active. The long extensors of the fingers, being unopposed, overextend the proximal joints, and flexor digitorum superficialis flexes the proximal interphalangeal joints. Fig. 24.16.1 Thenar wasting in a patient with a severe median nerve lesion.

section 24 Neurological disorders 6184 In the hand, there is wasting of the hypothenar muscles, interossei, and the medial part of the thenar eminence. Movements of abduction and adduction of the fingers are weak, as is adduction of the extended thumb against the palm. Sensory loss affects the dorsal and palmar aspects of the medial side of the hand and the medial one and a half fingers. The ulnar nerve may be damaged by dislocations or fracture dislocations at the elbow and is sometimes compressed in individuals who habitually lean on their elbows. This is most likely to happen in those performing heavy manual work or if there is an excessive carrying angle at the elbow, as may occur after a previous malunited supracondylar fracture of the humerus ('tardy ulnar palsy'). In this case, the ulnar nerve is often palpably enlarged in the ulnar groove and for a short distance proximally. Ulnar nerve lesions are not infrequent in leprosy when the enlargement of the nerve tends to be maximal at a little distance above the elbow. Entrapment may also occur in the cubital tunnel which is formed by an aponeurotic band between the two heads of flexor carpi ulnaris under which the nerve passes. Distinguishing between lesions at the ulnar groove and at the cubital tunnel aponeurosis is difficult and may require detailed neurophysiological assessment and imaging. Education of the patient about the mechanism of damage to the ulnar nerve and avoidance of leaning on the elbow reduced symptoms in a small randomized controlled trial (RCT)

in mild disease. Night splinting to avoid excessive elbow flexion is often recommended but did not offer extra benefit in one trial. In severe progressive cases lasting more than three months surgery may be considered, although many improve spontaneously or remain mild, and surgery has never been compared in a RCT to conservative treatment alone. The lesion should first be confirmed by nerve conduction studies and imaging with ultrasound or MRI. The alternative operations are transposition of the nerve from behind to in front of the medial epicondyle, decompression of the nerve where it passes through the cubital tunnel, or medial epicondylectomy. Meta-analysis suggests that simple decompression and decompression with transposition are equally effective in idiopathic ulnar neuropathy at the elbow, including when the nerve impairment is severe, each giving improvement in about 70% of patients. The operation performed will depend on the experience of the surgeon and intraoperative findings. Lesions at the wrist or in the hand

Damage to the ulnar nerve at the wrist will spare the dorsal branch, so that cutaneous sensation over the dorsum of the hand and fingers is spared. A lesion just proximal to the wrist will give rise to sensory impairment on the palmar aspect of the hand and fingers alone, and weakness of all the ulnar-innervated intrinsic hand muscles. A slightly more distal lesion spares the superficial branch of the nerve and therefore produces no sensory deficit. Finally, damage to the deep palmar branch spares the hypothenar muscles, but causes weakness of the other ulnar-innervated small hand muscles. Lesions at the wrist or in the hand are usually the result of compression by ganglia or by repeated occupational trauma. Damage to the deep palmar branch, for example, may be caused by firm pressure in the palm from a screwdriver or drill or bicycle handlebars. If occupational pressure is the cause, recovery follows cessation of the precipitating cause. Should improvement fail to occur after an appropriate interval, surgical exploration to establish whether a ganglion is present is merited. It is not always easy on clinical grounds to decide whether the lesion is at the elbow or the wrist. Compression of the nerve in the cubital tunnel, for example, may spare the branches to flexor carpi ulnaris and flexor digitorum profundus. In these circumstances, nerve conduction studies may be helpful, as they may in distinguishing between lesions of the ulnar nerve and damage to the eighth cervical and first thoracic spinal roots. MRI or ultrasound is also helpful to localize the lesion site.

Lumbosacral plexus Lesions of the lumbosacral plexus are not common. The plexus may be involved in pelvic malignancy, such as from carcinoma of the uterine cervix, bladder, prostate, or rectum, or be the site of a local neural tumour. It may be compressed by a haematoma in patients receiving anticoagulant therapy or who have haemophilia, or be involved in fractures of the pelvis. The lumbosacral plexus may be compressed against the rim of the pelvis by the fetal head during parturition, with consequent weakness of the anterior tibial and peroneal muscles, and sensory impairment in the distribution of the fourth and fifth lumbar dermatomes. The superior gluteal nerve may also be affected. Recovery is initially good but may not be complete. The plexus may be affected in diabetic (or rarely nondiabetic) lumbosacral radiculoplexus neuropathy (diabetic amyotrophy). Femoral nerve (L2–4) This nerve arises from the lumbar plexus, crosses the iliac fossa between psoas and iliacus, and enters the thigh deep to the middle of the inguinal ligament. In the iliac fossa it supplies iliacus and, in the thigh, pectineus, sartorius, and quadriceps femoris, and anterior cutaneous branches to the front of the thigh. The continuation of the femoral nerve is the saphenous nerve, which supplies the skin over the medial aspect of the lower leg as far as the medial malleolus.

Fig. 24.16.2 'Claw-hand' deformity in a patient with an ulnar nerve lesion.

24.16 Diseases of the peripheral nerves 6185 Damage to the femoral nerve causes weakness of knee extension, wasting of quadriceps, loss of the knee reflex, and sensory impairment over the anterior thigh and in the distribution of the saphenous nerve in the medial calf. With a proximal lesion, there may also be weakness of hip flexion from paralysis of iliacus. The femoral nerve may be injured in fractures of the pelvis or femur, in dislocations of the hip, in childbirth, and at times during operations on the pelvis or hip. It may be involved by psoas abscesses or tumours, or in wounds of the thigh. It is commonly involved in large psoas muscle haematomas in individuals with haemophilia and in diabetic radiculoplexus neuropathy, but sometimes no cause is found. There is usually gradual recovery. Owing to the rapid dispersion of the branches in the thigh, partial lesions are common from wounds at this site. The nerve to quadriceps is most often injured, and the resulting paralysis causes considerable difficulty in walking because the knee cannot be locked in extension and gives way, especially when descending stairs. The saphenous nerve is sometimes damaged in surgery for the treatment of varicose veins.

Obturator nerve (L2–4) The nerve emerges from the lateral border of psoas, crosses the lateral wall of the pelvis, and enters the thigh through the obturator foramen where it supplies gracilis, adductor longus and brevis, adductor magnus, obturator externus, and sometimes also pectineus, and the skin over the lower medial aspect of the thigh. Damage to the obturator nerve results in weakness of adduction and internal rotation at the hip, pain in the groin, and sensory impairment on the medial part of the thigh. The nerve may be involved in pelvic fractures, hip and pelvic surgery, and neoplastic infiltration, and can be damaged by the fetal head or forceps during parturition.

Lateral cutaneous nerve of the thigh (L2, L3) This nerve arises from the lumbar plexus, passes obliquely across the iliacus, and enters the thigh under the lateral part of the inguinal ligament. It supplies the skin over the anterolateral aspect of the thigh. Meralgia paraesthetica is a common pure sensory entrapment neuropathy resulting from compression of this nerve usually as it passes under the inguinal ligament. It is more common in men and obese individuals, or may occur in pregnancy or childbirth, and may be unilateral or bilateral. The symptoms consist of numbness in the territory of the nerve, combined with tingling or burning paraesthesiae provoked by prolonged standing or after excessive walking. Neurophysiology is diagnostically unhelpful. Treatment is not usually required. Weight loss may be helpful, and in many instances the condition subsides spontaneously. Rare cases with troublesome pain may benefit from lidocaine plasters or capsaicin cream. Occasionally local corticosteroid injection or surgical decompression are tried, without good evidence that they are better than conservative treatment.

Sciatic nerve (L4, L5, S1–3) The sciatic nerve enters the thigh through the sciatic notch. It is composed of the tibial and peroneal divisions which are usually bound together within a common sheath, the tibial division lying medially. It descends through the posterior aspect of the thigh, initially deep to gluteus maximus, and supplies semitendinosus, semimembranosus, and the long head of biceps through its peroneal division. It separates into the tibial and common peroneal nerves in the lower thigh, which supply all the muscles below the knee, and both nerves contribute to the formation of the sural nerve. Partial lesions often affect the peroneal division more severely than the tibial. Total interruption of the sciatic nerve gives rise to foot drop. Walking is possible, but the patient cannot stand on the toes or the heel of the affected foot and the ankle is unstable. All movement below the knee is paralysed. If the injury is in the upper thigh, flexion of the knee is also weak. The skin is anaesthetized (with absent sweating) over the entire foot except for the medial border which is supplied by the saphenous nerve. Pressure sores may develop. The anaesthesia extends upwards on the posterolateral aspect of the calf in its lower two-thirds. Beyond this area of complete anaesthesia, there is a wide zone in which sensibility may be diminished. The ankle reflex is lost

but the knee reflex is retained. The sciatic nerve may be involved in pelvic tumours and can be injured by fractures of the pelvis or femur, during hip replacement operations, or by intramuscular injection to the buttock in locations other than the recommended upper outer quadrant. After the radial and ulnar, it is implicated in gunshot wounds more frequently than any other nerve. Incomplete lesions of the nerve may be caused by pressure of the nerve against the hard edge of a chair in individuals who fall asleep while intoxicated. Similar lesions may occur in people with diabetes, in whom the peripheral nerves are more susceptible to pressure neuropathy. The syndrome of root pain and sciatica is considered in Chapter 19.4.

Tibial nerve (L4, L5, S1–3) After separating from the peroneal division of the sciatic nerve in the lower thigh, this nerve passes through the popliteal fossa and enters the calf deep to gastrocnemius through the fibrous arch of soleus. It descends through the calf to the medial side of the ankle, passes beneath the flexor retinaculum, and divides into the medial and lateral plantar nerves. It supplies popliteus, all the muscles of the calf, and, through the plantar nerves, the small muscles of the sole of the foot and sensation to the sole. When the nerve is interrupted, the patient is unable to plantarflex or invert the foot, flex the toes, or stand on the ball of the foot. Paralysis of interossei leads to a claw-like deformity of the toes. Sensation is lost over the sole. Causalgia may arise after partial lesions. Injury to the distal portion of the nerve by a penetrating injury or deep wound of the calf gives rise to paralysis of the intrinsic muscles of the foot but spares the muscles acting at the ankle. Sensation is lost on the sole of the foot and this may be accompanied by pain. If the injury is distal to the origin of the branches to flexor hallucis longus and flexor digitorum longus, the lesion may escape detection because paralysis of the small foot muscles and sensory loss over the sole may be overlooked. The tibial nerve is very rarely compressed under the flexor retinaculum (tarsal tunnel syndrome), usually precipitated by osteoarthritis or post-traumatic deformities at the ankle, or tenosynovitis. Burning pain and tingling paraesthesiae occur in the sole, usually after prolonged standing or walking. The condition is generally unilateral. Careful examination may demonstrate wasting of the intrinsic muscles in the medial aspect of the foot, and sensory impairment over the sole. Nerve conduction studies may be helpful diagnostically. Treatment is by surgical section of flexor retinaculum. Morton's metatarsalgia (also known as intermetatarsal neuroma) is a syndrome of lancinating pain, numbness, or paraesthesiae,

section 24 Neurological disorders 6186 usually in one of the web spaces at the base of the toes, especially the third web space. The pain occurs especially on weight-bearing. Removing the shoe and massaging the foot or manipulating the toes may bring relief. It is not a neoplasm but probably perineural fibrous tissue provoked by chronic compression of a plantar nerve branch. Ultrasound is useful in diagnosis. Treatments include orthoses, ultrasound-guided injection of corticosteroids or sclerosing alcohol, radiofrequency ablation, or neurectomy surgery.

Common peroneal nerve (L4, L5, S1, S2) After separating from the tibial division of the sciatic nerve in the lower part of the thigh, the common peroneal nerve descends through the popliteal fossa, winds around the neck of the fibula, and divides into its superficial and deep branches. The superficial peroneal nerve passes down in front of the fibula, supplies peroneus longus and brevis, and emerges in the lower leg, supplying the skin on the lateral aspect of the lower leg. It crosses the extensor retinaculum and supplies the skin on the dorsum of the foot and the second to fifth toes. The deep peroneal branch continues to wind around the fibula, pierces the anterior intermuscular septum, and descends on the anterior interosseous membrane. It innervates tibialis anterior, extensor digitorum longus, extensor hallucis longus, and peroneus tertius. It passes deep to the extensor retinaculum after which it supplies extensor digitorum brevis and the skin of the adjacent sides of the first and

second toes. Damage to the common peroneal nerve is more frequent than injury to its two branches because of its vulnerable superficial position at the neck of the fibula. It gives rise to foot drop, with paralysis both of dorsiflexion and eversion at the ankle and of toe extension. Cutaneous sensation is impaired over the lateral aspect of the lower leg and ankle, and on the dorsum of the foot. It is distinguished from an L5 root lesion by preservation of ankle inversion power. The common peroneal nerve may be compressed at the neck of the fibula by habitually sitting with the legs crossed, prolonged squatting or kneeling, pressure during sleep or while anaesthetized, and various other events. It can be damaged by traction caused by fractures of the tibia and fibula, and is sometimes damaged by ischaemia in the anterior tibial compartment syndrome. Paralysis caused by external pressure frequently gives rise to a local conduction block usually with satisfactory recovery within weeks. A foot-drop orthosis may be helpful while recovery is awaited. Rare progressive cases require imaging.

Sural nerve (L5, S1-2) This arises from the sciatic nerve and descends to the back of the calf, winds around to the lateral side of the ankle, and supplies the skin of the lateral border of the foot. Sensory impairment occasionally results from pressure on the nerve in the back of the calf, for example, by tight ski boots. This nerve is the one most commonly chosen on the rare occasions when a nerve biopsy is needed.

Generalized neuropathies Neuropathies related to metabolic and endocrine disorders

Diabetes mellitus A significant degree of peripheral neuropathy develops in about 15% of patients with diabetes, although many more have either minor symptoms without signs, or asymptomatic neuropathy on examination or nerve conduction study. The most common type is distal sensory polyneuropathy of metabolic aetiology, and fewer patients have (multi)focal neuropathy due to ischaemia or microvasculitis. The most common form is a chronic slowly progressive symmetrical distal (length-dependent) sensory polyneuropathy, causing numbness and tingling paraesthesiae in the toes and feet, and less often in the fingers. Aching or lancinating pains in the feet and legs, particularly at night, may be a troublesome feature. Examination may reveal loss of vibration sense in the feet, depression of the ankle jerks, and distal cutaneous sensory impairment. Loss of the sense of pain may result in foot ulcers or Charcot's osteo-neuroarthropathy; impaired sensation may give an ataxic gait. Some patients have a pure small fibre neuropathy with spontaneous burning pain, and reduced sensation to temperature and pinprick, but normal reflexes and preserved sensation to vibration, light touch, and position. Infrequently there is an acute onset of painful diabetic polyneuropathy, associated with either poor diabetic control and precipitate weight loss ('diabetic neuropathic cachexia'), or a rapid improvement in glycaemic control ('insulin-triggered acute painful neuropathy'). Autonomic neuropathy frequently accompanies the sensory neuropathy and may be the predominant manifestation. It rarely occurs in isolation. Symptoms referable to the alimentary tract include dysphagia from oesophageal involvement, episodes of vomiting related to gastric atony (gastroparesis), and episodic nocturnal diarrhoea, often alternating with periods of constipation. Those related to the genitourinary system include erectile dysfunction, retrograde ejaculation, bladder atony with difficulty in voiding, and urinary retention with overflow. Vascular sympathetic denervation sometimes results in orthostatic hypotension, and cardiac parasympathetic denervation may cause an elevated resting heart rate and the absence of beat-to-beat variation with deep breathing. Pupillary disturbances usually take the form of a reduced response to light. Gustatory facial sweating provoked by the smell and taste of food can be troublesome. Anhidrosis may occur distally in the limbs; if it is extensive and also affects the trunk, heat intolerance can result. Mononeuropathies tend to occur more commonly in older people with diabetes. They may develop insidiously or have an abrupt onset with pain. Of the cranial nerves, the nerves to the external ocular muscles, particularly the

third and sixth, and also the facial nerve, are affected most often. Unlike the effects of compression of the third nerve by an aneurysm, pupillary reflexes are often spared. On the trunk, isolated radiculopathies may occur. The likely cause of all these is microvascular ischaemia and most patients make a good spontaneous recovery in a few months. In the limbs, the lesions tend to occur at the common sites of compression or entrapment. It seems likely that the nerves of people with diabetes exhibit an excessive vulnerability to damage from pressure. Diabetic lumbosacral radiculoplexus neuropathy (also known as diabetic amyotrophy or diabetic proximal neuropathy) is an uncommon severe multifocal neuropathy typically affecting older obese individuals with type 2 diabetes associated with profound subacute weight loss. It consists of severe asymmetrical proximal and distal weakness. Less commonly it is symmetrical. The onset is over days to months, often with severe pain, but with little sensory loss. The knee jerks are usually depressed or absent.

Inflammatory

24.16 Diseases of the peripheral nerves 6187 lesions including microvasculitis have been demonstrated in nerve biopsies, leading to trials of pulsed corticosteroids, which may reduce pain but have not been proven to benefit weakness. Most patients improve spontaneously over a year or two. A rare variant of this is the syndrome of 'painless diabetic motor neuropathy' that may cause weakness of all limbs developing over months with partial spontaneous improvement. The causation of diabetic neuropathy is uncertain. It tends to occur more often in people with poorly controlled diabetes, but the correlation is not close. In type 2 diabetes it may be the presenting symptom or occur for the first time on initiation of treatment with insulin. There is evidence to suggest that diabetic microangiopathy is important in the genesis of isolated nerve lesions. Metabolic factors are probably more important in the origin of the symmetrical polyneuropathies, but their nature is uncertain. An increased concentration of sorbitol in nerves secondary to hyperglycaemia may be involved in causing nerve fibre dysfunction. People with diabetes are more at risk of developing some other neuropathies including entrapment neuropathies and chemotherapy-induced neuropathy. Diabetes is the most common cause of neuropathy in the Western world, but cannot reliably be excluded by a normal fasting blood glucose: if suspected, HbA1c and/or an oral glucose tolerance test should be done. Some studies suggest patients with prediabetes (impaired glucose tolerance or impaired fasting glycaemia) may also have an increased risk of neuropathy, even if they do not have diabetes.

Treatment. Enhanced blood glucose control reduces the risk of development of clinical neuropathy in type 1 and probably type 2 diabetes, and reduces nerve conduction and vibration threshold abnormalities in both types, but at the expense of an increased risk of severe hypoglycaemic episodes. Acute-onset neuropathies usually recover adequately over months, but chronic sensory (and autonomic) polyneuropathy usually persists and progresses slowly even with enhanced glycaemic control. There are no other specific treatments of proven benefit. Care of the feet is vitally important in diabetic sensory neuropathy, to prevent the development of chronic ulceration. Medication for neuropathic pain is described in the section 'Treatment of neuropathies in general'. Postural hypotension can be improved by raising the head of the bed at night, high fluid and salt intake, and compression stockings; more severe cases may require treatment with the α -agonist midodrine and fludrocortisone. Gastroparesis may respond to metoclopramide, domperidone, or erythromycin. In extreme cases, persistent vomiting may necessitate a roux-en-Y gastroenterostomy. Diabetic diarrhoea can be helped by low-dose tetracycline or diphenoxylate, loperamide, or codeine phosphate. An atonic bladder can be managed in the earlier stages by regular voiding, lower abdominal compression, and straining. More severe cases should undergo urodynamic studies and

are usually best managed by intermittent self-catheterization. Urinary tract infections should be treated promptly. Bladder neck resection can be useful in carefully selected cases. Erectile dysfunction may be treated with one of the phosphodiesterase inhibitors, sildenafil, tadalafil, or vardenafil, or intrapenile injections of alprostadil (prostaglandin E1) for resistant cases.

Uraemia
 Uraemic neuropathy occurs in patients with severe chronic renal failure especially those on long-term haemodialysis. The symptoms are usually predominantly sensory, with numbness and tingling paraesthesiae, and burning in the feet. Restless legs syndrome and cramps are often conspicuous (see Section 24.21). A distal motor neuropathy may be associated and occasional cases are purely motor. The condition is not necessarily improved by increased haemodialysis but does improve after kidney transplantation. Failure to clear 'middle molecules' that are toxic to axons has been proposed but not proved to be the mechanism. The nerve trunks in the arm and forearm are at risk during surgery for placing an arterio-venous fistula for dialysis. Symptoms may be produced by surgical damage, ischaemia, sometimes partly attributable to shunting, and compression.

Hypothyroidism
 Compression of the median nerve in the carpal tunnel in hypothyroidism has already been discussed. Rarely a generalized mixed motor and sensory neuropathy develops. This improves on treatment of the hypothyroidism. The slow contraction and relaxation observed in the tendon reflexes is due not to a disturbance of peripheral nerve function, but to an alteration in the contractile mechanism of the muscle fibres.

Acromegaly
 In addition to carpal tunnel syndrome, acromegaly may cause a sensory and motor polyneuropathy. The peripheral nerves may be thickened because of an overgrowth of endoneurial and perineurial connective tissue. A similar neuropathy is occasionally observed in pituitary gigantism.

Critical illness polyneuropathy
 A generalized polyneuropathy involving widespread axonal degeneration may develop in patients with prolonged stays in intensive care units with sepsis, systemic inflammatory response syndrome, and multiple organ failure. The neuropathy is discovered when the patient is too weak to wean from the ventilator. It is difficult to distinguish from critical illness myopathy and often both occur together. The precise cause is unknown. It is particularly likely to occur after the use of prolonged neuromuscular junction blockade, hyperglycaemia, and high-dose corticosteroids. Intensive insulin therapy is proven to reduce the incidence and severity of neuromyopathy, and early rehabilitation is beneficial. There is no specific treatment but the neuropathy usually improves slowly over a year or so and satisfactory recovery may occur.

Other metabolic disorders
 Symmetrical sensory and autonomic polyneuropathy probably does occur with cirrhosis but most cases are the result of the alcoholism that is its most common cause. A mild, painful, sensory neuropathy is occasionally encountered in primary biliary cirrhosis, sometimes related to xanthomatous deposits in the cutaneous nerve trunks.

Toxic neuropathies
 Industrial and environmental
 Alcohol See 'Deficiency neuropathies'.

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Acrylamide
 Acrylamide monomer was formerly a cause of peripheral neuropathy because it was absorbed through the skin by workers manufacturing the nontoxic polymers used in waterproofing and other industries. It caused a distal sensory and motor neuropathy with prominent numbness and disequilibrium. Distal axonal degeneration occurred and slow improvement followed cessation of exposure. With proper safety precautions this neuropathy should not occur.

Arsenic
 Arsenical poisoning is occasionally seen as a result of accidental or homicidal ingestion of insecticides containing arsenic, or from indigenous medicines in India. Gastrointestinal symptoms develop after acute ingestion, followed by a mixed sensory and motor neuropathy after one to three weeks. Desquamation of the skin of the feet and hands takes place after about six weeks, and white lines (Mees' lines) appear in the nails. There is a systemic

illness with anaemia and abnormal liver function. The skin may become generally pigmented or show focal 'raindrop' pigmentation, and hyperkeratosis of the palms of the hands and soles of the feet may appear. Slow recovery from the neuropathy occurs with removal from exposure. Chelating agents are of value in treating the nonneurological complications, but it is uncertain whether they are effective for the neuropathy. Lead neuropathy is now rare in the United Kingdom, although it was encountered as a consequence of the contamination of drinking water by lead pipes in old buildings. Subclinical neuropathy may be detectable in lead workers. It remains a hazard in certain parts of the world from the use of lead glazes in pottery. Lead poisoning usually causes a triad of abdominal pain with constipation, anaemia, and neuropathy. The neuropathy may be predominantly motor and affect the upper much more than the lower limbs. It is frequently asymmetrical and typically produces weakness of first the finger and then the wrist extensors. The 'lead colic' that may occur is probably a manifestation of autonomic involvement. Severe chronic lead poisoning causes bluish discoloration of the gums just below the teeth, especially if they are carious. The neuropathy improves on cessation of lead intake. Chelating agents accelerate removal of lead but it is uncertain which of dimercaprol, edetate, penicillamine, and 2,3-dimercaptosuccinic acid (DMSA) is the best. Mercury Exposure to inorganic mercury salts and organic mercurial compounds may lead to neurological damage. There was an outbreak of poisoning in Minamata Bay, Japan, related to the consumption of fish contaminated by organic mercury. Dementia, cortical blindness, and ataxia occur, together with paraesthesiae, the last due perhaps to involvement of the dorsal root ganglia. Peripheral neuropathy was also a component of 'pink disease' in infants, consisting of anaemia, light sensitivity, skin rash, weight loss, and hypotonia. It was caused by the inorganic mercury in teething powders. Thallium This is present in certain pesticides and rodent poisons, and was formerly used as a depilatory agent. Accidental or homicidal poisoning is occasionally encountered. Acute ingestion causes nausea, vomiting, and diarrhoea. In severe cases coma develops rapidly. In milder cases there are central nervous symptoms including anxiety and choreoathetosis, and the development of a progressive, very painful, sensory, and motor neuropathy. Alopecia is characteristic and develops later, after about two or three weeks, and renal damage may occur. Both Prussian blue to bind thallium in the gut and chelating agents to clear thallium from the body have been used as treatment. Organophosphates Organophosphates, especially tri-ortho-cresylphosphate, have been widely used as lubricants, insecticide crop sprays, antiparasitic sheep dip, and in chemical warfare. The original description of organophosphate poisoning was in relation to illegal liquor distillation in the United States of America during the prohibition era (ginger Jake paralysis). A large outbreak occurred in Morocco from contaminated cooking oil. Accidental or suicidal acute poisoning with high doses causes an acute muscarinic syndrome with diarrhoea, sweating, salivation, and miosis. After 12 hours to 4 days, patients develop generalized weakness, possibly due to neuromuscular blockade, confusion, and even coma. Recovery from this begins after 1 or 2 weeks. However, between 1 and 3 weeks after the acute exposure, some patients develop a subacute predominantly motor neuropathy—'organophosphate-induced delayed polyneuropathy'. Recovery is slow and often incomplete. Chronic low-dose exposure to organophosphates (at doses insufficient to cause acute symptoms) does not cause neuropathy. Other industrial substances Carbon disulphide, used in the manufacture of rayon, occasionally gives rise to a mild sensory neuropathy. Neuropathy may occur as a result of industrial exposure to the organic solvents n-hexane and methyl-n-butyl ketone. The former is also encountered as a consequence of solvent abuse ('glue sniffing'); n-hexane, which has an irritant action, has been used as a solvent in certain glues. Other industrial agents causing neuropathy are ethylene oxide and methyl bromide. Trichlorethylene (or an impurity) has

caused trigeminal neuropathy. Drug induced Bortezomib The proteasome inhibitor bortezomib, an antineoplastic agent used for multiple myeloma, frequently causes a painful subacute sensory axonal neuropathy, and rarely a more acute sensory-motor neuropathy that can resemble Guillain-Barré syndrome. Isoniazid A mixed motor and sensory neuropathy may be produced by isoniazid and is more likely to occur in individuals who acetylate the drug slowly. The neuropathy is related to interference with pyridoxine metabolism. Axonal degeneration occurs in the peripheral nerves. The neuropathy recovers slowly when the patient stops taking the drug; this may be prevented by giving pyridoxine, which does not interfere with the antituberculosis action of the isoniazid.

24.16 Diseases of the peripheral nerves 6189 Nitrofurantoin Excessively high blood levels of nitrofurantoin as may occur in patients with reduced renal function, can cause a rapid-onset mixed motor and sensory neuropathy, which may be confused with Guillain-Barré syndrome. Nucleoside analogue reverse transcriptase inhibitors in HIV The nucleoside analogue reverse transcriptase inhibitors (zalcitabine, didanosine, and stavudine) cause a dose-dependent, subacute, painful, sensory axonal neuropathy, for which reason these drugs are now rarely used. The neuropathy continues to progress for some weeks after the patient stops taking the drug but this eventually improves. It may be difficult to distinguish from the painful neuropathy caused by HIV itself without withdrawal of the drug. Painful neuropathy in a patient on most modern anti-HIV drugs is much more likely to be due to the HIV disease than to the drugs. Phenytoin After taking phenytoin for years, patients may report symptoms of a mild sensory neuropathy. More commonly the neuropathy is asymptomatic but detectable on clinical and especially neurophysiological examination. Platinum Oxaliplatin, cisplatin, and carboplatin chemotherapy may cause a painful predominantly sensory neuropathy after taking several courses. Recovery from the neuropathy is variable and often limited. Ototoxicity is more frequent, causing high-tone deafness and tinnitus. Oxaliplatin also causes an acute cold-sensitive dysaesthesia, which improves quickly. Despite much research, no substance has yet been found to prevent this neurotoxicity. Pyridoxine Pyridoxine, if taken in large doses as 'megavitamin therapy', causes a severe sensory neuropathy with numbness of the feet and an unsteady gait. It is disputed whether chronic doses as low as 100 mg daily cause neuropathy, the daily requirement being only 2 mg. Taxanes The taxanes, paclitaxel and docetaxel, used in cancer treatment, cause a dose-dependent, predominantly sensory axonal neuropathy. It presents with numbness and paraesthesiae in the feet and worsens with each dose. With high doses weakness develops. If the drug is stopped, the neuropathy worsens for some weeks before improving, a phenomenon called 'coasting'. Thalidomide Thalidomide, used in the treatment of some vasculitides and multiple myeloma, also causes a dose-dependent, predominantly sensory neuropathy. It presents with painful paraesthesiae and cramps in the legs. It may be associated with palmar erythema, brittle nails, and tremor. It improves if the drug is stopped. Vincristine Vincristine produces a dose-dependent axonal neuropathy, and its therapeutic use in neoplasia is limited by this side effect. Patients first develop distal paraesthesiae and lose their ankle reflexes. If the drug is continued, they gradually develop distal sensory loss and may eventually develop weakness that comes on quite rapidly. The neuropathy improves satisfactorily if the drug is withdrawn. Other substances Other drugs that may give rise to neuropathy are doxorubicin, amiodarone, chloroquine (with myopathy), dapsone, disulfiram, ethambutol, gold, metronidazole, misonidazole, nitrous oxide (with a myelopathy), podophyllin, suramin, and zimeldine. This list is not exhaustive and if a patient with an unexplained neuropathy is taking drugs of any sort, it is worth checking whether any of the drugs is reported to cause neuropathy.

Deficiency neuropathies

Alcoholic neuropathy This usually occurs on a background of nutritional deficiency. The dietary intake of the person abusing alcohol is high in carbohydrates and low in vitamins. Moreover, such individuals are known to have a reduced capacity to absorb thiamine. A direct toxic effect of alcohol on peripheral nerves may also be involved. The clinical features of alcoholic neuropathy are similar to those of thiamine deficiency (see next), sometimes with coexistent alcohol-induced cerebellar ataxia or myopathy. Other deficiency states may coexist, such as the Wernicke-Korsakoff syndrome. Improvement may take place with B vitamin (especially thiamine or benfotiamine) replacement and reduced alcohol intake, but it is beset with the usual difficulties met in treating patients with alcohol problems.

Vitamin B12 deficiency Vitamin B12 deficiency, from whatever cause, is a common cause of a distal sensory neuropathy, with sensory ataxia, sensory loss, and paraesthesiae, either in isolation or with a myelopathy or other central nervous system manifestations. Haematological changes are not always present. The peripheral neuropathy improves more satisfactorily with treatment than the central disturbances. This condition is considered in detail in Chapter 22.6.6. Vitamin B12 blood levels are unreliable: a mildly low level (>140 pg/ml) cannot necessarily be assumed to be the cause of a neuropathy, but increased serum methylmalonic acid and homocysteine are useful markers of significant B12 deficiency which may occur even at low normal serum levels (<350 pg/ml). A peripheral neuropathy is one component of Nigerian ataxic neuropathy, in which the other features are posterior column degeneration, sensorineural deafness, and optic atrophy. It has been suggested that an interference with vitamin B12 metabolism by cyanide derived from cassava in the diet, combined with nutritional deficiency, is responsible.

Coeliac disease There is an association between coeliac disease and some neurological syndromes including cerebellar ataxia and peripheral neuropathy. In patients with malnutrition or vitamin B12 or folate deficiency, this is easily explained. Most patients with neurological manifestations experience preceding gastrointestinal symptoms before developing peripheral neuropathy. Nevertheless, some patients do develop a peripheral neuropathy, usually a symmetrical, distal, sensory axonal neuropathy, in their absence. This now justifies at

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least screening for antibodies associated with coeliac disease in patients with otherwise unexplained axonal neuropathy. Whether the associated neuropathy is caused by subtle nutritional deficiency or an unidentified toxic factor is not known. Regardless of this, improvement after institution of a gluten-free diet has been reported.

Thiamine deficiency (See also Chapter 11.2.) Thiamine deficiency is the cause of dry beri-beri which occurs in severely malnourished communities, especially those subsisting on diets largely made up of polished rice, and medical conditions that reduce thiamine intake, most commonly chronic alcohol abuse, hyperemesis of pregnancy, and after gastric surgery. Initial symptoms of fatigue, irritability, and cramps are followed by the development of a painful sensory neuropathy, sometimes with sensory ataxia. In severe cases, involvement of the recurrent laryngeal nerves may lead to hoarseness of the voice. The neuropathy may be associated with cardiomyopathy ('wet beri-beri'). The diagnosis may be supported by a reduced activity of erythrocyte transketolase, which requires thiamine as a cofactor. Distal axonal degeneration occurs in the peripheral nerves and slow recovery ensues with vitamin replacement.

Strachan's syndrome Strachan's syndrome, originally described in Jamaica but also observed in other parts of the world under conditions of nutritional deprivation, is characterized by the combination of a painful sensory neuropathy, optic neuropathy, and deafness, in association with orogenital dermatitis. There may also be features of a myelopathy. It is assumed to be due to deficiency of the B vitamins, but

the precise deficit has not been identified. It may improve with B vitamin and folate supplementation. Pyridoxine deficiency As well as high doses of pyridoxine causing neuropathy, as described earlier, pyridoxine deficiency may contribute to the neuropathy that occurs in nutritional deficiency states. Isoniazid neuropathy is related to an interference with pyridoxine metabolism.

Vitamin E deficiency Vitamin E deficiency occurs in some hereditary disorders and in hepatobiliary and bowel disorders that impair its absorption. It produces a multisystem neurological disorder in which cerebellar ataxia is the most prominent problem but peripheral neuropathy also occurs. It may be diagnosed by measuring plasma concentrations of α -tocopherol, the most active form of vitamin E.

Inflammatory and postinfective neuropathies

Leprosy Peripheral nerve involvement in leprosy is considered in Chapter 8.6.28.

Guillain-Barré syndrome Guillain-Barré syndrome is the most common cause of acute neuromuscular paralysis in developed countries. Its annual incidence is about 1 per 100 000 throughout the world, being more common in men and older people. It consists of weakness of two or more limbs developing over a few days, with extremes of a few hours to up to 4 weeks. The tendon reflexes are usually (but not always) reduced or absent in weak limbs. The illness often, but not necessarily, causes paraesthesiae, pain, and sensory loss. There are no signs of central nervous involvement. In two-thirds of cases there has been an infective illness between 1 and 6 weeks, most commonly 1 or 2 weeks, earlier. The infection is most commonly an uncharacterized upper respiratory tract infection but alternatively gastroenteritis. About 25% of cases are due to preceding *Campylobacter jejuni* infection, but 15% result from a preceding cytomegalovirus infection, 5–10% from Epstein-Barr virus, and 1–5% from mycoplasma. Many other associated infections have been reported but not proved by large-scale epidemiological studies. The onset is usually with the simultaneous development of weakness of the limbs, paraesthesiae, and numbness. Pain, including back or root pain, may be a prominent feature and may precede the weakness. Weakness may be proximal, distal, or generalized in distribution, but is usually fairly symmetrical. The facial and bulbar muscles are commonly involved and sometimes the ocular muscles. About 25% of patients develop such severe respiratory muscle weakness for which they need intubation and artificial ventilation. Rarely a complete 'locked-in' state may develop. Autonomic disturbances include tachycardia, hypertension, and then later postural hypotension, bladder atony, and ileus. Papilloedema sometimes develops. This same clinical picture may be caused by any of three pathological entities. In Europe and North America, acute inflammatory demyelinating polyradiculoneuropathy is the underlying pathology in more than 90% of cases. Its pathogenesis is unclear but the hypothesis that it is due to a T-cell-mediated autoimmune response to one of several peripheral nerve myelin proteins is giving way to the idea that it is caused by a complement-fixing antibody directed against an unidentified ganglioside or combination of gangliosides. In China, Japan, and Mexico most cases are caused by acute motor axonal neuropathy. In such cases preceding *Campylobacter jejuni* infection is common and antibodies to the ganglioside GM1, GD1a, or both are usually present in the serum. Epitopes resembling the terminal sugars of these gangliosides are present in the bacterial walls of the *Campylobacter jejuni* strains, which induce acute motor axonal neuropathy. The antibodies probably produce the neuropathy by reacting with gangliosides on the axolemma or at the motor nerve terminals, then blocking nerve conduction or inducing axonal degeneration. There is also a less common acute motor and sensory axonal neuropathy. Diagnosis is largely clinical, often supported by neurophysiological and cerebrospinal fluid findings, but sometimes all investigations are normal. In AIDP, nerve conduction studies typically show motor nerve conduction block, slowing of motor nerve conduction, often multifocal, and reduced sensory nerve action potential amplitudes. In the axonal forms of the disease, the changes are those of an

axonal neuropathy. During the first week, routine neurophysiological tests may be normal. Accurate identification of the neurophysiological type may require serial studies. The cerebrospinal fluid usually has an increased protein concentration (but often normal in the first week), and normal or sometimes slightly increased leucocyte count (rarely more than 10 and by definition not more than 50/ μ l), predominantly lymphocytes. Antibodies to gangliosides, especially GM1, may be present, especially in the axonal forms. The differential diagnoses are acute muscle dysfunction (including

24.16 Diseases of the peripheral nerves 6191 hypo- or hyperkalaemia), neuromuscular junction disorders, other causes of neuropathy (including drugs, toxins, and vasculitis), and cauda equina, cord, and brain-stem causes of paralysis. A worse outcome is predicted by older age, preceding diarrhoea and more severe weakness. About a quarter of patients have a benign course, never losing the ability to walk. About a quarter require artificial ventilation, accounting for most of the 5% who die, and 20% are left with persistent disability so severe that they need help walking. Of the remainder, most are able to walk with help by 1 month and without aid by 3 months, and return to work or their usual activities by 6 months. Some patients have persistent fatigue. The mainstays of management are careful monitoring for the development of respiratory failure (by forced vital capacity) and cardiac arrhythmia, venous thromboembolism prophylaxis, and excellent intensive care. Plasma exchange or intravenous immunoglobulin (2 g/kg) improve the rate and extent of recovery if given within the first two, and perhaps four weeks; a repeat course is often given to those not improving (RCT in progress). Corticosteroids are not beneficial. Pain may be a significant problem (see 'Treatment of neuropathies in general'). Careful positioning and physiotherapy are important to avoid pressure sores and contractures. Exercise programmes are probably useful for fatigue. Deterioration within nine weeks from onset is usually a 'treatment-related fluctuation' requiring a repeat course of immunoglobulin, but later relapse usually indicates the development of chronic inflammatory demyelinating polyradiculoneuropathy. Neurophysiology does not assist this distinction. Fisher syndrome A syndrome of ophthalmoplegia, ataxia, and loss of the tendon reflexes was described by Miller Fisher in 1956. Similar to Guillain-Barré syndrome, it commonly follows an infection, progresses for a few days, and then plateaus and eventually improves. As in Guillain-Barré syndrome, the cerebrospinal fluid protein concentration is usually increased. Facial and bulbar palsies also occur and are accepted as part of the syndrome, but patients with associated limb weakness are regarded as having an overlap with Guillain-Barré syndrome. In the pure cases, motor nerve conduction remains normal but sensory action potentials disappear. The prognosis is excellent even without immunotherapy. The diagnosis is usually straightforward, but confusion with botulism and diphtheritic neuropathy may arise. In most patients with Fisher syndrome, antibodies to ganglioside GQ1b are present in the serum and are probably important in causing terminal nerve damage. Formes frustes of Fisher syndrome, with only some of the features, are sometimes encountered. Bickerstaff's brain-stem encephalitis is similar to Fisher syndrome with additional signs of central nervous system involvement, including altered consciousness and extensor plantar responses. In addition there may be an increased cerebrospinal fluid cell count and abnormalities in the brain stem visible on MRI. Chronic inflammatory demyelinating polyradiculoneuropathy Chronic inflammatory demyelinating polyradiculoneuropathy is a chronic progressive or relapsing disorder with weakness and sensory changes in the limbs developing over more than 8 weeks. Patients whose symptoms stabilize in less than 4 weeks are regarded as having the AIDP form of Guillain-Barré syndrome (or acute-onset chronic inflammatory demyelinating polyradiculoneuropathy), whereas those whose

symptoms progress over 4–8 weeks are considered to have subacute inflammatory demyelinating polyradiculoneuropathy. The three disorders probably constitute a spectrum. Chronic inflammatory demyelinating polyradiculoneuropathy is as an important treatable form of chronic neuropathy which should be distinguished from the many less treatable causes of chronic axonal neuropathy. Its prevalence has ranged from 2 to 9 per 100 000 in different studies. Clinical features suggestive of chronic inflammatory demyelinating polyradiculoneuropathy are proximal and distal weakness of all limbs, loss of all tendon reflexes without much muscle wasting, and raised cerebrospinal fluid (CSF) protein. There may or may not be significant sensory loss. Nerve conduction studies are key to making the diagnosis, and should be repeated if the diagnosis is uncertain. The hallmarks of chronic inflammatory demyelinating polyradiculoneuropathy are multifocal slowing of motor nerve conduction, often with partial conduction blocks, and prolonged duration of compound muscle action potentials. Sensory nerve action potentials are often reduced or absent. Raised CSF protein, and thickened nerves on imaging, are supportive but not always present. In typical cases, the clinical features are symmetrical but about 10% of patients have an asymmetric or multifocal disorder called the Lewis–Sumner syndrome or ‘multifocal acquired demyelinating sensory and motor neuropathy’. There are also pure motor, pure sensory, and focal variants. The first-line treatment is either corticosteroids (daily prednisolone reducing from 60 mg, or monthly pulses of dexamethasone or methylprednisolone); or intravenous immunoglobulin (initially 2 g/kg). Treatment usually needs to be continued for months or longer. Compared with immunoglobulin, corticosteroids have a lower response rate but are much cheaper and more likely to induce a longer remission. There is no consensus on the regime for long-term immunoglobulin, but the largest trial used 1 g/kg every 3 weeks, and the dose and interval may be adjusted according to the response, which should be assessed by formal outcome measures. Many patients choose to switch to subcutaneous immunoglobulin which may be more convenient with fewer adverse effects. Most patients improve, but those failing to respond should be referred to a specialist to confirm the diagnosis, and to consider further treatments including plasma exchange, azathioprine, or cyclophosphamide.

Multifocal motor neuropathy Multifocal motor neuropathy typically causes chronic distal asymmetric weakness in the upper limbs without sensory loss, often associated with IgM antibodies to ganglioside GM1. The diagnosis depends on nerve conduction studies identifying multiple regions of motor nerve conduction block with preserved sensory nerve conduction through the same nerve segment. Rare patients have no identified conduction block. The only proven treatment is intravenous immunoglobulin (as for chronic inflammatory demyelinating polyradiculoneuropathy, mentioned earlier) but this needs to be repeated approximately every month. Multifocal motor neuropathy may be worsened by corticosteroids.

Lyme disease Lyme disease is a multisystem disease caused by tick-borne spirochaetes belonging to the genus *Borrelia* (see Chapter 8.6.33). About 3 months after infection and without necessarily having had a preceding rash or arthritis, a small proportion of infected patients

section 24 Neurological disorders 6192 develop lymphocytic meningitis, facial palsy, painful radicular symptoms, and/or rarely a more severe generalized asymmetrical polyradiculoneuropathy. Some develop peripheral nerve lesions without ever having symptomatic meningitis. Serum antibodies to *Borrelia* are helpful in diagnosis but are common in endemic areas. In a hospital setting measurement of serum/cerebrospinal fluid antibody index is very specific but does not detect all cases. Nerve biopsies are not usually needed to make the diagnosis but may show extensive inflammatory infiltrates although the spirochaetes are not identifiable. Treatment is

usually given in the form of parenteral ceftriaxone but oral doxycycline is a possible alternative for mild cases. HIV infection A variety of neuropathies may be related to HIV-1 infection, particularly types tending to occur in different phases of the disease. At the time of seroconversion or soon afterwards, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, or multifocal vasculitic neuropathy may develop and precede other features of HIV infection. In the later AIDS phase, a distal symmetrical polyneuropathy is common. It is a slowly progressive disorder predominantly affecting small sensory fibres that may be painful and similar to the toxic neuropathy produced by reverse transcriptase inhibitors mentioned earlier. In advanced cases an aggressive lumbosacral polyradiculoneuropathy from cytomegalovirus infection is encountered. HIV infection and its treatment are discussed in Chapter 8.5.23.

Herpes zoster Varicella-zoster virus commonly causes 'shingles': neuropathic pain/itching/paraesthesiae in the distribution of a sensory dermatome, with (or without) a vesicular rash. Less commonly there is involvement of more than one dermatome, plexopathy, motor radiculopathy, facial palsy, myelopathy, or meningoencephalitis. Acute antiviral treatment is recommended. Aciclovir does not prevent postherpetic neuralgia, which may be treated with standard medications for neuropathic pain (see 'Treatment of neuropathies in general') or locally with lidocaine plasters or capsaicin cream.

Sarcoid neuropathy Facial palsy is the most common peripheral nerve manifestation of sarcoidosis (see Chapter 18.12). It may be bilateral and accompanied by uveitis and parotitis. Less commonly subacute or fluctuating multiple cranial nerve palsies occur. More rarely, almost any pattern of peripheral neuropathy has been seen, including multiple mononeuropathy and a Guillain-Barré syndrome-like picture, albeit usually more subacute. Other manifestations of sarcoidosis, such as erythema nodosum, arthritis, enlarged lymph nodes, uveitis, and abnormal chest radiographs, are not always present and the diagnosis has to be considered in a variety of neuropathies. The cerebrospinal fluid is abnormal in about half the patients with peripheral nerve sarcoidosis. If an accessible nerve can be biopsied, sarcoid granulomas may clinch the diagnosis. Corticosteroids are the mainstay of treatment.

Diphtheritic polyneuropathy Diphtheria (Chapter 8.6.1) used to be a serious, even fatal, disease of children. It was almost completely prevented in children by the advent of immunization. As immunity wanes, occasional cases are now seen in adults. It most commonly causes infection of the pharynx (often with a visible grey pseudomembrane), or occasionally post-traumatic cutaneous ulcers. Peripheral neuropathy is caused by the release of an exotoxin that interferes with Schwann cell function, probably by affecting protein synthesis, and produces segmental demyelination. The nerves are not invaded by the bacterium. Between 1 and 7 weeks after pharyngeal infection, patients may develop numbness of the tongue and face and a bulbar palsy. The bulbar palsy and respiratory involvement may be so severe as to require artificial ventilation. Paralysis of accommodation and sometimes of the external ocular muscles may occur. Weakness and sensory loss may develop in the limbs, sometimes as the bulbar palsy is beginning to improve. Neuropathy may progress for many weeks, often with a biphasic time course. The disease also causes myocarditis. Nerve conduction studies show slowing of motor nerve conduction. The cerebrospinal fluid protein concentration becomes increased and the cell count may be raised. In particular in those cases with a normal cell count, there is a possibility of confusion with Guillain-Barré syndrome. Diagnosis can be made by culturing *Corynebacterium diphtheriae* from the throat, or identifying its toxin or DNA in throat swabs. Treatment is supportive; antitoxin seems beneficial only if given within two days of onset of pharyngitis.

Vasculitic peripheral neuropathy Vasculitic peripheral neuropathy usually presents as a painfully progressive multifocal or asymmetric neuropathy, or sometimes as multiple mononeuropathies or symmetrical polyneuropathy, and sometimes without

pain. The neuropathy is typically distal, lower limb predominant, sensory or sensory-motor, with a stepwise time course. It may precede or follow systemic manifestations of vasculitis. It is caused by many types of systemic vasculitis, most commonly ANCA- associated small vessel vasculitides, but also polyarteritis nodosa, infections including hepatitis C virus-associated cryoglobulinaemia, lupus, drug induced, or paraneoplastic. In rheumatoid arthritis, carpal tunnel syndrome and ulnar nerve lesions due to joint derangement are the most common peripheral nerve manifestations, but rheumatoid vasculitis may cause florid multiple mononeuropathies or sometimes a slowly progressive distal sensory neuropathy, or one restricted to the digital nerves. Sometimes vasculitis exclusively affects peripheral nerves, called nonsystemic vasculitic neuropathy, which includes some diabetic syndromes. Diagnosis may be confirmed by biopsy of an affected tissue, including peripheral nerve, muscle, or skin, showing vascular damage and mural inflammation. This is one of the principal indications for nerve biopsy, which should preferably be done in a specialist centre to minimize surgical and laboratory artefact. Treatment of vasculitic neuropathy is the same as the treatment for the underlying disorder. Corticosteroids (usually oral prednisolone) are the mainstay of treatment. In many, especially severe cases, an immunosuppressive agent is also given. Pulsed intravenous (or oral) cyclophosphamide for 3 months followed by azathioprine is commonly used. Patients may require treatment of neuropathic pain and neurorehabilitation including ankle-foot orthoses. The neuropathy usually greatly improves over 1–2 years. Sjögren's syndrome may cause several types of neuropathy, including vasculitic neuropathy, sensory ataxic neuronopathy

24.16 Diseases of the peripheral nerves 6193 related to dorsal root ganglionitis, or a painful small fibre neuropathy (see next). Sometimes the trigeminal ganglion is affected in isolation. Neoplastic and paraneoplastic neuropathy Direct invasion of cranial nerves or spinal roots may occur in malignant infiltration of the meninges and of the brachial and lumbosacral plexus from local malignancies. Malignant infiltration is usually painful. Infiltration of peripheral nerves is most commonly from malignant lymphomas. Rarely, generalized infiltration may occur to produce multifocal neuropathy or even an acute neuropathy resembling Guillain-Barré syndrome. CSF cytology requires at least 5 ml of fresh CSF and may need to be repeated as sensitivity for detection of malignant cells is low. Paraneoplastic neuropathy may develop as a nonmetastatic, autoimmune complication of carcinoma, most often bronchial or gastric, and occasionally with lymphoma. The underlying neoplasm often pursues an unusually indolent course, suggesting that the autoimmune process is holding the neoplasm in check, but may be identified by positron emission tomography scanning. The neuropathy may antedate the discovery of the carcinoma by up to 3 years. A wide variety of clinical pictures has been reported. The most common syndrome is the subacute sensory neuronopathy (dorsal root ganglionopathy) usually associated with a small cell lung carcinoma and anti-Hu antibodies. This presents with a severe sensory ataxia and areflexia, often worse in upper limbs and with autonomic disturbance, or sometimes burning pain. Sensory neuronopathy may also be idiopathic or caused by Sjögren's syndrome or HIV. Other paraneoplastic neuropathies include potassium channel antibody-associated neuromyotonia, or vasculitis. Carcinoma of the bronchus is associated with other types of neuropathy, including a slowly progressive mixed sensory and motor neuropathy. Paraneoplastic neurological syndromes often occur in combinations. Gynaecological cancers are particularly associated with a cerebellar syndrome and antibodies to Purkinje cells (anti-Yo antibodies). Peripheral neuropathy may be part of this syndrome. Paraneoplastic neuropathies may stabilize after removal of the underlying tumour, but rarely improve and immunotherapy is rarely beneficial. Paraprotein-associated neuropathy Both peripheral neuropathy and monoclonal gammopathy of undetermined significance

(MGUS) become more common with advancing age, so the association is not necessarily causative. In a demyelinating neuropathy, an IgM paraprotein is usually causative, but the presence of an IgG or IgA MGUS is usually coincidental as these patients (and some with IgM MGUS) behave in every respect like patients with chronic inflammatory demyelinating polyradiculoneuropathy without a paraprotein. In an axonal neuropathy, the presence of any paraprotein is probably coincidental unless there is amyloidosis or a malignant plasma cell dyscrasia. The most common syndrome is an IgM paraprotein-associated demyelinating neuropathy, half of whom have antibodies to myelin-associated glycoprotein. The characteristic features are of a slowly progressive distal, predominantly sensory, demyelinating neuropathy, often with a postural tremor and ataxia. Neurophysiology shows characteristic predominantly distal motor slowing. Nerve biopsy may show widely spaced myelin lamellae. Most patients have MGUS, but bone marrow biopsy and CT body scan are recommended to identify the minority of patients with identical neurological features who have Waldenström's macroglobulinaemia. About one-third of patients respond to intravenous immunoglobulin, rituximab, cyclophosphamide, bendamustine, or combinations. In the rare CANOMAD syndrome (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies), antibodies are present against gangliosides GQ1b or GD1b. Other rare syndromes of MGUS-associated neuropathies are likely due to as-yet unidentified antibody properties of their paraproteins. Malignant plasma cell dyscrasias may affect the peripheral nervous system. Multiple myeloma deposits may compress spinal nerve roots, causing pain and radicular symptoms as well as cord compression, but does not usually cause a neuropathy except as an adverse effect of treatments such as bortezomib or thalidomide. The mixed cryoglobulins in essential cryoglobulinaemia, sometimes associated with hepatitis C infection, cause a vasculitic multiple mononeuropathy. The treatment is that of the underlying condition. The POEMS syndrome (polyneuropathy, organomegaly, oedema, monoclonal protein, and skin changes) is a multisystem paraneoplastic disorder with osteosclerotic myeloma (or solitary plasmacytoma or Castleman's disease), usually IgG or IgA lambda paraprotein, very high serum concentration of vascular endothelial growth factor, and a mixed axonal and demyelinating neuropathy, often painful. Not all the features in the name are required; papilloedema and thrombocytosis may occur. Sclerotic bone lesions should be sought by CT or PET of spine, pelvis or whole body. Treatment may be by irradiation, melphalan-based chemotherapy, or peripheral blood stem cell transplantation. Amyloidosis The various forms of amyloid disease are described in Chapter 12.12.3. The peripheral nerves may be involved in primary amyloid light-chain amyloidosis (due to plasma cell dyscrasia such as myeloma, typically with lambda light chains), or in familial amyloid polyneuropathy (see Genetic neuropathies), but not in secondary amyloidosis due to chronic inflammation. The clinical features are similar, typically with a painful sensory (predominantly small fibre) polyneuropathy with early prominent autonomic dysfunction (as described earlier for diabetes). Carpal tunnel syndrome is common, because of deposits in the flexor retinaculum. Large fibre sensory and motor involvement occur later. Sometimes the neuropathy is asymmetric or multifocal. Amyloid deposits are present in the peripheral nerve trunks, which may be enlarged, and in the dorsal root and sympathetic ganglia. Carpal tunnel syndrome (without generalized neuropathy) is also frequent in patients with amyloidosis due to wild-type transthyretin, or to $\beta 2$ -microglobulin in long-term haemodialysis. Diagnosis is by biopsy of an affected tissue, with measurement of serum free light chains or serum and urine electrophoresis (Bence-Jones protein). Amyloid light-chain amyloidosis may respond to chemotherapy or peripheral blood stem cell transplantation. Pain and autonomic symptoms may require treatment as described here earlier for diabetic neuropathy.

section 24 Neurological disorders 6194 Genetic neuropathies Charcot-Marie-Tooth disease and related disorders Charcot-Marie-Tooth disease (CMT, a hereditary motor and sensory neuropathy) usually presents during childhood or adolescence (sometimes much later) with difficulty in walking or because of foot deformity. There are over 60 causative genes, so patients are grouped into phenotypic types. Charcot-Marie-Tooth disease type 1 (CMT1) is caused by a demyelinating neuropathy with markedly slowed conduction velocities (upper limb motor conduction velocity <38 m/s). Charcot-Marie-Tooth disease type 2 (CMT2) is due to an axonal neuropathy with relatively preserved conduction velocities. Most types are dominantly inherited, but a family history may be absent. The clinical pictures of most forms of CMT are similar. Foot deformity is common and consists of a high arch, or pes cavus, and clawing of the toes, sometimes with an equinovarus deformity, often causing mechanical pain. (A high arch without bony deformity is not specific for CMT and may be due to foot muscle wasting from any severe axonal neuropathy). Muscle weakness tends to affect distal leg muscles, sometimes with an 'inverted champagne bottle' leg appearance (Fig. 24.16.3), and may give bilateral foot drop with a high stepping gait. Weakness and wasting of the small hand muscles may appear later. The tendon reflexes become depressed or lost, and there is a variable degree of distal sensory loss. Sensory action potentials are paradoxically often severely affected despite minimal or no sensory symptoms or signs. Progress of the disease is slow and cases with little disability or that are asymptomatic are common. The most common form is CMT1a, accounting for 70% of all cases. It is caused by duplication of the gene for peripheral myelin protein 22 (PMP22). The onset is most frequently in the first decade. Foot deformity and scoliosis occur more often than in CMT2, sensory loss and ataxia tend to be greater, and generalized tendon areflexia is usual. The peripheral nerves may be palpably thickened. The next most common is a mutation in GJB1 (coding for connexin-32) causing X-linked CMT; women may be asymptomatic or only mildly affected by an axonal neuropathy, whereas men usually have a somewhat multifocal demyelinating neuropathy which may be confused with chronic inflammatory demyelinating polyradiculoneuropathy on neurophysiology or have intermediate conduction velocity. Typically the abductor pollicis brevis muscle is disproportionately weaker than the first dorsal interosseous. The third most common is a mutation in myelin protein zero. The genetic diagnosis of CMT is developing rapidly. If first-line single gene tests are negative then next-generation sequencing can simultaneously test a panel of multiple genes but is expensive and still identifies only a quarter of patients with axonal neuropathy. An appropriate diagnostic strategy in suspected genetic neuropathy is first to assess whether axonal or demyelinating by neurophysiology. If demyelinating, test PMP22 duplication first, then GJB1 if no male-male transmission, then a gene panel. If axonal, classify clinically into one of three phenotypes for which gene panels are available: sensory predominant (hereditary sensory neuropathy), motor predominant (hereditary motor neuropathy), or mixed motor-sensory (CMT2). Rare forms cause severe early-onset demyelinating neuropathy presenting in infancy, or tremor. Affected individuals may be helped by advice on foot care perhaps from a podiatrist, the use of orthotic appliances which improve mechanical pain and gait, and sometimes by surgical correction of foot deformity or tendon transfer. As yet, there are no disease modifying therapies for any type. Hereditary neuropathy with liability to pressure palsies This is a common, relatively mild, autosomal dominant disorder, usually caused by a deletion of the same PMP22 gene which is duplicated in CMT1a. It is typically diagnosed when a patient has evidence of several nerve entrapments (especially carpal tunnel syndrome and/or ulnar neuropathy) together with a mild generalized demyelinating neuropathy shown on nerve conduction studies. Many patients are asymptomatic and a few have pain. Treatment is by decompression of any symptomatic

entrapments. Distal hereditary motor neuropathies Hereditary motor neuropathies resemble CMT but lack significant sensory involvement. There are multiple causative genes, but even modern gene panels identify only a minority of patients. Some types have upper limb predominance (such as GARS or BSCL2) and some have upper motor neuron signs. Distal wasting and weakness are sometimes instead due to a distal myopathy, a distinction that can be difficult even with electromyography. Hereditary sensory (and autonomic) neuropathies Hereditary sensory and autonomic neuropathies are much less common than CMT. As the name implies they are usually predominantly sensory and autonomic but motor involvement does occur, leading sometimes to overlap with the phenotype of CMT. They predominantly affect the small sensory nerve fibres subserving pain and temperature. As the autonomic abnormalities are generally milder Fig. 24.16.3 Patient with Charcot-Marie-Tooth disease type 1 (CMT1) showing symmetrical distal lower limb muscle wasting.

24.16 Diseases of the peripheral nerves 6195 than the sensory abnormalities, they may be called hereditary sensory neuropathies. The sensory loss often leads to a mutilating acropathy, with neuropathic joint degeneration (Charcot joints) and chronic cutaneous ulceration, particularly of the feet (Fig. 24.16.4). Neuropathy as part of multisystem genetic diseases (See also Section 12.) Neuropathy may be one manifestation of the many forms of hereditary ataxia, spastic paraplegia, mitochondrial disease, disorders of lipid metabolism, or of DNA repair. For example, peripheral nerve involvement occurs in metachromatic and globoid cell leucodystrophy, adrenomyeloneuropathy, Fabry's disease (predominantly small fibre), hereditary high-density lipoprotein deficiency (Tangier disease), hereditary abetalipoproteinaemia, and cholestanolosis. Giant axonal neuropathy is a rare, childhood-onset, autosomal recessive disorder characterized by segmental axonal enlargements containing accumulations of neurofilaments due to a mutation in the gigaxonin gene. Affected children usually have abnormally curly kinky hair and may have central nervous system abnormalities. Porphyria (See also Chapter 12.5.) A predominantly motor neuropathy may complicate acute severe attacks in the rare autosomal dominant disorders of acute intermittent and variegated porphyria and hereditary coproporphyria, and in the recessively inherited δ -aminolaevulinic acid dehydratase deficiency. The neuropathy is usually preceded by colicky abdominal pain and mental disturbances including confusion, psychosis, and epilepsy. The neuropathy develops acutely during an acute attack of porphyria and resembles Guillain-Barré syndrome. It is often predominantly proximal, affects the motor more than sensory nerves and may affect the cranial nerves. Autonomic features include tachycardia, hypertension, pupillary dilatation, constipation, and sweating. The best diagnostic screening test is measurement of urine porphyrins during an acute attack. Acute attacks should be treated with intravenous glucose and haem arginate to reduce the formation of porphyrin precursors. Familial amyloid polyneuropathy A painful axonal polyneuropathy similar to amyloid light-chain amyloidosis may be caused by several genetic conditions. The most common are those related to point mutations in the gene for transthyretin. The neuropathy begins with the involvement of small nerve fibres, leading to a distal loss of pain and temperature sensation and autonomic failure; occasionally the neuropathy is demyelinating. Spontaneous pain is often a feature and a mutilating acropathy may develop. The onset is commonly in the fourth or fifth decade and the disorder is slowly progressive, leading to death within about 10 years. Transthyretin is produced mainly in the liver and liver transplantation may halt progression of the disease (see Chapter 12.12.3). Amyloid stabilizers such as tafamidis and diflunisal may slow progression, but highly effective gene silencing therapies are becoming available. Hereditary amyloid neuropathy can also be caused by

mutations in the gene for other proteins which have differing clinical features. In the Iowa form, the amyloid is derived from a mutated form of apolipoprotein A1 and causes a painful predominantly sensory neuropathy. In the Finnish form, there is a mutation in the gene for the plasma protein gelsolin, and the neuropathy affects the cranial nerves and is associated with a corneal lattice dystrophy. Refsum's disease Refsum's disease is a rare, autosomal recessive, progressive multisystem disorder causing features including demyelinating motor-sensory polyneuropathy, ataxia, pigmentary retinal degeneration, anosmia, deafness, cardiomyopathy, and ichthyosis. The presentation is usually with night blindness during adolescence. The disorder is usually due to mutations in the PHYH gene. The best diagnostic test is raised serum phytanic acid. Treatment is with a diet low in phytanic acid, and sometimes plasma exchange for acute exacerbations. Chronic idiopathic axonal polyneuropathy Despite extensive investigation, the cause of about one-quarter of cases of late-onset symmetrical polyneuropathy remains unknown. Such cases are probably heterogeneous and may reflect undiagnosed alcohol abuse, carcinoma, or forms of CMT2. For those in whom no cause can be found the term 'chronic idiopathic axonal polyneuropathy' is often used. This is a syndrome of slowly progressive, predominantly sensory neuropathy in older people. Numbness and paraesthesiae, often painful, spread from the toes up the legs and become associated with unsteadiness. It progresses very slowly over years and rarely becomes seriously disabling, although the pain may be distressing and require treatment (see 'Treatment of neuropathies in general'). In some patients, there is evidence of impaired glucose or lipid metabolism, and it is likely that in some the underlying cause is related to the metabolic syndrome.

Fig. 24.16.4 Chronic foot ulceration and deformity in a case of hereditary sensory neuropathy.

section 24 Neurological disorders 6196 Small fibre neuropathy This is an abnormality predominantly of the small sensory (A δ and C) nerve fibres affecting pain, temperature, and autonomic function. Typical symptoms are chronic painful paraesthesiae, often feeling burning hot or cold, starting distally in the feet. On sensory examination, some patients have hypersensitivity with hyperalgesia and distortion of sensation so that normally nonpainful stimuli appear painful (allodynia), and others have reduced sensitivity to pinprick and temperature. Large-diameter nerve fibre functions remain relatively normal, including power, coordination, reflexes, and sensation to light touch, vibration, and joint position. Conventional clinical neurophysiological tests are normal because the sensory nerve action potentials derive from the large, not the small, nerve fibres. Various investigations are used in some specialist centres to support the diagnosis which otherwise has to be made on clinical grounds. Probably the most reliable test is skin biopsy to assess reduction of intraepidermal nerve fibre density, though this correlates poorly with pain. Alternatives include quantitative sensory testing of temperature thresholds, corneal confocal microscopy, contact heat- or laser-evoked potentials, sympathetic skin response, laser Doppler imaging of flare response, or microneurography. There are many possible underlying causes, some treatable, most commonly diabetes or prediabetes, but also dyslipidaemia, chronic kidney disease, alcohol, HIV, hepatitis C, vitamin B12 deficiency, coeliac disease, Sjögren's syndrome, amyloidosis, drug-induced (especially chemotherapy), paraneoplastic, various genetic causes (including sodium channelopathies), and many cases are idiopathic. Treatment is of the underlying cause, but there are rare acute steroid-responsive cases. Some cases of fibromyalgia are due to small fibre neuropathy. The syndrome with erythema of the feet during exacerbations of pain is termed erythromelalgia. Symptomatic treatment is with drugs for neuropathic pain such as amitriptyline, pregabalin, and duloxetine, or local treatment with capsaicin cream 0.075% or lidocaine 5% medicated plasters. FURTHER READING Birch R, Bonney C, Wynn Parry CB (1998). Surgical disorders of the peripheral nerves. Churchill Livingstone, Edinburgh. Collins MP, et al. (2010).

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