Current Practice

PRACTICAL NEUROLOGY

Peripheral Neuropathy

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After being a somewhat neglected facet of neurology, disorders of peripheral nerves have received a considerable degree of attention during the past few years, and advances in knowledge of the causation of and pathological changes in these diseases have led to more satisfactory clinical management. In this brief article a description will be given of the salient clinical features of the commoner types of disorder affecting the peripheral nerves, the techniques currently employed in their diagnosis, and the general principles adopted in treatment.

Clinical Features

It is clinically useful to distinguish between neuropathies that display a widespread symmetrical involvement of the peripheral nerves (polyneuropathy) and others in which there is involvement of a single nerve (mononeuropathy) or several individual nerves (multiple mononeuropathy).

Symmetrical Neuropathy

This may affect motor and sensory function separately or concomitantly. In general, longer nerve fibres are more vulnerable, so that muscle weakness and wasting tend to be more noticeable in the periphery of the limbs, and sensory loss and paraesthesiae to affect the extremities with a "glove and stocking" distribution. The tendon reflexes are frequently lost. More rarely, a selectively proximal distribution of motor weakness is encountered, which may occur in the acute Guillain-Barré syndrome and porphyric neuropathy. Selective involvement of the cranial nerves is seen at times, or the cranial nerves may be affected as part of a more widespread neuropathic process.

It has been realized in recent years that some neuropathies primarily take the form of a degeneration of axons which may "die back" from the periphery. In others, though axonal breakdown may occur, the primary damage is to the Schwann cells, resulting in segmental demyelination of the nerve fibres.[1] Recovery after the former process is by axonal regeneration and is slow and often incomplete; recovery after the latter is by remyelination, which may take place rapidly and frequently leads to full restoration of function.

Autonomic Neuropathy

Disturbances of autonomic function may occur in the peripheral neuropathies. The symptoms of greatest importance in this connexion are loss of sweating; loss of vascular reflexes, which may lead to postural hypotension; disturbances of bowel function, including constipation and diarrhoea; bladder atony; and impotence.

Mononeuropathy and Multiple Mononeuropathy

Lesions of individual peripheral nerves give rise to localized symptoms related to the distribution of the particular nerve that is affected. If there are multiple isolated lesions, a patchy involvement will result, but this may summate to produce a relatively symmetrical clinical picture if the process is sufficiently widespread, and it may then be difficult to distinguish from that of a symmetrical polyneuropathy.

Causation

Toxic Neuropathies

Though a wide variety of neurotoxic substances may cause peripheral nerve damage, toxic neuropathy is a relatively uncommon event. Lead neuropathy is manifested by motor weakness with wrist drop and foot drop and may be associated with colicky abdominal pain and anaemia. Arsenical neuropathy produces mixed motor and sensory damage, which may be accompanied by gastrointestinal symptoms, especially if acute poisoning has occurred, and by cutaneous changes—erythema or an exfoliative dermatitis after acute poisoning, or pigmentation in chronic cases.

Among organic substances, the most notorious agent is triorthocresyl phosphate. It was responsible for a large number of cases in Morocco a few years ago. Acrylamide, a substance with widespread uses, has recently been shown to cause neuropathy,[2] and isoniazid and nitrofurantoin are the two drugs that most commonly lead to peripheral nerve damage. These four last-named agents all produce a symmetrical mixed motor and sensory disturbance.

Deficiency Neuropathies

In malnourished communities beri-beri is an important form of neuropathy. In more sophisticated parts of the world alcoholic neuropathy is the equivalent disorder. Thiamine deficiency is generally considered to be the main nutritional deficiency in both, though lack of other vitamins may also contribute. In alcoholic neuropathy sensory symptoms usually predominate over motor involvement, often with painful burning paraesthesiae distally in the legs and tenderness of the soles of the feet. Isoniazid neuropathy is the result of inter-

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ference with pyridoxine metabolism. It is of interest that some individuals inactivate isoniazid much less rapidly than normally, this being dependent upon genetic factors.[3] Such persons have a greater risk of developing neuropathy. A largely sensory neuropathy may be encountered as a result of vitamin B_{12} deficiency, either alone or in combination with subacute combined degeneration of the cord or the other manifestations of vitamin B_{12} deficiency. Neuropathies are also seen in association with intestinal malabsorption, and, though presumably related to vitamin deficiency, a clear demonstration of this is not always forthcoming on investigation.

In both the toxic and the nutritional neuropathies it is generally true that axonal degeneration rather than segmental demyelination is the most conspicuous pathological change.

Metabolic Neuropathies

Diabetic neuropathy is a complex process. The commonest variety is a mild, predominantly sensory neuropathy manifested by tingling and numbness in the feet and sometimes also in the hands. At times a severe sensory neuropathy occurs (diabetic pseudo-tabes), in which the loss of postural afferents leads to sensory ataxia, and damage to pain nerve-fibres to neuropathic joint degeneration and trophic ulcers. The cause of this neuropathy has yet to be established with certainty. It may appear insidiously in longstanding diabetes or be the presenting manifestation in mild maturity-onset diabetes. Its occasional abrupt onset after a period of diabetic ketosis or on initiating treatment suggests that metabolic factors are of direct importance. Autonomic manifestations, including nocturnal diarrhoea, difficulty in emptying the bladder or urinary retention, impotence, and sometimes Argyll-Robertson pupils, may occur in cases of diabetic sensory neuropathy or in relative isolation.

Acute intermittent porphyria may give rise to a predominantly motor neuropathy,[4] which may affect the proximal rather than the distal muscles and which can therefore be mistaken for a myopathic disorder. Sometimes precipitated by the administration of barbiturates or sulphonamides, this neuropathy may be associated with colicky abdominal pain and psychiatric manifestations.

A relatively uncommon metabolic neuropathy is that resulting from primary amyloidosis.[5] Apart from the associated involvement of other systems, the features of the neuropathy are distinctive, initially with dissociated distal pain and temperature loss and autonomic involvement. Palpable thickening of the nerves may be detectable. Neuropathy may also occur in myxoedema. Commonly this takes the form of compression of the median nerve in the carpal tunnel and this may be the presenting symptom of the condition. Much less frequently a more diffuse neuropathy is encountered.

Uraemic neuropathy[6] has recently gained clinical importance by virtue of its occurrence in patients with renal failure under treatment by periodic haemodialysis. Usually it is mainly sensory in type, but distal motor weakness in the limbs may occur and is sometimes profound.

Inflammatory and Infective Neuropathies

Leprous neuritis is the result of direct infection of the peripheral nerves by the leprosy bacillus; the nerves may become irregularly thickened because of granulomatous infiltration. The disease often begins in a patchy manner with areas of cutaneous sensory loss or with isolated peripheral nerve lesions, the ulnar nerves often being affected in this way. Damage to pain nerve-fibres may result in mutilating trophic lesions.

Much more common in Britain is the Guillain-Barré syndrome. This consists of an acute neuropathy which tends to involve motor function to a greater extent than sensation and is sometimes accompanied by facial and bulbar weakness. The condition may follow an upper respiratory tract infection after an interval of two to three weeks. A similar syndrome may be related to infectious mononucleosis. Though the Guillain-Barré syndrome was at one time believed to represent a direct viral infection of the peripheral nerves, it now seems clear that it is a cell-mediated delayed hypersensitivity reaction, which gives rise predominantly to demyelination rather than axonal breakdown.[7] Certain cases of relapsing and chronic progressive polyneuropathy have a similar basis,[8] as may some symmetrical neuropathies occurring during the course of systemic lupus erythematosus[9] and perhaps other collagen disorders.

Diphtheritic neuropathy is now rare. The peripheral nerve damage is the result of an action of diphtheria toxin on the Schwann cells, causing demyelination, and the disorder should perhaps therefore be classed as a toxic neuropathy. Local paralysis producing dysphagia and palatal weakness occurs at about 10 days after the onset of the infection in pharyngeal diphtheria, followed by a symmetrical paralysis of the limbs which develops 4-6 weeks after the onset.

Sarcoidosis occasionally affects the peripheral nerves, and this is not necessarily accompanied by other manifestations of the disease. It gives rise to a multiple mononeuropathy with a particular tendency to affect the facial nerves. The nerves are infiltrated with sarcoid granulomatous tissue.

Vascular Neuropathies

Multiple isolated peripheral nerve lesions resulting from vascular lesions are encountered in a number of the collagen disorders, most characteristically in polyarteritis nodosa, but also in systemic lupus erythematosus, rheumatoid arthritis, and occasionally in scleroderma.

It has now been established that the isolated peripheral nerve lesions that may occur in diabetes, such as an oculomotor nerve palsy, are caused by infarcts related to diabetic microangiopathy. The proximal motor neuropathy in the legs that has been referred to as "diabetic amyotrophy" is of this nature.[10]

Nerve Compression Syndromes

Localized nerve damage may result from external pressure, as in the well-known Saturday night paralysis of the radial nerve or of the lateral popliteal nerve at the neck of the fibula from prolonged crouching or sitting in a cross-legged position. Repeated pressure for some occupational reason may be responsible, such as compression of the deep palmar branch of the ulnar nerve by a tool held in the hand. More extensive pressure lesions of nerves may be encountered in patients who have remained immobile for long periods because of drug overdosage, particularly if they have lain on a hard surface or if the blood pressure has been low. It is likely that in these pressure lesions the nerve damage is the result of ischaemia.

Nerve compression may be the consequence of intrinsic factors, such as compression of the ulnar nerve at the wrist by a ganglion or by "entrapment" as a nerve passes through an anatomical canal or under a ligament. Examples of entrapment neuropathies are the carpal and cubital tunnel syndromes, the latter being compression of the ulnar nerve at the elbow as it lies under the aponeurotic band between the two heads of flexor carpi ulnaris.[11] Osteoarthritis of the elbow or a previous supracondylar fracture that has increased the carrying angle of the elbow may predispose to damage of the ulnar nerve at this site. A further instance is the syndrome of meralgia paraesthetica due to compression of the lateral femoral cutaneous nerve as it passes under the inguinal ligament, giving rise to numbness and burning paraesthesiae over the lateral aspect of the thigh. In Bell's palsy it is assumed that oedema of the facial nerve

from some inflammatory reaction leads to compression of the nerve as it runs through the narrow facial canal.

It has become evident in recent years that the nerves in patients with certain generalized neuropathies, such as that due to diabetes, may be more vulnerable to pressure, both from external causes and from anatomical entrapment. A familial susceptibility to pressure neuropathy has been described,[12] and such individuals probably have a mild generalized neuropathy that renders them unduly liable to sustain pressure palsies.

Neoplastic Neuropathies

Direct invasion of the peripheral nerve trunks by carcinoma or lymphosarcoma may occur, and a variety of tumours may arise locally in nerves. Of greater interest are the non-metastatic neuropathies seen as a remote effect of carcinoma, most commonly carcinoma of the bronchus.[13] These may take two forms: firstly, a purely sensory neuropathy with distal sensory loss and paraesthesiae, resulting from a degeneration of dorsal root ganglion cells; and, secondly, a symmetrical distal mixed motor and sensory neuropathy in which there is demyelination of the axons in the nerve trunks. Both tend to develop insidiously and may antedate the discovery of the underlying carcinoma by as much as three years. The cause of carcinomatous neuropathy has not yet been established.

Hereditary Neuropathies

These are more frequent than is generally appreciated, many cases of "idiopathic" pes cavus and other foot deformities being due to this cause. The commonest condition is peroneal muscular atrophy, which has recently been shown to be a genetically heterogeneous disorder.[14] Most cases display a dominant pattern of inheritance with an onset of symptoms, usually foot deformity, during childhood or adolescence. Progression is generally very gradual, and spontaneous arrest of the disease may take place. In other cases, termed hereditary hypertrophic neuropathy, the peripheral nerves may be greatly thickened. In a further variety, hereditary sensory neuropathy, there is a purely sensory disturbance, beginning with selective loss of pain and temperature sensation distally in the legs and sometimes leading to chronic ulceration and destruction of the bones in the feet.[15]

In a number of different types of inherited neuropathy the underlying metabolic defect has now been established, but a consideration of these rare disorders falls outside the scope of this article.

Diagnosis

In many cases the diagnosis of a peripheral neuropathy is straightforward, particularly when it is associated with some more widespread pre-existing disorder. At other times, despite extensive investigation, the cause remains elusive. It should always be remembered that neuropathy may be the presenting feature of a generalized condition which may not be obvious unless a careful search is made. Thus absence of glycosuria does not exclude diabetes as a cause, since the patient may have a high renal threshold for glucose, and if B_{12} deficiency is suspected, a serum B_{12} estimation should be performed as the haematological manifestations can be minimal. When neuropathy is the presenting feature of carcinoma, serial observations may be required as at first the new growth may be too small to be detectable.

The precise clinical features of the neuropathy frequently provide a guide as to its likely cause. A careful history and examination may therefore narrow down the diagnostic possibilities and reduce unnecessary investigation by indicating the most profitable initial tests. Thus the occurrence of a mononeuropathy or multiple mononeuropathy would raise the possibility of intrinsic or extrinsic compression, a vascular cause (including diabetes) or granulomatous, amyloid, or malignant infiltration. A symmetrical neuropathy would be more in favour of a generalized process such as nutritional deficiency, a diffuse metabolic disturbance, or a toxic agent. A purely sensory neuropathy would require the consideration of diabetes, carcinoma, leprosy, or vitamin B_{12} deficiency, and also hereditary sensory neuropathy. Prominent autonomic involvement should put one on the alert for diabetes or amyloidosis, and thickening of the nerves for leprosy, hereditary hypertrophic neuropathy, or amyloidosis.

Of the investigations used in the diagnosis of neuropathies, only the more specifically neurological ones need discussion here. In cases in which it is uncertain on clinical grounds whether a neurological condition is due to peripheral nerve disease, a myopathic disorder, or disease of the central nervous system, electromyography and the examination of motor and sensory nerve conduction may be of considerable assistance in confirming a disturbance of peripheral nerve function. When there is a generalized neuropathy the type of abnormality detected electrically may also be useful. In those neuropathies in which there is primarily an axonal degeneration the nerve conduction velocity either falls within normal limits or is only moderately reduced. In those in which segmental demyelination takes place the conduction velocity may be greatly diminished.[16] In patients with isolated peripheral nerve lesions localized abnormalities of nerve conduction may exist. This can be helpful in distinguishing cases of the carpal tunnel syndrome from other causes of paraesthesiae in the hands, or in defining the level of an ulnar nerve lesion—in the palm, at the wrist, or at the elbow.

The protein content of the cerebrospinal fluid is raised in many types of neuropathy, so lumbar puncture is not often of assistance in their differential diagnosis. In the Guillain-Barré syndrome, however, and also in hereditary hypertrophic neuropathy, the protein level may be very substantially increased, and this can be of diagnostic importance. In the cases of peripheral neuropathy associated with infections mononucleosis there may also be an inflammatory cellular response.

In selected cases nerve biopsy can be diagnostic when other investigations have failed to define the cause. A positive answer is most likely to be given where there is disease of the vasa nervorum, such as an arteritis, or of the supporting tissues, as with granulomatous infiltration or amyloidosis.

Treatment

When the neuropathy is discovered to be due to some general metabolic disorder such as diabetes, a collagen disease, or an inflammatory process such as leprosy or sarcoidosis, treatment is clearly primarily directed towards the causative condition. The same is true of nutritional and toxic neuropathies.

In the milder cases of the Guillain-Barré syndrome no specific treatment may be required. Severer cases should be admitted to a neurological unit because of the risk of respiratory muscle involvement, which may develop with some rapidity. The same is true of porphyric neuropathy. The place of treatment with corticosteroids in the Guillain-Barré syndrome has never been adequately assessed, but there is no doubt that some cases respond, and this is also true of the chronic progressive and relapsing cases, though large doses of steroids or A.C.T.H. may be required.

The Saturday-night radial nerve palsy or pressure palsy of the lateral popliteal nerve are both commonly associated with a local demyelinating lesion, so that full recovery occurs in a few weeks. While recovery is awaited, an appliance to correct the wrist-drop or foot-drop is helpful, but electrical stimulation

of the paretic muscles, as is sometimes advocated, is not needed. The majority of cases of Bell's palsy are similar and recover spontaneously without treatment. In a small proportion axonal degeneration occurs, and recovery has to take place by axonal regeneration. A dental prosthesis to elevate the angle of the mouth during this time may reduce the ultimate facial asymmetry. For the very small proportion in which axon regeneration fails to take place a plastic operation to restore facial symmetry is desirable. There is evidence that treatment with A.C.T.H. in the acute stage will reduce the risk of axonal degeneration,[17] but the precise place of this in treatment has not yet been established.

Provided that there is no underlying cause such as rheumatoid arthritis or myxoedema, which requires separate attention, cases of the carpal tunnel syndrome with troublesome nocturnal paraesthesiae but without evidence of muscle weakness and wasting or significant sensory loss can be treated conservatively in the first instance. Such cases are often due to a tenosynovitis at the wrist. Cases occurring during pregnancy should also be treated conservatively, as recovery usually ensues after delivery. A reduction in the use of the hands and splinting of the wrists at night may suffice, and injection of the carpal tunnel with a steroid may give at least temporary relief. If these measures fail, or if definite evidence of nerve damage is present when the patient is first seen, treatment by surgical division of the flexor retinaculum is indicated. For ulnar nerve lesions at the elbow, if there is significant disability, and in particular if there is evidence of progression, anterior transposition of the nerve should be performed. Many patients with meralgia paraesthetica are obese, and loss of weight may lead to abatement of the symptoms. Otherwise, decompression of the nerve under the inguinal ligament can be undertaken, though this is not always effective.

In chronic neuropathies with distal weakness in the limbs orthopaedic appliances for foot-drop can be of assistance, and in the early-onset cases of hereditary neuropathy orthopaedic correction of foot deformity and sometimes tendon transplantation may lead to substantial improvement in function.

REFERENCES

1 Thomas, P. K., In *5th Symposium on Advanced Medicine*, edited by R. Williams, 1969, p. 323. London, Pitman Medical.
2 Garland, T. O., and Patterson, M. W. H., *British Medical Journal*, 1967, **4**, 134.
3 Knight, R. A., Selin, M. J., and Harris, H. W., *Transactions of the Conference on the Chemotherapy of Tuberculosis*, 1959, **18**, 52.
4 Ridley, A., *Quarterly Journal of Medicine*, 1969, **38**, 307.
5 Chambers, R. A., Medd, W. E., and Spencer, H., *Quarterly Journal of Medicine*, 1958, **27**, 207.
6 Asbury, A. K., Victor, M., and Adams, R. D. *Archives of Neurology*, 1963, **8**, 413.
7 Asbury, A. K., Arnason, B. G., and Adams, R. D., *Medicine*, 1969, **48**, 173.
8 Thomas, P. K., Lascelles, R. G., Hallpike, J. F., and Hewer, R. L., *Brain*, 1969, **92**, 589.
9 Johnson R. T., and Richardson, E. P., *Medicine*, 1968, **47**, 337.
10 Raff, M. C., Sangalang, V., and Asbury, A. K., *Archives of Neurology*, 1968, **18**, 487.
11 Feindel, W., and Stratford, J., *Canadian Journal of Surgery*, 1958, **1**, 287.
12 Earl, C. J., Fullerton, P. M., Wakefield, G. S., and Schutta, H. S., *Quarterly Journal of Medicine*, 1964, **33**, 481.
13 Brain, W. R., and Adams, R. D., in *The Remote Effects of Cancer on the Nervous System*, edited by Lord Brain and F. H. Norris, 1965, p. 216. New York, Grune and Stratton.
14 Dyck, P. J., and Lambert, E. H., *Archives of Neurology*, 1968, **18**, 603 and 619.
15 Spillane, J. D. and Wells, C. E. C., *Acrodystrophic Neuropathy*, 1969. London, Oxford University Press.
16 Gilliatt, R. W., *Proceedings of the Royal Society of Medicine*, 1966, **59**, 989.
17 Taverner, D., Kemble, F., and Cohen, S. B., *British Medical Journal*, 1967, **4**, 581.

TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Solutions for Intravenous Feeding

A few days of semi-starvation produce little adverse effect in the healthy individual, but after major trauma, extensive surgery, or burns, and in the presence of sepsis or some instances of oliguric renal failure, catabolism occurs at a much faster rate than usual. The body stores of a 70 kg. man consist of 100–200 g. of carbohydrate, chiefly in the form of glycogen, which may all be utilized in 24 hours or less. After exhaustion of the stores, breakdown of body tissues occurs unless adequate calories are supplied ; this results in muscle wasting, delayed wound healing, lowered resistance to infection, and a prolonged convalescence.

Maintenance of nutrition is best achieved via the alimentary route whenever possible, even if it necessitates the use of a nasogastric tube. The use of the intragastric route requires an intact and properly functioning gastrointestinal tract, which is not found in some undernourished patients with chronic intestinal disease, malignant tumours, and gastrointestinal obstruction. In these situations, and in some instances where catabolism is increased, intravenous feeding is necessary to provide the essential ingredients contained in a normal diet.

Twenty-five to 30 calories per kilogram per day are required for maintenance purposes. In hypercatabolic states the requirements are higher, and 3,000 to 3,500 calories should be supplied in each 24 hours. It has been suggested that an extra allowance of 13% should be made for every degree centigrade above the normal body temperature. The most convenient way of supplying calories is as carbohydrate or fat.

Carbohydrate

In order to supply a significant number of calories without an excessive volume of fluid the concentration of a sugar solution has to be greater than 10%. *Glucose* solutions in this strength rapidly cause thrombophlebitis, especially in small vessels, and so are not suitable for prolonged use except via the inferior vena cava. In addition, even when hypertonic glucose solutions are given slowly glycosuria and an osmotic diuresis often result. *Fructose* has several advantages over glucose. It is less sticky and irritant to veins and hence can be given via small peripheral veins. The proportion lost in urine is less than that when using glucose. *Sorbitol* solutions are also relatively non-irritant to veins, but require oxidation to fructose in the liver before they can be utilized.

Fats

The chief advantage of fat emulsions is that they supply 9 calories per gramme as opposed to 4·1 for carbohydrate and protein. There are two alternative types of fat emulsion, soya bean oil and cotton seed oil. The lipid is kept emulsified by the use of egg phosphatide as a stabilizer, and the solution is made isotonic with glycerin.

In practice it has been found that cotton seed oil is substantially more toxic than the soya bean preparation Intralipid.