Occasional review

Treatment of peripheral neuropathies

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SUMMARY There are three general approaches to treatment of peripheral neuropathy. First, an attempt should be made to reverse the pathophysiological process if its nature can be elucidated. Second, nerve metabolism can be stimulated and regeneration encouraged. Third, even if the neuropathy itself cannot be improved, symptomatic therapy can be employed. This review outlines the options available for each approach.

Peripheral neuropathies are common. They result from diseases of the nerves themselves or as consequences of systemic illnesses. Many neuropathies are due to well-defined causes such as diabetes, uraemia, or nutritional deficiencies, but a large number are of unknown cause. Therapeutic measures currently available are often not very good, and this leads to both patient and doctor frustration. Some facts are known, however, and we thought it useful to summarise the current state of knowledge. Three kinds of therapy are possible. If the aetiology of the neuropathy is identified, then therapy directed to the underlying illness may be beneficial to the neuropathy. Regardless of whether the aetiology of the neuropathy is known or unknown, it may be possible to improve nerve function with therapy directed to improving nerve metabolism itself. If it is impossible to reverse the neuropathy, it still may be possible to be helpful with symptomatic therapy. Treatment of peripheral entrapment neuropathies, which can be very successful, is a large topic by itself and is covered elsewhere.¹

THERAPY DIRECTED TO UNDERLYING ILLNESS

Diabetic Neuropathy

Diabetes mellitus causes several different forms of neuropathy, including symmetrical sensorimotor neuropathy, mononeuropathy multiplex with a form involving proximal muscles called diabetic amyotrophy and autonomic neuropathy. The mononeuropathy multiplex carries a fairly good prognosis in general,² and symptomatic treatment with good

control of diabetes is all that is necessary. Although symptoms of early autonomic neuropathy might be reversible,^{3,4} the disorder when advanced carries a poor prognosis and an increased mortality rate⁵ and requires careful symptomatic therapy of derangements such as postural hypotension.⁶ Autonomic neuropathy is not known to improve significantly with better control of blood sugar even if the polyneuropathy improves.⁷

The symmetrical sensorimotor polyneuropathy does not often improve spontaneously. The pathogenesis of this neuropathy is unsettled⁸ and various mechanisms have been proposed: hyperglycaemia,⁹ ischaemia,^{10,11} myoinositol deficiency,¹² sorbitol accumulation,¹² and lipid abnormalities.¹³ One of the difficulties in assessing therapy has been objective measurement since there it has been questioned whether nerve conduction studies provide useful information.¹² There is evidence that nerve conduction studies can detect subclinical neuropathy and that abnormality on these studies correlates with clinical severity of the neuropathy.¹⁴ On the other hand, other studies show no clear correlation.¹⁵ Hyperglycaemia itself may contribute to slowing of conduction.^{9,16}

The results of vigorous control of the blood sugar in controlling the progression of the symmetrical polyneuropathy have been a subject of continued controversy. While it has appeared that in general the likelihood of neuropathy is related to the duration and severity of the hyperglycaemia,^{17,18} certainly some apparently well-controlled patients develop neuropathy while others with poor control have no clinical evidence of neuropathy.¹⁹ Studies in animals rendered diabetic with streptozotocin show that with close control of blood sugar, slowing of motor nerve conduction can be prevented.^{20,21}

Human studies on the efficacy of improved glu-

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cose control show mixed results. A number of investigations,²²⁻²⁴ although not all,²⁵ have shown improvement in nerve conduction studies within hours or days. This effect is likely to be a metabolic change due to reduction of hyperglycaemia and may not have clinical significance. On the other hand, hyperglycaemia itself may have a major role in the production of pain.^{26,27} Studies of improved control of blood sugar over weeks or a few months using insulin conventionally or with pump infusion have shown benefit for nerve conduction values,²⁸⁻³³ clinical sensory function³⁴ and reduction in pain.^{35,36} Two recent reports show convincing improvements in nerve conduction studies after continuous subcutaneous insulin infusion for six months.^{24,27} One investigation has demonstrated that nerve conduction studies with ischaemic resistance may be helpful in documenting improved nerve function with better blood sugar control.³⁸

Two long-term controlled studies of glucose control have now appeared. A two-year randomised prospective study showed that stricter control with conventional methods of insulin treatment was useful in maintaining or improving sensory nerve function as measured by vibration.³⁹ A similar three-year clinical trial failed to demonstrate benefit of better control, but patients in this study all had a duration of diabetes of less than 2 years with only mild peripheral nerve abnormalities and the difference in glucose control of the two groups was less than anticipated.⁴⁰

Myoinositol content of diabetic nerve is deficient, but the results of treatment of diabetic neuropathy with myoinositol have been ambiguous. While there are reports of improvement in nerve conduction velocity in diabetic rats with an associated increase in nerve myoinositol content,^{20,41} other studies show no benefit.⁴² Similarly in humans, some studies show benefit^{43,44} while others do not.⁴⁵

Alldose-reductase inhibitor therapy has theoretical value in preventing accumulation of sorbitol. Most of the early studies with alrestatin, including double-blind placebo controlled investigations, have shown a beneficial effect,⁴⁶⁻⁴⁸ although there is one study which did not.⁴⁹ Four more recent studies have been carried out with the more potent inhibitor, sorbinil. Three have demonstrated a significant improvement in nerve conduction parameters;⁵⁰⁻⁵² two have shown reduction in pain along with improvement in other symptoms;^{51,52} and one has even found a beneficial effect on autonomic function.⁵¹ The fourth study found no effect on either nerve conduction or symptoms;⁵³ the authors suggest that their failure to demonstrate an effect might have been due to the fact that their patients had more advanced disease than those in the other studies.

A variety of other modes of therapy have been tried and initial reports of some of these are encouraging. These include the use of vitamin B₆ (given because of possible B₆ deficiency),⁵⁴⁻⁵⁶ vitamin B₁₂ (given because of possible B₁₂ deficiency)⁵⁷ and lipoic acid (given because of decreased lipid synthesis).⁵⁸

On the basis of the data known so far, it seems prudent to maintain as good control of blood sugar as possible. Although other manipulations may eventually prove valuable, definitive and substantial clinical utility has not yet been demonstrated for any of them.

Uraemic neuropathy

A symmetrical sensorimotor neuropathy is a frequent complication of renal failure and seems not dependent on the nature of the underlying renal disorder. Effective haemodialysis is generally agreed to improve or stabilise the neuropathy and in some early cases complete recovery can occur.⁵⁹⁻⁶² A few reports suggest that haemodialysis is ineffective.^{63,64} Occasional worsening of neuropathy following haemodialysis probably reflects inadequate dialysis and suggests that dialysis time should be increased.^{65,66} Increasing dialysis frequency without increasing dialysis time is ineffective.^{67,68} A recent report suggests that in addition to dialysis time the mean blood urea level should be considered.⁶⁹ Deficiency of vitamin B₁₂ with dialysis must also be suspected in dialysis failure.⁶¹ A few reports raise the issue that lack of removal of "middle molecules" may result in persistence of symptoms.^{70,71} Peritoneal dialysis, and in particular, continuous ambulatory peritoneal dialysis, may be superior to haemodialysis in controlling uraemic neuropathy.⁷²

Renal transplantation has produced a clear cut improvement in virtually all cases in a period of six to twelve months.⁷³⁻⁷⁵ One study has demonstrated that modifying the diet by reducing protein and fluid intake will allow reduction in the frequency of dialysis without deleterious effect on the neuropathy.⁶² Recently, biotin is showing some promise as a therapeutic agent.⁷⁶

Neuropathy in Metabolic Disorders

Hypothyroid neuropathy is responsive to thyroid replacement.⁷⁷ The rare neuropathy in hyperthyroidism has been shown to improve as the hyperthyroidism is corrected.⁷⁸ Refsum's disease responds favorably to restriction of phytol intake.^{79,80} Plasmapheresis has also been demonstrated to be useful.⁸¹ In leukodystrophies such as metachromatic leukodystrophy, neuropathy has not improved using selective enzyme replacement⁸² or vitamin A deficient diets.⁸³ In Fabry's disease, attempted enzyme replacement has provided no clear be-

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nefit;⁸⁴⁻⁸⁵ however, repeated haemodialysis or renal transplantation have provided some relief of neuralgic pain.⁸⁶ In abetalipoproteinaemia there is a peroxidation defect which can be improved by a low fat diet and high dose of vitamin A and E; with this regimen a number of patients with neuropathy have plateaued or improved.⁸⁷⁻⁸⁹

Acute intermittent porphyria

Pathogenesis of porphyric neuropathy is uncertain, but may be due to high serum porphyrin levels. Administration of a high carbohydrate load, for example intravenous levulose, inhibits delta-amino-levulinic-acid and through a feedback mechanism lowers porphyrin levels.⁹⁰ Pyridoxine is recommended in a dose of 100 mg twice a day,⁹⁰ and one report suggests use of steroids.⁹¹ Haematin, which will lower the synthesis of porphyrins by feedback inhibition of delta-amino-levulinic-acid, has been used with limited success.⁹² It is difficult to be sure which of these methods is most appropriate. The patient should be apprised of the potential of certain drugs (barbiturates, antibiotics, sulphonamides and anticonvulsants) to precipitate an acute attack of porphyria.

Alcoholic and nutritional neuropathy

Neuropathy in the alcoholic has been thought to be due to thiamine and/or folate deficiency,⁹³⁻⁹⁵ although there has been some evidence implicating a direct effect of alcohol.⁹⁶ Administration of thiamine has been thought to be useful⁹⁶ although there are no controlled trials. Stopping drinking is the key-stone of successful therapy. Disulfiram has been helpful in this regard although the latter may itself induce neuropathy.⁹⁷ Neuropathy occurring with nutritional deficiency of vitamin B₁, B₆, folate or riboflavin responds favorably to replacement therapy.⁹⁶ Patients with neuropathy in the setting of chronic fat malabsorption may be vitamin E deficient and replacement therapy can improve the neuropathy.⁹⁷ Patients treated with INH may become vitamin B₆ deficient and supplementation prevents occurrence of neuropathy.⁹⁸⁻⁹⁹ Neuropathy is only one element of the vitamin B₁₂ deficiency syndrome. It is critical to treat deficient patients with vitamin B₁₂ and there is ordinarily clinical improvement but there is actually only little evidence that the neuropathy itself is benefited. One study has shown improvement in nerve conduction velocity,¹⁰⁰ and in another study of one patient there was improvement of proximal motor strength.¹⁰¹

Toxins and drugs

A large number of drugs¹⁰² and industrial toxins¹⁰³ are known to produce neuropathy. The major prob-

lem is the diagnosis; once it is established that neuropathy is due to a certain agent, the best way to treat it is to avoid further exposure. Screening of industrial populations of subclinical neuropathy may lead to identification of unsuspected toxins which can then be eliminated. The role of early diagnosis is brought out by the recent occurrence of neuropathy due to dimethyl-aminopropionitrile (DMAPN) in two industrial plants in Massachusetts and Maryland.¹⁰⁴⁻¹⁰⁵ Screening of individuals who were exposed to DMAPN (whether symptomatic or asymptomatic) in these two plants resulted in detection of several cases of neuropathy. After the removal of the chemical, there has been a decline in incidence.

Guillain-Barre syndrome

Guillain-Barre syndrome is an acutely developing paralytic illness which has no specific treatment available at present. After an initial surge of enthusiasm with the use of steroids where a majority of patients were reported to improve,¹⁰⁶⁻¹⁰⁷ subsequent steroid trials have yielded different results, either that the drug was ineffective¹⁰⁸⁻¹⁰⁹ or that it shortened the recovery time, but did not effect the eventual outcome of the disease.¹¹⁰⁻¹¹¹ A London-based cooperative trial even suggested that steroids were harmful by leading to a greater incidence of chronic disease.¹¹² ACTH was investigated in a double-blind study with a slightly accelerated return of function but with prolonged length of hospitalisation.¹¹³ ACTH and steroids appear to provide no major benefit and probably should not be used.

All other drug therapies for Guillain-Barre syndrome are essentially experimental. The efficacy of immunosuppressants remains in doubt. Three studies report some improvement with azothioprine¹¹⁴⁻¹¹⁶ and in another 6-mercaptopurine improved a single patient.¹¹⁷ On the contrary, intravenous cyclophosphamide has led to increasing mortality.¹¹⁸ Transfer factor therapy has been employed, but results of therapy were not clear since the patient may have improved spontaneously.¹¹⁹ A polyunsaturated fatty acid diet has reportedly helped one patient.¹²⁰ Another potential therapy which has not yet been utilised is lymphocytapheresis,¹²¹ which can remove abnormal lymphocytes.

A possible role for humoral factors in Guillain-Barre syndrome has been identified¹²²⁻¹²⁴ and this has provided a theoretical rationale for the use of plasmapheresis. Largely anecdotal preliminary results were mostly encouraging.¹²⁵⁻¹³¹ A number of controlled trials of plasmapheresis have now been undertaken. Two were negative¹³²⁻¹³³ while a third showed benefit in rapidity of improvement.¹³⁴ Be-

nefit was sufficient so that economic value could be demonstrated. The reasons for the differences in these studies are not clear although it may be that the patients were more acute in the successful investigation. A preliminary report of a multicenter trial from the USA is also favorable.¹³⁵ Detailed analysis of all of this data, when it is available, may demonstrate circumstances when plasmapheresis is indicated.

Careful attention to respiratory function, including tracheostomy when indicated, is critical in taking care of patients with severe disease.¹³⁶⁻¹³⁷ For patients who spend long periods of time immobilised in bed, anticoagulation is useful to prevent pulmonary embolism.¹³⁸ Autonomic dysfunction with hypotension, hypertension and cardiac arrhythmias, require careful attention.

Chronic and relapsing inflammatory polyneuropathy

This chronic form of neuropathy is an uncommon consequence of Guillain-Barre syndrome, and is characterised by slowed nerve conduction and an elevation of CSF protein. The treatment is somewhat more promising than for Guillain-Barre syndrome itself. Several reports emphasise the efficacy of steroids with a response rate of 40 to 100%.¹³⁹⁻¹⁴⁶ Some patients become steroid dependent,¹⁴¹ and in others severe relapses can occur with small reductions in dose.¹³⁹ There are suggestions that if nerve conduction velocities have not returned to normal during therapy, relapse is likely to occur during steroid withdrawal.¹⁴¹ The use of the immunosuppressant, azathioprine, has also been promising,¹⁴⁶⁻¹⁴⁸ and it might well be utilised in patients resistant or intolerant to corticosteroid treatment.¹⁴⁸ Recently, plasmapheresis has been advocated, and benefit can be appreciated after only several exchanges.¹⁴⁶⁻¹⁴⁹⁻¹⁵⁵ Chronic *relapsing* disease may do better than chronic *progressive* disease¹⁵⁶⁻¹⁵⁷ and the predominant demyelination form will improve more than the form with extensive axonal destruction.¹⁵⁸ Immunosuppressants used in conjunction with plasmapheresis have been found to be useful in one patient with repeated relapses, and furthermore, the frequency of plasmapheresis could be reduced.¹⁵³ In another patient infusion of plasma was similar to that of plasma exchange.¹⁵⁹ A study of four patients with total lymphoid irradiation showed some utility for this technique if all else has failed.¹⁶⁰ At the present time, corticosteroid therapy remains the method of choice since it is the only therapy proven in controlled trials.

Note should be made that there are some patients with apparent hereditary neuropathy who have some clinical features of chronic inflammatory polyneuropathy and who respond to prednisone.¹⁶¹

Systemic lupus erythematosus may also present with this neuropathy, and steroid therapy is useful.¹⁶²

Neuropathy of paraproteinemia

The paraproteinemias include benign monoclonal gammopathy, multiple myeloma, osteosclerotic myeloma, Waldenstrom's macroglobulinaemia and cryoglobulinaemia. Peripheral neuropathy is a common manifestation¹⁶³⁻¹⁶⁴ and this may be due to a direct effect of the protein on the peripheral nerve.¹⁶⁵⁻¹⁶⁶ In the circumstances other than benign monoclonal gammopathy, treatment would ordinarily be given to the underlying disorder and this may have some beneficial effect on the neuropathy.¹⁶³⁻¹⁶⁴⁻¹⁶⁷ For the situation of a solitary osteosclerotic myeloma, radiation¹⁶⁴⁻¹⁶⁸⁻¹⁷² has a definitive role. Chemotherapy of a benign monoclonal gammopathy (as if it were multiple myeloma) with drugs such as melphalan or prednisone and azathioprine may have some role.¹⁶⁴⁻¹⁷³ Plasmapheresis, presumably by removing abnormal proteins, has had some value in benign monoclonal gammopathy,¹⁶⁵⁻¹⁶⁶⁻¹⁷⁴ multiple myeloma,¹⁶⁶⁻¹⁷⁵ osteosclerotic myeloma,¹⁶⁶ Waldenstrom's macroglobulinaemia¹⁷⁶⁻¹⁷⁷ and cryoglobulinaemia.¹⁷⁵⁻¹⁷⁸

The neuropathy of primary amyloidosis is difficult to treat. The carpal tunnel syndrome can be treated with surgery, and the postural hypotension associated with the autonomic neuropathy may be helped symptomatically with elastic stockings.¹⁷⁹ Nothing is known which can reverse the neuropathy itself. There is one report that the neuropathy may be responsive to dimethylsulfoxide (DMSO),¹⁸⁰ but this is not a general experience.¹⁸¹ Survival in primary amyloidosis may be improved with colchicine although the neuropathy may not be influenced.¹⁸²⁻¹⁸³ Other studies are investigating the potential use of melphalan plus prednisone.¹⁷⁹

Paraneoplastic and neoplastic neuropathies

Neuropathy in association with malignant disorders (carcinoma, lymphoma, leukemia) occurs in 2 to 10% of cases and may be only part of a paraneoplastic syndrome with other neurological features.¹⁸⁴ Relationship of remission of the malignancy to improvement in neuropathy is not well established, although there are anecdotal reports where treatment of the primary disorder was correlated with improvement in neuropathy.¹⁸⁵ Radiation to nerves or plexuses infiltrated by tumor may lead to improvement.¹⁸⁶

Leprosy

Leprosy involves peripheral nerves in most cases, and since there are about 15 million cases in the world, leprosy may be the most common cause of

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neuropathy. Therapy with dapsone has been standard, but emergence of dapsone resistance has led to new WHO recommendations: for paucibacillary cases, dapsone plus rifampicin; for multibacillary cases, dapsone, rifampicin and clofazimine.¹⁸⁷⁻¹⁹⁰ Reversal reactions accompanied by acute neuritis should be treated with corticosteroids.¹⁸⁷ Chronic therapy is needed for lepromatous disease. Even with satisfactory treatment of the leprosy, complete recovery from nerve damage is impossible due to scarring of the nerves.

Herpetic and post-herpetic neuralgia

Painful lesions in acute herpes zoster have been treated by a variety of methods in order to speed up recovery and prevent post-herpetic neuralgia. Although high dose steroids or ACTH have been suggested to improve the acute pain,¹⁹¹⁻¹⁹³ at least one double-blind study could not confirm this effect.¹⁹⁴ On the other hand, high dose oral steroids given acutely may reduce the duration of post-herpetic neuralgia.¹⁹⁴ Steroids given by the epidural route have had good success in several studies for both relief of acute pain and prevention of post-herpetic neuralgia.¹⁹⁵⁻¹⁹⁶ Antiviral chemotherapy will probably prove to be the best type of therapy. Vidarabine has been carefully assessed in immunosuppressed patients and both speeds healing and reduces the duration of post-herpetic neuralgia.¹⁹⁷⁻¹⁹⁸ Three controlled, double-blind studies have demonstrated value of intravenous acyclovir therapy in accelerating healing and relieving acute pain, although in the present regimens post-herpetic neuralgia was not influenced.¹⁹⁹⁻²⁰¹ Oral therapy with this agent is a future consideration.²⁰² Human leukocyte interferon has also been shown to speed recovery from varicella infections in children with cancer.²⁰³ There is only limited experience with other agents including intralesional triamcinolone,²⁰⁴ dehydroemetine,²⁰⁵ and adenosine monophosphate.²⁰⁶

Post-herpetic neuralgia is more frustrating to treat. Intralesional triamcinolone has been used just as in acute zoster.²⁰⁴ Cryocautery²⁰⁷ and vasopressin²⁰⁸ have also been used with some success. The main approach to therapy, however, has often been purely symptomatic.

Vasculitic neuropathy

Neuropathy caused by a systemic vasculitis often has the clinical form of mononeuritis multiplex although more generalised neuropathies can be seen. Aetiologies include polyarteritis nodosa, rheumatoid vasculitis, Wegener's granulomatosis, allergic angiitis, lymphomatoid granulomatosis, granulomatosis of Churg and Strauss and rarely sys-

temic lupus erythematosus. These patients have been traditionally treated with corticosteroids and success with these agents has been demonstrated.²⁰⁹⁻²¹¹ More recently, following successful use of cyclophosphamide in patients with Wegener's granulomatosis,²¹² cytotoxic agents have been demonstrated to be more efficacious than corticosteroids alone in other forms of systemic vasculitis.²¹³⁻²¹⁶ One successful regimen includes cyclophosphamide therapy adjusted to reduce the total neutrophil count no lower than 1000 to 1500 per cubic millimeter along with alternate day corticosteroids.²¹³

THERAPY DIRECTED TO NERVE METABOLISM

Vitamins, frequently in excess ("megavitamins"), are often prescribed for patients with neuropathies from causes other than nutritional. There is no published evidence for this and no benefit for the patient except possibly psychological. Indeed, it has now been demonstrated that megadoses of pyridoxine will itself cause a neuropathy.²¹⁷ Toxicity has been seen at doses as low as 500 mg daily.²¹⁸ ACTH stimulates neuronal protein synthesis²¹⁹ and for this reason might be useful for nerve regeneration; although initial direct test of this hypothesis in rats produced encouraging results,²²⁰ this benefit could not be reproduced.²²¹ Thyroxine can accelerate peripheral nerve regeneration,²²² but doses required for effect in man induced thyrotoxicosis.²²³ Nerve growth factor²²⁴ which has significant potential value for nerve regeneration has never been used clinically. Early experimental studies have demonstrated a beneficial effect of a high-peak pulsed electromagnetic field on the regeneration of nerve.²²⁵

Isaxonine

Isaxonine (N-isopropyl-amino-2-pyrimidine phosphate) speeds nerve regeneration,²²⁶⁻²²⁸ most likely by stimulation of axonal sprouting.²²⁹ Double-blind clinical trials with electrophysiological investigations have shown that isaxonine has a protective effect on neuropathy induced by vincristine,²³⁰ that the quality and speed of recovery is improved in patients with peripheral facial paralysis,²³¹ and that there has been improvement in patients with diabetic neuropathy,²³² alcoholic neuropathy²³³ and traumatic neuropathies.²³⁴ Significant hepatic toxicity, however, has led to the drug being removed from current clinical study.

Gangliosides

Gangliosides, types of complex glycolipids, as extracted from bovine brain, have been proposed as useful for peripheral neuropathy. Gangliosides are a constituent of nerve cell membrane and are particu-

larly concentrated at nerve terminals and in nerve growth cones.²³⁵⁻²³⁸ It has been demonstrated that exogenously administered ganglioside can be incorporated into nerve cell membrane.²³⁹⁻²⁴⁴ Gangliosides have been demonstrated to encourage neurite formation,²⁴⁵⁻²⁴⁶ enhance the degree of axonal elongation²⁴⁷ and to encourage neuromuscular junction formation in tissue culture.²⁴⁸ In several experimental circumstances, gangliosides have been demonstrated to speed recovery after axonotmesis. This was first demonstrated for the pre- and post-ganglionic sympathetic fibres of the cervical sympathetic innervation to the cat nictitating membrane²⁴⁹ and has been demonstrated by several investigators for the rat sciatic nerve^{242 250 251} and tail nerve.²⁵² Gangliosides seem to promote more rapid reinnervation of muscle by stimulation of the sprouting process.^{242 253 254} There is evidence also that gangliosides have improved the neural trophic influences on muscle²⁵¹ and can accelerate axonal transport after nerve crush.²⁵⁵ Gangliosides have been shown to have beneficial effect on experimental neuropathies including carbon disulfide,^{255 256} nitrofurantoin and alcohol²⁵⁷ and the neuropathy in experimental diabetic mice.^{258 259}

A number of studies have already been carried out in man with intramuscular gangliosides. Two carefully controlled studies have shown improvement of signs and symptoms in alcoholic neuropathy²⁶⁰ and uraemic neuropathy,²⁶¹ but without differences in electrophysiologic parameters with respect to control groups. Other studies have shown significant changes in these physiological parameters with respect to control groups in both alcoholic^{262 263} and diabetic²⁶³⁻²⁶⁵ neuropathies. A recent double-blind, cross-over study of 140 diabetic patients showed improvement in both physiologic parameters and symptoms.²⁶⁶ A number of additional studies have given some support²⁶⁷ and the clearest result is when the medication is continued for six months.²⁶⁸ Administration of gangliosides has been shown to be useful in preventing neuropathic effects of vincristine in patients undergoing chemotherapy for neoplastic disease.²⁶⁹ A controlled study of patients with Bell's palsy compared ganglioside treatment with steroid and vitamin therapy.²⁷⁰ Patients were divided into neuropraxic and axonotmetic groups (on the basis of whether the damage was mainly to myelin or axons) and the most significant benefit was the reduction in the incidence of permanent facial nerve impairment in the axonotmetic group. A controlled trial was carried out in patients with nerve lesions of the upper limb treated by neurolysis, and gangliosides produced a shorter recovery time and better improvement measured in terms of clinical and electromyographic

parameters in comparison to the group of patients receiving standard therapy.²⁷¹ It would appear from the experimental work that gangliosides would certainly be useful in speeding recovery from axonotmetic nerve injury.

SYMPTOMATIC THERAPY

Analgesics such as aspirin may provide symptomatic relief, although the frequency that is useful does not seem to have been documented in the literature. With severe weakness, splints to improve a foot drop or wrist drop may make the patient more functional. Exercises can be of value to increase strength and to prevent contractures. Exercise programmes must be developed carefully, however, since overstretching and overwork can damage muscle.²⁷² Keeping muscle warm will promote optimal function.²⁷² When there is sensory loss, patients must be warned to protect their anaesthetic skin from burns or other trauma to prevent ulceration. The plantar ulcer can be prevented by avoiding prolonged pressure on the soles and daily foot soaking followed by application of vaseline lotion to seal in moisture.²⁷³

Psychotropic drugs

There have been a moderate number of successful reports of tricyclic antidepressants as useful for various types of neuropathic pains. Tricyclic agents have been shown to be useful by themselves for diabetic neuropathy,²⁷⁴⁻²⁷⁶ and for post-herpetic neuralgia.²⁷⁷ Tricyclics in combination with phenothiazines are also useful for diabetic neuropathy,²⁷⁸⁻²⁸¹ post-herpetic neuralgia,²⁸² other types of neuropathies²⁷⁸ and other types of intractable pain.²⁸³ It is of note that phenothiazines seem not to be useful analgesics by themselves²⁸⁴ but do seem to be useful in potentiating the effect of tricyclic agents. (An apparent exception to this rule is chlorprothixene which in a high-dose pulse of therapy can be useful for post-herpetic neuralgia although with many side effects).²⁸⁵ Tricyclic agents have been used also in combination with lithium for painful syndromes²⁸⁶ but apparently not for neuropathy. The mode of action of tricyclic therapy in relieving symptoms of neuropathy is not certain. Pain has been responsive to electroconvulsive shock treatment,²⁸⁷ tricyclic agents have been shown to be useful in chronic, apparent psychosomatic pains²⁸⁸ and in improvement of pain of various other types. There is a demonstrated correlation of improvement of pain with improvement of a coexisting depression.²⁸⁹ Such observations make it appear that the effect is mainly psychological. There is some rationale for suggesting, however, that it may have a direct effect in central pain pathways. The similarity of tricyclics to opiates has been suggested²⁹⁰ and it has been

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demonstrated that amitriptyline potentiates morphine analgesia by a direct action on the central nervous system.²⁹¹ Many authors stress the fact that tricyclic agents inhibit serotonin uptake and hence should have a function in blocking the serotonergic part of the central pain pathway. Evidence for this view has been provided by showing that potent serotonin uptake inhibitors such as zimelidine²⁹² and clomipramine^{293 294} are useful in relieving neuralgic symptoms after nerve injury for post-herpetic neuralgia. Trazodone, a non-tricyclic antidepressant which also inhibits serotonin uptake, may benefit symptoms in diabetic neuropathy.²⁹⁵ Recently, it has been demonstrated that effect of imipramine in treating painful diabetic neuropathy came on more rapidly and at a lower dose than that needed for antidepressant action.²⁷⁶

Anticonvulsant drugs

The use of phenytoin for neuropathy was first suggested by Ellenberg²⁹⁶ who found improvement in 68% of his patients with diabetic neuropathy within only several days of initiating therapy. This result has been confirmed in one double-blind study,²⁹⁷ but in two similar, carefully controlled studies, there was no beneficial effect.^{275 298} Following the introduction of carbamazepine for trigeminal neuralgia by Blom in 1963,²⁹⁹ this anticonvulsant was used in a number of other neuropathic conditions. Three carefully controlled, double-blind studies have shown a value of carbamazepine in diabetic neuropathy.³⁰⁰⁻³⁰² One study, however, did not find a beneficial effect.²⁷⁵ Carbamazepine has also found some usefulness in post-traumatic paresthesia,³⁰³ post-lumbar sympathectomy,³⁰⁴ phantom-limb pain,³⁰⁵ and post-herpetic neuralgia.^{306 307} It is the feeling of many people who use these agents than anticonvulsants may be more useful if the pain is paroxysmal in type and less useful if the pain is consistent and burning in type.³⁰⁸ The evidence seems stronger for carbamazepine than for phenytoin, and for tricyclic agents more than anticonvulsants.²⁷⁵

Other drugs

There has been one uncontrolled report of amphetamine for the symptomatic relief of diabetic neuropathy.³⁰⁹ Levodopa has been shown to be useful for postherpetic neuralgia.³¹⁰

Physical methods of therapy

Although many patients will undoubtedly find some temporary benefit from massage, vibration, use of liniments, whirlpool therapy, heat or cold, there have been no studies documenting their efficacy, and their effect in any event would be only short-lived. There has been some enthusiasm for the use

of transcutaneous electrical nerve stimulation for neuropathic pain following the demonstration of Wall and Sweet³¹¹ that this modality can be useful in post-traumatic neuralgia. A number of other investigators have demonstrated its usefulness in painful nerve injury.^{312 313}

Transcutaneous electrical nerve stimulation is also useful for post-herpetic neuralgia^{314 315} and causalgia.³¹⁶ There seems to be some benefit from transcutaneous electrical nerve stimulation in generalised neuropathic symptoms as well.^{315 317-319} Transcutaneous electrical nerve stimulation has greater short-term success than long-term success, but there is a significant incidence of patients who find it useful even after one year of treatment.³¹⁵ Acupuncture has been recently touted as useful for pain,^{320 321} but there have not been any studies of this in peripheral neuropathy, except for post-herpetic neuralgia.^{322 323} All of these measures using physical techniques may work by a local mechanism of counter-irritation to influence local circuits in the spinal cord to block incoming painful impulses. Additionally, they may activate "endogenous antinociceptive processes"³²⁴ such as endorphins, which act in a more generalised fashion to relieve pain.

Galvanic muscle stimulation is not used frequently today except by some physicians for facial muscles after a Bell's palsy. It is clear that such stimulation does not increase the rate of nerve regeneration, but it may preserve muscle bulk temporarily by preventing atrophy while waiting for regeneration to occur.^{272 325 326}

Surgical therapy

Surgical intervention is not ordinarily undertaken in generalised peripheral neuropathies. For causalgias or reflex sympathetic dystrophies, it might be useful to have a sympathectomy for the region of pain, either by injecting the sympathetic ganglia, surgical removal of the ganglia, or infusion of the painful limb with guanethidine.^{327 328} Focal nerve blocks can be undertaken,³²⁹ and epidural steroids can be utilised.^{195 330} Electrical stimulators similar to transcutaneous electrical nerve stimulators can be implanted directly on the peripheral nerve for treatment of chronic pains.^{331 332} Other more invasive procedures include posterior column stimulation³³³ and central surgical procedures such as chordeotomy, thalamotomy or frontal lobotomy.³³⁴

Autonomic neuropathy

Postural hypotension can be a major problem for patients with a significant autonomic component to their neuropathy. Elastic garments, primarily on the lower extremities, can help. Pharmacological

methods include mineralocorticoids, such as fludrocortisone, and vasoactive agents, such as ephedrine.³³⁵ Gastroparesis, due to loss of vagal innervation of the stomach, can be treated with metoclopramide.³³⁶

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