Recent Studies of the Nervous System

J. G. McLeod, D Phil, MRACP, Associate Professor of Medicine, University of Sydney, Australia

Neurological research in the Department of Medicine has been directed mainly towards the study of diseases of peripheral nerve and muscle and disorders of the extrapyramidal system.

DISEASES OF PERIPHERAL NERVES

Over the past three years, we have studied the electrophysiological and pathological changes in the nerves of patients with different types of peripheral neuropathy. Pathological studies are performed on the sural nerve which is biopsied under local anaesthesia. Two or three centimetres of nerve are removed at the level of the lateral malleolus, and a portion of the nerve is immediately fixed in Flemming's solution so that quantitative studies may be made of the numbers and fibre-diameter distribution of the myelinated fibres in the nerve. Another portion is fixed in formalin, and later stained with 1 per cent osmic acid so that single nerve fibres may be teased out and examined microscopically (McLeod et al., 1969). A third portion is fixed for electron microscopic examination.

Two major pathological processes may affect peripheral nerves; axonal degeneration and segmental demyelination. Axonal degeneration affects both the axon cylinder and the myelin sheath of the nerve fibre, and is caused by damage to the nerve cell. Fibres that have regenerated after axonal degeneration are characterised by abnormally short internodal lengths. In contrast, segmental demyelination is caused by damage to the Schwann cell and affects only the myelin sheath, the axon initially remaining intact. Fibres that have regenerated after segmental demyelination are characterised by pronounced variability in the internodal lengths.

The findings in some of the different types of peripheral neuropathy will be considered in more detail.

Alcoholic Neuropathy

Conflicting opinions have been expressed on the nature of the underlying pathology in alcoholic neuropathy, since both axonal degeneration and segmental demyelination have been described by previous investigators. We
had the opportunity of performing electrophysiological studies and sural nerve biopsies on 11 patients with alcoholic neuropathy (Walsh and McLeod, 1970). There was significant slowing of motor and sensory conduction in the peripheral nerves of all the patients, and the predominant pathological change was found to be axonal degeneration. Both large and small diameter myelinated fibres were affected by the pathological process. In patients whose peripheral neuropathy was of acute onset caused by a bout of heavy drinking and poor diet, numerous fibres undergoing active axonal degeneration were seen in the sural nerves. In contrast, in patients with a chronic neuropathy, where there was a long history of heavy alcohol intake and good diet, few fibres were seen to be actively degenerating, but regenerated fibres were conspicuous. Our findings suggest that there is a process of continual degeneration and regeneration in the peripheral nerves of chronic alcoholic patients, and that acute alcoholic excess may lead to widespread active axonal degeneration in the nerves, which may be the result of acute thiamine deficiency.

The ultrastructural changes in alcoholic neuropathy are presently being studied. It will be of interest to see whether they are similar to those seen in the neuropathy associated with thiamine deficiency in experimental animals (Prineas, 1970a).

Toxic Neuropathies
Peripheral neuropathy is an almost invariable adverse effect of vincristine therapy. By means of serial nerve conduction studies it was shown that the

![Fig. 1. Single fibres teased from sural nerve of a patient with vincristine neuropathy. The majority of fibres were undergoing axonal degeneration, a and b, but occasional fibres were remyelinating after segmental demyelination, c. Arrows indicate nodes of Ranvier.](image-url)
Peripheral neuropathy progressed for several weeks after cessation of the drug, but gradual recovery then occurred over a period of many months. The pathological changes were mainly those of axonal degeneration, which suggested that the toxic effects were on the metabolism of the neurone rather than the Schwann cell (Fig. 1) (McLeod and Penny, 1969).

Arsenic poisoning causes a very severe neuropathy, with axonal degeneration of both myelinated and unmyelinated nerve fibres. Similar pathological changes may be seen in the neuropathies caused by thallium, isoniazid, thalidomide, and gold poisoning (Walsh, 1970a).

**Lymphomas**

During the study of vincristine neuropathy, it was observed that some patients with lymphoma had electrophysiological and clinical evidence of a neuropathy before beginning the drug.

It is well recognised that peripheral neuropathy may occur as a complication of carcinoma of the lung and other organs, but the incidence of peripheral neuropathy as a complication of lymphoma is less well documented. Walsh (1970b) investigated 62 patients with Hodgkin's disease, reticulum cell sarcoma, lymphosarcoma, and chronic lymphatic leukaemia and found electrophysiological evidence of peripheral neuropathy in over 30 per cent of cases. None of the patients had been treated with neurotoxic drugs. The underlying pathological changes in the peripheral nerves were those of axonal degeneration and segmental demyelination. Walsh's study indicates that sub-clinical peripheral neuropathy is common in the lymphomas, occurring at least as frequently as in carcinoma of the lung. The cause of the neuropathy is unknown, but it does not appear to be the result of direct infiltration of the nerves by lymphomatous tissue. The metabolism of both the Schwann cell and neurone is affected in these diseases.

**Multiple Myeloma**

Walsh (1970c) also studied the incidence and nature of peripheral neuropathy in multiple myeloma. Of 23 patients studied 9 had electrophysiological evidence of peripheral neuropathy. Axonal degeneration had occurred in all the nerves studied. None of the nerves was affected by amyloid, and it was considered that the degenerative changes resulted from some effect of the disease process on the metabolism of the nerve cells.

**Spinocerebellar degenerations**

In eight patients with Friedreich's ataxia of early onset in the first decade and an autosomal recessive mode of inheritance, there were consistent
abnormalities of motor and sensory conduction in the peripheral nerves. Histological examination of the sural nerves revealed a significant loss of large diameter fibres, and relatively short internodal lengths in the remaining myelinated fibres. Unmyelinated fibres were not affected. The loss of large-diameter myelinated fibres in the disease would account for the clinical findings of impaired light touch, position and vibration sense, and two point discrimination (McLeod, 1970a).

The autosomal dominant type of Friedreich's ataxia often has a later age of onset and slower rate of progression. The electrophysiological and histological changes in this type of the disorder are similar to those in the more commonly occurring autosomal recessive type.

Our investigations on the other types of hereditary ataxia are not completed, but suggest that the peripheral nerves are spared or only mildly affected in such conditions as hereditary spastic paraparesis, Holmes type of familial cerebellar degeneration, and the olivo-ponto-cerebellar degeneration.

Electrophysiological and pathological studies may provide a means of early detection of some types of hereditary ataxia, and provide a basis for genetic counselling.

Charcot-Marie-Tooth Disease
Dyck and Lambert (1968) drew attention to the fact that Charcot-Marie-Tooth disease was a heterogeneous group of inherited disorders, and that a similar clinical picture resulted from three distinct pathological conditions affecting the lower motor neurone. Our own investigations support their earlier observations (McLeod, 1970b).

The most common pathological appearance in the sural nerves of patients with peroneal muscular atrophy is that of a hypertrophic neuropathy, with onion bulb formations and segmental demyelination of individual nerve fibres (Fig. 2). Gross slowing of nerve conduction is the rule in such patients. Less common in our experience is the type of Charcot-Marie-Tooth disease in which there is mild slowing of conduction and in which the underlying pathological changes are those of axonal degeneration.

Anterior horn cell degeneration may also cause a hereditary distal muscular atrophy, and we have now studied patients with the condition from five different families. In three of the families the mode of inheritance was dominant in two patients; no other members of their families were affected. There was denervation of the wasted muscles, but motor and sensory conduction in the peripheral nerves was normal, and sural nerve biopsies were also normal. The condition is presumably related to other genetically determined
spinal muscular atrophies such as the Kugelberg–Welander syndrome and Werdnig–Hoffman disease.

**Demyelinating Neuropathies**

Prineas (1970b) has studied the natural history of sporadically occurring acute, subacute, recurrent and chronic progressive polyneuropathies of undetermined cause. Clinical features of prognostic value were defined and a classification based on the natural history of this group of neuropathies was proposed. The limitations of this approach to the further study of this heterogeneous group of disorders was emphasised, and attention was drawn to the paucity of pathological studies that have been reported in neuropathies of this type. All recent cases of unexplained polyneuropathy seen in this Department have been subjected to nerve biopsy for histological and ultrastructural examination, and the findings correlated with electrophysiological and clinical findings. Evidence has been obtained that there may be several distinct varieties of recurrent demyelinating idiopathic polyneuropathy. One form of recurrent polyneuropathy is characterised by the occurrence of large endoneurial
deposits of amyloid-like fibrils (Prineas et al., 1970). In another type of relapsing neuropathy in which such deposits were absent, the fine-structural changes accompanying myelin breakdown have been defined and it has been noted that destruction of myelin appeared to be initiated by macrophages invading apparently intact nerve fibres and burrowing along the sheath within the intraperiod lines. No extracellular vesicular dissolution of myelin similar to that described by others in the Landry-Guillain-Barré syndrome was observed, and it would appear that the pathogenesis of myelin destruction differs in recurrent idiopathic polyneuropathy from that seen in the Landry-Guillain-Barré syndrome (Prineas, 1970c).

PERIPHERAL NERVE GRAFTING
No satisfactory technique has been developed in man for the repair of large defects in peripheral nerves resulting from injuries. Attempts to bridge the gap by means of homografts through which the fibres may regenerate have usually been frustrated by unfavourable immune responses. In experimental animals, we have found that such responses can be significantly lessened by means of immunosuppressive agents and that effective regeneration will take place through the homograft (Pollard et al., 1970). Defects in the peripheral nerves of rats and monkeys were repaired with homografts united to the host nerve by means of vein cuffs and tissue adhesive. Regeneration was evaluated by clinical, electrophysiological and histological means. Re-innervation of distal muscles occurred in 20 of 21 rats treated with immunosuppressive agents compared with 9 of 20 control animals. In monkeys, re-innervation occurred in all 5 animals treated with immunosuppressive therapy compared with 2 of 6 controls. Withdrawal of immunosuppressive therapy after six weeks did not result in deterioration of function. It is concluded that regeneration through homografts is significantly enhanced by administration of immunosuppressive agents, and that this technique for repair of large defects in peripheral nerves is worthy of trial in man.

MYASTHENIA GRAVIS
Goldstein and Whittingham (1966) reported that guinea-pigs immunised with calf thymus developed an autoimmune thymitis and a defect of neuromuscular transmission of the type found in myasthenia gravis. We have attempted to reproduce this experimental model of myasthenia gravis in guinea-pigs and rats by immunological methods, but have consistently failed to produce clinical or electrophysiological evidence of myasthenia even though the delayed hypersensitivity reaction, serological testing, and thymic histology
testified to the adequacy of the immunisation. Our investigations have failed to support the findings of Goldstein and his co-workers (Jones et al., 1970).

We have also studied the effect of germine diacetate on neuromuscular transmission in experimental animals (Brennan et al., 1971). Flacke et al. (1966) reported that germine diacetate, a veratrum alkaloid, improved the force of muscle contraction in patients with myasthenia gravis. Our studies on rats and guinea-pigs indicate that, unlike the anticholinesterases, the germine acetates act directly upon the muscle fibres, and that they do not significantly impair the release of acetylcholine from the nerve endings. They enhance the force of muscle contraction even in the presence of anticholinesterase drugs, and may prove a useful adjunct to therapy in those patients with myasthenia gravis who have failed to respond to conventional therapy.

DYSTROPHIA MYOTONICA
Huff et al. (1966) reported that in patients with dystrophia myotonica there was an exaggerated insulin response to an oral glucose load. We have confirmed their findings by demonstrating that hypersecretion of insulin occurred in 19 of 20 patients with clinical and electromyographic evidence of dystrophia myotonica (Walsh et al., 1970). Since the disease has an autosomal dominant mode of inheritance but may not manifest itself clinically in an individual until the third or fourth decade, it is important to have means of detecting the condition early in life in order to assist with genetic counselling. We have therefore investigated insulin secretion in the clinically unaffected relatives of patients with dystrophia myotonica. Of 25 such people studied in two families, abnormalities of insulin secretion were present in 11. Although follow-up studies will be necessary to confirm the proposition, it seems likely that these people will develop clinical manifestations of the disease later in life. It is suggested that hypersecretion of insulin is a consistent abnormality in the disease, and that, together with electromyography and slit-lamp-examination of the lens, measurement of the insulin response to an oral glucose load may be of value in the early detection of heterozygotes.

PARKINSON'S DISEASE
George Selby at the Royal North Shore Hospital, Sydney, has made an extensive study of all aspects of Parkinson's syndrome over the past 12 years (Selby, 1967a, 1968a). He reported a careful analysis of the results of stereotactic surgery in over 300 patients whom he personally examined preoperatively and at long intervals after operation (Selby, 1967b). Rigidity and tremor were significantly improved in over 80 per cent of cases, and some improvement in manual dexterity and in the various gait disorders was
observed in over 70 per cent of his patients. Disorders of speech, however, improved in only 22 per cent of patients after unilateral thalamotomy, and aggravation of dysarthria and further loss of voice volume was a complication of bilateral thalamotomy in almost 25 per cent of cases (Selby, 1967b). A detailed investigation of the effects of L-dopa therapy is currently in progress. The results of this study will assist towards a critical evaluation of the respective roles of medical and surgical treatment in the modern management of Parkinson's disease (Selby et al., to be published).

It has been assumed that the pathology of Parkinson's disease was confined to the basal ganglia and the substantia nigra; changes in the cerebral cortex have so far received little attention. Selby (1968b) has analysed the pneumoencephalograms of 250 patients with Parkinson's disease of varying aetiology and has demonstrated that significant cortical atrophy occurred in 57 per cent of cases. This cortical atrophy correlated statistically with the degree of rigidity, the severity of gait disorders, and the patient's general incapacity. It was more pronounced in patients with intellectual defects. These patients were more prone to develop mental confusion after thalamotomy and the results of operation were not as successful as in those with normal pneumoencephalograms.

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