The Neurology and Neuropathology of the Occupational Neuropathies

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Recent advances in experimental neuropathology have made possible a classification of the human neuropathies based on histopathological reactions of peripheral nerve. This has provided a more rational and easily understood approach to peripheral nerve disease than the older classifications that were based solely on etiology, and were mere compilations of long lists of conditions, e.g., alcoholic neuropathy, diabetic neuropathy, sulfonamide neuropathy, etc. An etiologic classification remains of great use when the agent responsible for the nerve damage is obvious, but this approach is of little help in the common clinical situation where a patient has an unexplained progressive deterioration of peripheral nerve function. It is in this situation that the modern clinico-pathological approach proves most helpful in defining the problem and allows the best chance of prescribing the correct treatment. This report reviews the relevant basic anatomy and pathology of peripheral nerve and then correlates these with the clinico-pathological phenomena observed in some occupational neuropathies.

A. BASIC ANATOMY

A peripheral nerve consists of large numbers of axons. These are the processes of nerve cells located either in the anterior horns of the spinal cord (motor neurons), in spinal ganglia (sensory neurons), or autonomic ganglia (e.g. sympathetic neurons). All peripheral axons are surrounded by Schwann cells. The Schwann cells of many motor and sensory fibers form myelin sheaths along the axon leaving gaps at nodes of Ranvier. Many small, sensory and sympathetic axons have no myelin sheath, and are slow conducting. The somatic motor axons terminate on specialized regions of muscle, the motor end plates, and conduct impulses which are responsible for muscle contraction and movement. The anterior horn cell has only one axon which is totally peripheral in its distribution. The peripheral axons of spinal ganglion neurons innervate a variety of peripheral sensory receptors while their central axons enter the spinal cord, via the dorsal root, and project for variable distances. Like other central axons, these are ensheathed by oligodendrocytes instead of Schwann cells.

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Figure 1 is a diagramatic representation of the relevant anatomy of the peripheral and central nervous systems.

B. OUTLINE OF THE CLINICO-PATHOLOGICAL CLASSIFICATION OF THE POLYNEUROPATHIES

1. Demyelinating neuropathies.
2. Chronic, often hereditary neuropathies.
3. Vascular neuropathies.
4. Neuropathies in which the axon and nerve cell body primarily are affected (axonal neuropathies, "dying-back" neuropathies, central-peripheral, distal axonopathies).

1. Demyelinating Neuropathies

(a) Classic Example. — Postinfectious idiopathic neuropathy (Guillain-Barré).

(b) Pathogenesis and Pathology (Theory). — The patient in some way has become sensitized to his own peripheral myelin and there is an attack on the myelin by sensitized lymphocytes. The axon is spared unless incidentally damaged in the inflammatory destruction of myelin. The disease may be simulated in animals after injection with suspensions of heterogenous peripheral myelin.

(c) Distribution. — Many spinal roots and nerves are involved resulting in diffuse areflexia and weakness. Especially striking is weakness of intercostal muscles, swallowing muscles, and facial muscles. Motor deficit is usually much worse than sensory. The patients are often quadraplegic and require respiratory support.

(d) Onset. — Often abrupt, patients may be severely disabled within three or four days of the first symptom.

(e) Differential Diagnosis. — Hypokalemic paralysis, botulism and acute intermittent porphyria are occasionally confused with Guillain-Barré.

(f) Prognosis. — Usually is excellent for near complete recovery provided the patient's respiratory function can be maintained. Recovery is often 80% complete within six months of the onset.

(g) Treatment. — The most important therapy is pulmonary support. Since many of these patients have respiratory compromise (and it can appear suddenly), they should be observed with extreme vigilance in the early phases of the disease and, if possible, in a pulmonary intensive care unit. Corticosteroid

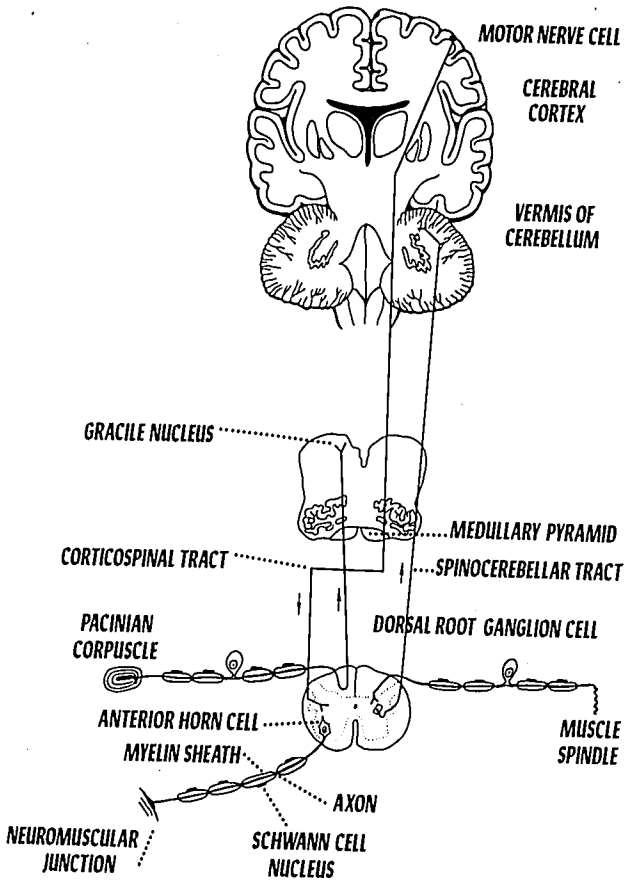

Fig 1. — Diagramatic representation of the relevant anatomy of the central-peripheral nervous systems.

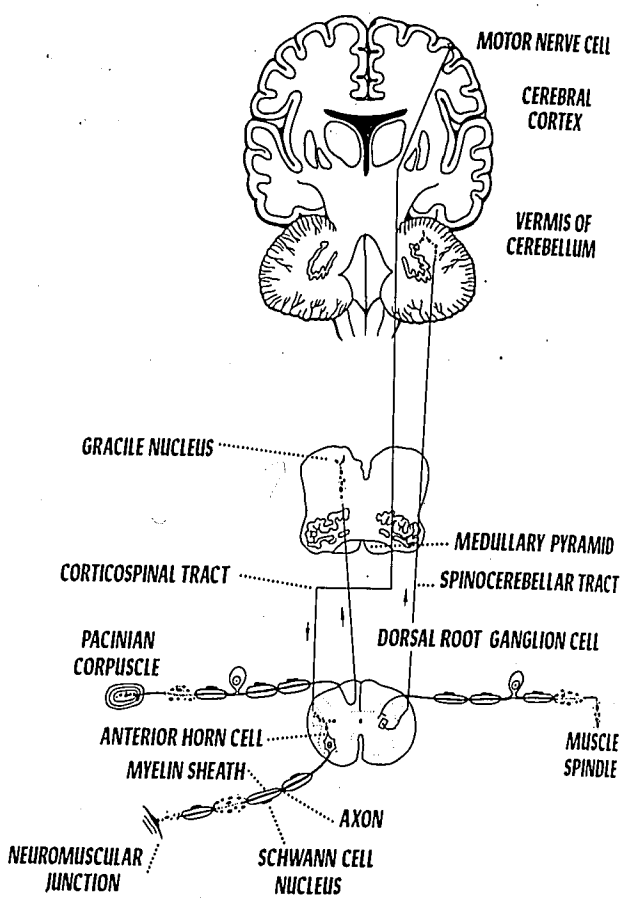

Fig 2. — Diagramatic representation of the areas affected in the central and peripheral distal axonopathies (axonal neuropathies, dying-back neuropathies).

therapy is advocated by some. If the patient needs a tracheostomy, however, corticosteroid therapy increases the risk of infection.

1. Clinical Diagnostic Tests

Nerve conduction times are usually prolonged. After two weeks the spinal fluid usually has increased protein and a few cells. Nerve biopsy is rarely indicated, and may show inflammatory cells within the nerve.

2. Chronic Familial Neuropathies

(a) Classic Examples. — Familial neuropathies (Dejerine-Sottas, Charcot-Marie-Tooth, amyloidosis, Refsum's disease.

(b) Pathogenesis. — Unknown. An error in phytanic acid metabolism has been identified in Refsum's disease.

(c) Distribution. — Usually a distal stocking-glove distribution is seen.

(d) Onset. — Slow, insidious.

(e) Differential Diagnosis. — If other family members are involved, the correct diagnosis is readily made. Spontaneous cases may be confused with spinal cord or muscle disease.

(f) Prognosis. — Usually is poor, with relentless but slow progression of neuropathy and systemic problems associated with the disease.

(g) Treatment. — Supportive therapy, genetic counseling.

(h) Clinical Diagnostic Tests. — Nerve biopsy is very useful and may be diagnostic if amyloid is seen. Genetic investigation may be helpful.

3. Vascular Neuropathies

(a) Classic Examples. — Periarteritis nodosa, diabetes mellitus mononeuropathy multiplex.

(b) Pathogenesis and Pathology. — Local small vessel occlusion is present in periarteritis and local small vessel occlusion or large vessel disease in diabetes. Mild degrees of ischemia may affect only the myelin.

(c) Distribution. — Patchy deficits are usually related to sensory and motor territory of one (mononeuropathy) or several (mononeuropathy multiplex) large nerves.

(d) Onset. — Abrupt or subacute often with pain present in area of nerve.

(e) Differential Diagnosis. — Rarely a problem if the underlying disease is known. The syndrome of bilateral femoral-lumbar root neuropathy (diabetic amyotrophy) in diabetics, presenting as proximal weakness, may be confused with amyotrophic lateral sclerosis or myositis.

(f) Prognosis. — Usually good in the diabetics, repair time varies with the degree and site of ischemic damage to nerve.

(g) Treatment. — Supportive. Strict control of diabetes desirable but often has little effect on the neuropathy.

(h) Clinical Diagnostic Tests. — Nerve biopsy may be

diagnostic in periarteritis but is of little help in diabetes. Spinal fluid protein is usually elevated in diabetes.

4. Axonal Neuropathies

(a) Classic Examples. — Nutritional neuropathy (alcoholic neuropathy), toxic neuropathies (arsenic, *n*-hexane, acrylamide, methyl *n*-butyl ketone, tri-*ortho*cresyl phosphate (TOCP), carbon disulfide, INH, Furadantin), and some metabolic diseases.

(b) Pathogenesis and Pathology (Theory). — The primary disease is in the nerve cell body or in the axon, the metabolic machinery becomes altered and axonal nutrition is impaired. The distal region of the largest and longest axons become poorly nourished and degenerate. If disease continues, the nerve fibers deteriorate proximally towards the cells of origin (dying-back). Figure 2 is a diagrammatic representation of this sequence of events.

(c) Distribution. — Endings of longest nerves (sciatic) are involved first. Symmetrical decrease in sensation and power in feet is accompanied or followed by similar symptoms in the hands (i.e., "stocking-glove" distribution).

(d) Onset. — Slow, insidious, often the patient is not disabled for months or years.

(e) Differential Diagnosis. — Seldom difficult, although on occasion, cases of motor neuron disease or compression of the cauda equina may mimic an axonal neuropathy.

(f) Prognosis. — Variable. If the toxin or deficiency can be corrected early, then complete recovery is the rule. If the process is not corrected early, there may be a permanent deficit.

(g) Treatment. — Early diagnosis of the cause of neuropathy and correction of the metabolic deficits are of primary importance.

(h) Clinical Diagnostic Tests. — Electromyograms usually show signs of denervation in muscle and nerve conduction time may be prolonged. Spinal fluid is often normal, may show a slight increase in protein. Nerve biopsy is seldom diagnostic.

C. CLINICAL AND PATHOLOGICAL ASPECTS OF THE OCCUPATIONAL NEUROPATHIES

The majority of the occupational neuropathies are caused by neurotoxins in the work area and the clinico-pathological profiles indicate that these neuropathies conform to the axonal type. There is some variation in both the distribution and morphology of the axonal changes amongst the major occupational neuropathies (TOCP, acrylamide, hexacarbons) but in general, the degree of change is proportional to the duration and level of exposure. The Neurotoxicology Unit at Albert Einstein has had clinical experience with human *n*-hexane[1] and acrylamide intoxication and considerable experimental experience with the hexacarbons *n*-hexane,[2] methyl *n*-butyl ketone[3] and 2,5-hexanedione,[4] and with acrylamide.[5] Therefore, this discussion is centered primarily on these compounds since the experimental diseases they produce provide excellent paradigms of the occupational neuropathies.

1. Neuropathology

Experimental studies with the hexacarbons and acrylamide have demonstrated that the development of peripheral neuropathy is associated with slowly progressive damage in vulnerable axons sited in both the peripheral *and* the central nervous systems. We have introduced the term "central-peripheral distal axonopathy" to describe this type of disease. This neologism replaces the terms axonal neuropathy, or "dying-back", the latter reflecting the pathological hallmark of these diseases in which axonal damage slowly ascends affected nerve tracts. Briefly, we intend the name to be used to describe those diseases of the dying-back type which are expressed as symmetrical, distal axonal degeneration occurring concurrently in the peripheral nervous system (PNS) and in selected tracts of the central nervous system, and which have the clinical stigmata of peripheral neuropathy.

The distribution of pathological changes is most readily appreciated in the experimental hexacarbon neuropathies since beginning axonal degeneration is associated with the formation of focal, giant axonal swellings. The changes commence concurrently in both the central and peripheral nervous systems before clinical signs are apparent. Vulnerable sites in the central nervous system are the distal ends of long ascending and descending tracts located in the spinal cord, medulla oblongata and cerebellum. Although a precise identification is difficult in animals, the affected areas seem to correspond to the gracile tracts in the medulla oblongata, the spino-cerebellar tracts in the cerebellar vermis and medulla oblongata, and the corticospinal and vestibulospinal tracts in the lumbar and sacral spinal cord. As clinical impairment develops, axonal swelling gives way to fiber disintegration in these areas, but swellings appear in more proximal regions of these tracts and in distal regions of shorter, less vulnerable spinal tracts.

In the peripheral nervous system, giant axonal degeneration also commences distally in vulnerable tracts. Specifically, vulnerable areas in hexacarbon neuropathies are the small tibial nerve branches which contain large diameter fibers supplying the calf muscles. Degeneration commences later in the distal regions of smaller diameter fibers contained within the posterior tibial and plantar nerves. With time and increasing clinical impairment, giant axonal swellings are found more proximally in affected tracts and, eventually, are distributed throughout the sciatic nerve, rarely ascending in motor fibers closer than the level of the dorsal root ganglion, or affecting the distal parts of sensory roots. Sensory and motor neurons are usually spared and do not display the pronounced reactive phenomena associated with axonal transection.

The distribution of PNS degeneration in experimental acrylamide neuropathy is somewhat different; axonal degeneration commences in the distal regions of sensory plantar nerves contemporaneously with changes in branches of the tibial nerves supplying the calf muscles. Pacinian corpuscles and primary afferent terminals of muscle spindles are especially vulnerable in cats intoxicated with acrylamide.

An accumulation of neurofilaments within axons is the characteristic feature of hexacarbon and acrylamide neuropathies. The accumulations are much larger and more frequent with hexacarbons than with acrylamide. In both types of neuropathy, neurofilament accumulation first occurs in the distal regions of the largest myelinated axons but, with time, the same change will affect smaller myelinated and nonmyelinated axons. In myelinated fibers, axonal swellings commence multifocally on the proximal sides of distal, non-terminal nodes of Ranvier. The pattern of pathology points to the node of Ranvier as the likely site for a direct toxic action. It is conceivable that the immediate effect at nodal regions is a partial blockade of anterograde axonal transport which restricts the volume of material passing along the fiber. This would account for the swellings on proximal sides of nodes of Ranvier and the axonal attenuation and myelin corrugation of adjacent, distal internodes. The simultaneous formation of ovoids distal to an axonal swelling might then result from a complete blockade of anterograde transport at that site.

The overall picture of nerve fiber degeneration which emerges

from these studies is incongruous with the broadly understood concept of "dying-back". Degenerative events commence distally and multifocally but not necessarily in the nerve terminal. There is no evidence of a distal → proximal movement of degeneration in affected fibers. Ovoid formation seems to commence distal to an especially abnormal position in the axon and, as such, this process is analogous to wallerian degeneration. It is clear that changes ascend affected nerve trunks, but it is unresolved whether there is any net retrograde spread of axonal damage in individual fibers, or whether different fibers within the affected tract commence degeneration at different times and at increasingly proximal levels as the neuropathy evolves.

The pathologic mechanisms underlying these central-peripheral distal axonopathies remain to be established. One hypothesis suggests that the metabolic machinery of the nerve cell body is progressively impaired and that distal axonal degeneration reflects a lack of material supply from the neuronal perikaryon. The presence of axonal regeneration during intoxication and the multifocal, distal and non-terminal distribution of degeneration, seem to argue against this hypothesis. Another theory suggests that there is a generalized disturbance either in the rate or the volume of axonal transport of materials. It seems unlikely that this is the *cause* of the degenerative process for the same reasons as cited above. However, the character and distribution of later degenerative events makes a focal block of axonal transport an attractive consideration. If changes in axonal transport do accompany fiber degeneration, the proximal regions of affected nerves should display a temporal increase in the degree of impairment as degeneration increasingly affects more proximal regions. A third hypothesis, as yet untested, is that the toxic substance exerts a direct effect on the axon and focally inactivates a substance or mechanism necessary for axonal integrity.

2. Clinical Neurology

The clinical manifestations of the occupational neuropathies are those previously outlined in section C, part 4, under the description of axonal neuropathies. The occupational neuropathies, with few exceptions, have a similar clinical presentation and a description of the clinical profile of the hexacarbon neuropathies, methyl *n*-butyl ketone and *n*-hexane, serve as a representative example.[7]

The most prominent feature of the clinical neurology of the hexacarbon neuropathies is the insidious onset of progressive distal weakness and sensory loss in the lower extremities. Slapping gait and difficulty in pincer movements or the grasping of heavy objects are common early signs. The majority of cases are of mild or moderate severity, and the sensory loss and weakness is confined to the distal extremities. The sensory deficit includes approximately equal loss of light touch, pricking pain and temperature discrimination. Vibration sense loss is usually much less and position sense loss is slight. Evidence of autonomic dysfunction or cranial nerve involvement is rare. Most individuals remain ambulatory, but a few severely involved cases may have weakness extending to hamstrings, hip flexors and extensors, thigh adductors and shoulder rotators.

Although many individuals experience mild or moderate weight loss, the majority do not feel "ill", have no cutaneous manifestations of disease, and are often able to continue walking during the early stages of neurotoxicity. It is a common observation that many affected individuals continue to show clinical progression for several weeks *after* removal from the toxic exposure. This delayed progression may include either electrodiagnostic or physical findings and is usually mild. Routine clinical laboratory tests, including cerebrospinal fluid protein, are usually normal, in keeping with the absence of signs of systemic illness. Electro-diagnostic findings, including electromyography and nerve conduction velocity, in general, correlate well with the severity of the clinical findings. Recovery is usually slow and, in the mild and moderate cases, complete. Despite the abundant experimental evidence of CNS damage produced in the course of hexacarbon intoxication, there are no reports of residual evidence of central nervous system damage in humans with industrial exposure to methyl *n*-butyl ketone or *n*-hexane. It seems very likely that in severe cases of hexacarbon intoxication, some individuals may sustain CNS damage; and, in one case report of a person with probable *n*-hexane intoxication following prolonged glue sniffing, it is stated that on recovery from a severe neuropathy, he was noted to have spasticity in the lower extremities.[8] The absence of such cases in the industrial exposure cases is puzzling. However, it is possible that the workers with neuropathy usually are part of an epidemic situation and thus are usually diagnosed relatively early, and only sustain minor, clinically-inapparent, CNS damage; or that long term follow-ups of severely involved individuals have yet to be reported.

There are some toxic industrial neuropathies whose unusual clinical features may be of help in early identification. Thus, lead neuropathy often presents as a wrist drop with few sensory findings, carbon disulphide often affects the cranial nerves, severe ataxia and palmar desquamation may accompany acrylamide intoxication, and severe gastro-intestinal symptoms and spasticity are often present with TOCP intoxication.

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