

Criteria for the diagnosis of peripheral neuropathies

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Is there a “gold standard”?

The diagnosis of a peripheral neuropathy is one of topographic localisation within the nervous system; not of aetiology. It is not a diagnosis in isolation as peripheral nerves are damaged consequent to some other condition, such as systemic exposure to exogenous agents in the environment and workplace. In subjects at risk, it is important to determine if and when peripheral nerves become affected, hopefully before clinical dysfunction and permanent damage occur. Many studies have employed clinical, electrophysiological, quantitative psychophysical sensory, and pathological procedures in the investigation of peripheral nerve disease. Their success has been less than optimal, mostly because of complexities in the peripheral nervous system and inherent procedural limitations.

Peripheral neuropathies can be divided into:

- Those which are bilaterally symmetrical—*polyneuropathies* (for example, most neurotoxins, diabetes mellitus)
- Those which are focal—*mononeuropathies* (nerve entrapment)
- *Multiple mononeuropathies* (vasculitides, leprosy, multifocal motor).

Other subdivisions are based on the predominant site of dysfunction:

- Axons—*axonopathies* (diabetes, organophosphates)
- Nerve cell bodies—*neuronopathies* (poliomyelitis, pyridoxine)
- Schwann cells and/or their myelin sheaths—*demyelinating neuropathies* (Guillain-Barré syndrome, acute arsenic poisoning).

There are also different types of peripheral nerve fibres: motor, sensory, and autonomic. Sensory fibres are divided into at least three groups anatomically, physiologically, and functionally:

- $A\alpha$ (or $A\alpha\beta$)—large diameter, myelinated, fast conducting; mediating vibration, position, and touch sensations
- $A\delta$ —small diameter, myelinated, slow conducting; mediating cold sensation

- C fibres—very small diameter, unmyelinated, very slow conducting; mediating hot and pain sensations.

Not all fibre types are affected in all peripheral nerve disorders; neuropathies can preferentially affect motor fibres (Guillain-Barré syndrome), sensory fibres (diabetes), or both (hereditary motor and sensory neuropathies—Charcot-Marie-Tooth disease, most neurotoxins). Most polyneuropathies affect all sensory fibres, but others mainly involve small fibres (amyloidosis, metronidazole toxicity).

The peripheral nervous system is thus more complicated than might appear at first glance; hence not all peripheral nerve functions or fibre types can be evaluated with a single test. This dilemma has been recognised for years, and with modern predilections for quantitation and state of the art technology, multifaceted approaches to evaluate peripheral nerves have been devised, perhaps the most complete to date being that of Peter Dyck's group at the Mayo Clinic (reviewed in Dyck¹). This methodology includes symptoms questionnaires, a neurological examination with special attention to peripheral nerve activities, quantitative sensory (QST) and autonomic testing, and nerve conduction studies. It was agreed that the diagnosis of a polyneuropathy required abnormalities in at least two types of evaluation, one of which is nerve conduction or quantitative autonomic testing (because of their objectivity).²

This approach has been widely adopted because each test measures a specific aspect of nerve function and has its own limitations. Symptoms questionnaires rely on subject recognition, thereby introducing a high level of subjectivity and variability; they cannot discern subclinical involvement. The clinical examination is the clinical examination—a nineteenth century construct thought to pale in comparison to the latest and greatest technological advances. Nerve conduction studies are objective, reproducible, and sensitive, but do not directly reflect symptoms or clinical impairment. The QST is a psychophysical test dependent on subject

cooperation, alertness, site of stimulation, site of study, etc.

In this issue of *Occupational and Environmental Medicine*, modifications of the Mayo Clinic methodology were employed by Jamal *et al* at the Institute of Neurological Sciences, Glasgow, and Buchanan *et al* at the ISD, Scottish Executive, Edinburgh, to assess peripheral nerve functions in UK sheep farmers and dippers chronically exposed to organophosphates. These authors had previously evaluated a large group of subjects in the field,³ using a symptoms questionnaire and QST. The current studies re-evaluated these parameters in a smaller sample of the same subjects in a clinic setting (Jamal *et al*), or compared them to a more comprehensive investigation utilising symptoms questionnaires, a neurological examination, nerve conduction studies, electromyography and single fibre electromyography, and QST of vibration, and hot and cold thresholds (Buchanan *et al*).

The following results are notable. There was little correlation between QST scores in the field and those in the clinic; this was attributed to the inadequate control of ambient temperature in the field (Jamal *et al*). In the more comprehensive study (Buchanan *et al*), subjects were divided into those without, or with possible or probable/definite neuropathy based on the screening abnormalities seen in the field. Among those with probable/definite neuropathy, 52% had abnormalities in the neurological examination or nerve conduction studies. The QST findings characterised the neuropathy as predominantly sensory of the small fibre type. It is somewhat problematic that one study found the screening procedure to be of limited reproducibility (Jamal *et al*), whereas the second study (Buchanan *et al*) used that screening procedure to characterise the presence and severity of neuropathy. Further, the diagnostic value of QST appears to be limited by technical factors in the field (Jamal *et al*) and by the findings that, although 52% of subjects (12/23) with probable/definite neuropathy had clinical and electrophysiological evidence for neuropathic dysfunction, 91% of them (21/23) had abnormalities on small fibre QST (Buchanan *et al*). What should be made of the nine (39%) in this group who had abnormal QST but no other evidence of neuropathic dysfunction?

This review suggests that confirmation of polyneuropathy is still imprecise. The most tried and true tests are the clinical examination and nerve conduction studies. However, even nerve conduction studies are problematic. The usual studies employ surface electrodes which only measure the velocities of the fastest conducting ($A\alpha$) fibres. Patients with “small fibre” neuropathies, therefore, can have normal velocities. The near

nerve technique, employing fine needle electrodes guided to peripheral nerves, can measure A δ fibre activity, but this is a more difficult, time consuming, and invasive procedure. C fibre activity cannot be measured in nerve conduction studies. When QST of large (A α) and small (A δ) myelinated fibres was compared with near nerve conduction studies in mild symptomatic diabetic neuropathy,⁴ A δ conduction abnormalities were closely related to cooling detection threshold abnormalities (also mediated by A δ fibres). Thus it could be argued that, in "small fibre" neuropathy, neuropathic dysfunction when measured by nerve conduction, would be found more frequently if the more sensitive technique had been employed. However, the conclusion of that same study was that in a mixed fibre neuropathy, such as that associated with diabetes, either conduction technique is more sensitive than QST. Finally, in a small study of farmers chronically exposed to organophosphates without neuropathic complaints, but with high vibration

thresholds at screening, the neurological examination was found to be the most sensitive test; subclinical polyneuropathy was not present or could not be diagnosed with either near nerve or QST studies.⁵

The problems seen in the current reports of potential neuropathic dysfunction in workers exposed to organophosphates underscore the difficulties of evaluating the peripheral nervous system clinically. Not only is there no "gold standard" for determining clinical neuropathic dysfunction, there is no single standard at all. For the present, the approach taken by these investigators seems reasonable, with the caveat that a good clinical neurological examination in the field would be a valuable addition to their protocol and attention to QST technical factors is requisite.

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- 3 **Pilkington A**, Buchanan, D, Jamal GA, *et al*. An epidemiological study of the relations between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy and neuropsychological abnormalities in sheep farmers and dippers. *Occup Environ Med* 2001;**58**:702–10.
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Answers to multiple choice questions on Baker's asthma by J Brisman, on pages 498–502

- (1) (a) false; (b) false; (c) false; (d) true; (e) false
- (2) (a) false; (b) false; (c) false; (d) true; (e) false
- (3) (a) true; (b) false; (c) true; (d) true; (e) true
- (4) (a) false; (b) true; (c) true; (d) true; (e) true