Enlargement of peripheral nerve is a physical sign that all neurologists know about, but which, like pes cavus, is extremely difficult to recognize in its milder forms. It is associated principally with two conditions – leprosy and hereditary motor and sensory neuropathy. It has also been noted in a number of others (Table 1).

**DETECTING ENLARGED PERIPHERAL NERVES BY PALPATION**

Potential sites for palpating nerves are shown in Fig. 1, based on experience in leprosy. Attempts to palpate such nerves are best made using the tips of the index, middle and ring fingers rolled backwards and forwards across the long axis of the nerve. Sometimes you can try to pick up the nerve between the thumb and middle finger as in the case of the ulnar nerve in the upper arm.

**Table 1** Differential diagnosis of enlarged peripheral nerves

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leprosy</td>
</tr>
<tr>
<td>Hereditary motor and sensory neuropathy</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Refsum’s disease</td>
</tr>
<tr>
<td>Perineuroma/localized hypertrophic neuropathy</td>
</tr>
<tr>
<td>Nerve tumours</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
</tbody>
</table>

**Figure 1** Sites of potentially palpable peripheral nerve enlargement in leprosy [Fig. 14.5 from Leprosy 2nd Edn. (1994), Hastings RC, Opromolla DVA (Eds.)].

---

*Michael Donaghy*

Department of Clinical Neurology, University of Oxford, Radcliffe Infirmary, Oxford OX2 6HE, UK

*Practical Neurology, 2003, 3, 40–45*
Only the most astute physician will be able to use his thumb to detect an enlarged superficial radial nerve in the anatomical snuffbox of someone with whom he is casually shaking hands. The best simile for an enlarged peripheral nerve is that it feels like a length of domestic electric cable. The ulnar nerve can be thickened to four or five times its normal diameter in leprosy, not that unusual in the Indian subcontinent.

Some normal nerves can be palpated easily, without being enlarged in the pathological sense. Well known examples include the superficial radial nerve running over the extensor pollicis tendon, the ulnar nerve behind the medial epicondyle at the elbow, the common peroneal nerve around the fibula head, and terminal sprigs of the peroneal nerve over the dorsum of the foot. It is extremely difficult to judge mild degrees of enlargement at these sites: other sites may be preferable, for example in some cases ulnar nerve enlargement may be better noted in the medial upper arm above the elbow.

Nerve enlargement can lead to entrapment within canals of otherwise normal calibre. Examples include the ulnar nerve in the cubital tunnel (Fig. 2) and the median nerve in the carpal tunnel. In suspected leprosy it is necessary to compare carefully the same nerve on both sides of the body in making the decision about whether a nerve is enlarged or not (McDougall 1996). Leprosy workers can be trained to palpate nerves systematically, and scoring systems have been developed: no enlargement (0); slightly

Figure 2 A hugely palpable ulnar nerve in the upper arm in leprosy. Note that the nerve enlargement has led to suspected secondary compression in the cubital tunnel, hence the scar reflecting surgical release (courtesy of Dr Colin McDougall).
enlarged (1 +); moderately enlarged (2 +); very enlarged (3 +) with additional note of nerve tenderness or pain (Croft et al. 1999).

LEPROSY

Leprosy is the only condition in which a palpably hypertrophied peripheral nerve is often central to the diagnosis. At the lepromatous end of the spectrum, symmetrical involvement with glove and stocking sensory loss due to dermal nerve involvement, often with autonomic neuropathic features, is the usual finding. At the tuberculoid end of the spectrum, one or a few individual nerves tend to be picked out. Three cardinal signs remain the basis for diagnosing leprosy (Pfaltzgraft et al. 1994; Report of the International Leprosy Association Technical Forum 2002; WHO 1995):

- Anaesthetic skin lesions. These usually consist of erythematous or hypopigmented macules and are often the first clinical sign of disease, but papules (raised) and nodules are also seen. A skin lesion due to leprosy typically shows loss or diminution of sensation to pin prick and/or light touch.
- Enlarged peripheral nerves. Nerve thickening usually appears later than the skin lesions. Depending on the delay in presentation and the clinico-immunological classification, the likelihood of detecting one or more enlarged nerves can vary from in as few as 20% of patients, to as many as 96%. In over 90% of those patients with nerve enlargement, it is detectable in either the ulnar or the peroneal nerve. Nerve function impairment is evident in the skin or muscles innervated by the enlarged nerve.
- Acid fast bacilli demonstrated on a skin smear (in a small proportion of cases). However, leprosy lesions in paucibacillary disease are skin smear negative and this constitutes the majority of cases in most endemic countries.

As a general rule one should be cautious about accepting nerve thickening alone, without sensory loss, muscle weakness or skin changes, as a reliable sign of leprosy (WHO 1995, 2002).

The technique of palpating nerves in suspected leprosy was eloquently described by R G Cochrane in 1964:

‘Never squeeze the nerve firmly ... remember always to examine the corresponding nerve on the other side; it is never safe to pronounce a nerve enlarged without comparing the one on the other side. Gross enlargement, of course, is obvious, but it is quite striking the number of times cases are diagnosed as leprosy with a remark that the ulnar nerve is enlarged, yet one can find no such enlargement. A good general rule is: if in doubt, the nerve is not enlarged’.

So technique is all-important, and those working as diagnostic assistants in leprosy clinics in endemic countries should be taught reliable methods for detecting enlarged nerves.

Over half a million new cases of leprosy are registered annually (WHO 2002). Of these, some 20% are at risk of developing a disability because of nerve function impairment. This 20% represents those patients whose nerve involvement by leprosy bacilli and/or inflammatory infiltrate affects the main sensory, or mixed motor and sensory nerve trunks. Interestingly, nerve function impairment commonly occurs for the first time during or after multidrug antibiotic treatment (Heinhardt et al. 1994, Croft et al. 2000). This distressing occurrence may lead to non-compliance with treatment yet can be treated with corticosteroids. Such nerve function impairment occurring during treatment is considered to represent a hypersensitivity reaction. The presence of pre-existing nerve trunk enlargement is a powerful predictor of subsequent treatment-related nerve function impairment (Croft et al. 2000).

HEREDITARY MOTOR AND SENSORY NEUROPATHY (HMSN)

Palpable nerve thickening occurs in about 30% of patients with type I (the demyelinated form) but not in type II (the axonal form) of hereditary motor and sensory neuropathy (Harling & Thomas 1980). The best nerve to palpate is the greater auricular nerve, which cannot usually be felt in normal people (Fig. 3). With the head inclined slightly away to tighten the neck muscles and skin, the fingeers of the palpating hand can be drawn across the side of the neck to try to feel the nerve. Sometimes an enlarged nerve is misdiagnosed. I well remember a patient with HMSN whose general practitioner’s referral letter stated that ‘his general health is otherwise good, apart from chronic cervical lymphadenopathy’. This turned out to be a nerve. Nerve thickening in hereditary motor and sensory neuropathy is thought to represent the summation of onion bulb formation around individual dysmyelinated nerve fibres, with all the associated redundant Schwann cell processes and collagen which that entails.
It is my informal impression that nerve enlargement is not present in nearly as many as 30% of the HMSN type I patients whom I see in my peripheral nerve clinic. However, that may be because it is most common in HMSN type IA, which accounts for 70% of HMSN type I, and is associated with the 17p11.2 reduplication on chromosome 17 providing a double dose of the PM P22 gene. Modern molecular genetics may mean that this diagnoses is made in general neurological clinics, thus obviating referral to specialist peripheral nerve clinics. The patients I see with HMSN tend to be those who cannot be diagnosed by routine molecular genetic tests. I cannot recall ever seeing a patient with palpable nerve enlargement who did not have the 17p11.2 reduplication.

**OTHER POLYNEUROPATHIES**

Diffuse nerve enlargement occurs in some patients with Refsum's disease. Other features are demyelinating polyneuropathy, with marked ataxia, retinitis pigmentosa and hearing impairment due to phytanic acid deposition. Infiltration of a nerve with amyloid protein might be expected to cause palpable enlargement. However, this was only noted in 1 out of 31 patients with primary systemic amyloidosis (amyloid immunoglobulin light chain deposition) (Kelly et al. 1979). There are only rare reports of palpable peripheral nerves in the various forms of familial amyloid polyneuropathy (Juliao et al. 1974; Sumino et al. 1983). An expert in hereditary amyloidosis revealed that she had never encountered nerve thickening in the condition (Riley 2002). So, looking for palpable nerve enlargement is unlikely to be helpful in those patients with small fibre sensory and autonomic peripheral neuropathies in whom you suspect amyloidosis.

Palpable nerve thickening has been reported occasionally in sarcoidosis. However the original material has been reviewed, revising the diagnosis to leprosy, and nerve hypertrophy is now not considered to be a feature of sarcoidosis (Matthews 1979).
localized hypertrophic neuropathy

Localized hypertrophic neuropathy has been noted, most commonly involving the brachial plexus (Van Es et al. 1997; Cusimano et al. 1988) but sometimes involving other more peripheral nerves such as the femoral (Takao et al. 1999) or proximal ulnar (Phillips et al. 1991). The clinical evolution may occur at varying speeds. Most typically an isolated lesion slowly evolves to affect the territory supplied by a single peripheral nerve. Palpation may reveal an enlarged nerve, which may be tender. Firm palpation may produce paraesthesiae or electric shock sensations referred to the skin territory supplied by the nerve.

Magnetic resonance imaging (MRI) can reveal areas of fusiform nerve enlargement at deeply buried sites not amenable to palpation. Interestingly, such MRI abnormalities may be noted in the brachial plexus of patients with multifocal motor neuropathy with conduction block (Van Es et al. 1997), although I have never encountered a multifocal motor neuropathy patient with palpable nerve enlargement. MRI

Figure 4 (a) The typical appearance of diffuse neurofibromas, mainly on small dermal nerve trunks, in neurofibromatosis. The patient had no abnormal neurological signs. (b) MRI of ulnar nerve neurofibroma (arrowed) 10 cm above elbow: T1-weighted (top), T1 + Gd enhanced (middle), and STIR (bottom) sequences. (Fig. 13.3(a) and (b) reprinted with permission from Brain's Diseases of the Nervous System, 11th Edition, Ed. Donaghy M. Oxford University Press 2001.)
demonstration of focally swollen brachial plexus trunks has been noted in the rare multifocal and demyelinating sensory and motor neuropathies. (MADSAM) (Van den Berg-Vos et al. 2000).

Electrophysiology in this diverse group of patients usually shows some degree of axonal degeneration, with associated focal demyelination and/or conduction block. Biopsies of localized hypertrophic mononeuropathy often reveal concentric laminar formations, superficially resembling the 'onion bulb' formations seen in hereditary motor and sensory neuropathy type I (Cusimano et al. 1988; Phillips et al. 1991). Immunostaining generally suggests that the proliferating cells are perineural, rather than Schwann, in origin (Bilbao et al. 1984). Interestingly, the term perineuroma is sometimes used. In reality the condition seems histologically diverse, with localized chronic inflammation noted in other cases (Cusimano et al. 1988).

NERVE TUMOURS
Palpably enlarged swellings along the course of both named, and smaller terminal, nerves is a well-recognized feature of neurofibromatosis type 1, von Recklinghausen's disease (Fig. 4). Caution should be exercised before asking a general surgeon to biopsy a skin lump which could be a nerve tumour, or other nerve swelling, for fear of severing underlying nerve fibres whose function may be intact. Bilateral greater auricular nerve enlargement has been noted in neurofibromatosis, and can cause diagnostic confusion in leprosy endemic areas (Gupta et al. 1997). Often neurofibromas along the peripheral course of nerves do not cause significant impairment of the function of that nerve, despite achieving considerable size. Of course, if a neurofibroma arises in a nerve at an entrapment site, most notably the intervertebral foramen, it does compromise nerve function progressively, and often painlessly. The situation is further confused by some patients with neurofibromatosis type 2, the central form, who develop slowly progressive focal peripheral nerve lesions without a nerve tumour or swelling being demonstrable even on detailed MRI studies of the course of the nerve (Trivedi et al. 2000).

ACKNOWLEDGEMENTS
I am most grateful to Drs Richard Croft and Colin McDougall for helpful discussions, particularly about leprosy, and to Mrs Joanna Wilkinson for preparing the manuscript.

REFERENCES