

- ⁴ Kopell HP, Thompson WAL. Pronator syndrome. A confirmed case and its diagnosis. *N Eng J Med* 1958;259:713-5.
- ⁵ Laha RK, Lunsford LD, Dujovny M. Lacertus fibrosus compression of the median nerve. Case report. *J Neurosurg* 1978;48:838-41.
- ⁶ Buchthal F, Rosenfalck A, Trojaborg A. Electrophysiological findings in entrapment of the median nerve at wrist and elbow. *J Neurol Neurosurg Psychiatry* 1974;37:340-60.
- ⁷ Laha RK, Dujovny M, De Castro SC. Entrapment of median nerve by supracondylar process of the humerus. Case report. *J Neurosurg* 1977;46:252-5.
- ⁸ Smith RV, Fisher RG. Struthers ligament: a source of median nerve compression above the elbow. Case report. *J Neurosurg* 1973;38:778-9.

Matters arising

Should Charcot-Marie-Tooth disease be genetically subgrouped on motor conduction velocity?

Sir: Based on clinical, electrophysiological and morphological studies Dyck and Lambert divided patients with Charcot-Marie-Tooth disease into what they considered to be two different disorders, which were reported separately in two papers.^{1,2} One was denoted hypertrophic because of the existence of onion bulbs (prominent segmental demyelination and remyelinations) whereas the other was designated neural and did not show onion bulbs. The dividing line in terms of motor conduction velocity (MCV) was set at 47, 45 and 40 m/s in the ulnar, median and lateral popliteal nerves respectively and individuals within any kinship would show similar velocities. A disorder of movement similar to that seen in patients with essential (familial) tremor was described in the hypertrophic variety only, as were plantar ulcers of the feet. Dyck and Lambert¹ also differentiated the hypertrophic Charcot-Marie-Tooth disease from Dejerine-Sottas disease. They reported two brothers with this latter disorder. One was chairbound and had a MCV in the ulnar and median nerves of 5 and 6 m/s respectively whereas the other, whose physical signs consisted only of absence of tendon jerks, showed a MCV of 42 and 44 m/s in the same nerves.

Credit and recognition should be given to Dyck and Lambert for drawing attention

to these important facts. However, it has become evident that (a) any clinical feature, including the disorder of movement similar to essential tremor,³ and plantar ulcers of the feet,⁴ could be seen in both types, (b) MCV in the lower limbs has proven to be of less value than in the upper limbs,³⁻⁶ (c) internode length is of little value in clearly distinguishing subtypes,^{5,6} (d) onion bulbs are also seen in the neural type.⁶ Gradually the concept of two different Charcot-Marie-Tooth diseases has lost support. Patients having an hereditary motor and sensory neuropathy with the type of inheritance, natural history, symptoms and signs of Charcot-Marie-Tooth disease that Dyck and Lambert categorise into two different disorders were recognised to be a single entity.

Authors with the most experience with this disorder have put forward a genetic classification of Charcot-Marie-Tooth disease based on MCV^{4,7} (concordance of conduction velocity in the upper limbs within each family). As with the original dividing line set by Dyck and Lambert^{1,2} there were kinships with both types, Thomas and Calne⁷ lowered the limit of MCV in the median nerve to 38 m/s, thus maintaining the division of the disorder into two genetically different types in terms of MCV. However, Harding and Thomas⁴ have written that in their study there were examples where MCV in the affected individuals fell "out of the appropriate cluster." Other authors have found affected individuals of the same family with widely different MCV. Myriantopoulos *et al*⁸ (see table III of their paper) and Davis *et al*⁹ (see kinship 27 in table II of their work) mentioned one family each and Brust *et al*¹⁰ quoted six families. In a detailed study Salisachs *et al*⁵ found that the MCV in the median nerves of two brothers with Charcot-Marie-Tooth disease were 48.3 and 28.3 m/s respectively. Teased fibre preparations (studied by Professor WG Bradley) showed similar changes in these two patients although segmental demyelination and remyelination were more marked in the latter. It is clear therefore that some kinships could not be categorised satisfactorily in the classification proposed by Dyck and Lambert^{1,2} even after the alteration in the dividing MCV as made by Thomas.^{4,7}

It is interesting that the limit set by Thomas and Calne⁷ in the median nerve would qualify one of the two patients of the kinship with Dejerine-Sottas disease

reported by Dyck and Lambert¹ (see above) as having the neural type of Charcot-Marie-Tooth disease. Davis *et al*⁹ studied many kinships and quoted others from the literature in which some affected members had MCV in the median nerve above 38 m/s whereas other cases of the same kinship had MCV values below this (see below the "intermediate" type, and fig 3 of their work). It is clear that in terms of classification, the lowering of MCV to 38 m/s in the median nerve has apparent advantages in some kinships but may not be helpful in others, since wherever this arbitrary dividing line is placed in terms of MCV there seem to be kinships with affected members above and below the line.

It has been claimed that although in Charcot-Marie-Tooth disease subgroups may exist, MCV is an inadequate means to define such subgroups.¹⁰ Some authors, who are keen to maintain part of the division suggested by Dyck and Lambert and thus classify in terms of MCV alone, consider the existence of widely different MCV in affected individuals of the same kinships as "potential flaw" in this genetic classification of the disease.⁴ Designating such findings as a "potential flaw" ignores the facts that (a) in few families have electrophysiological studies been made in several affected members, and (b) when such studies are available some have shown widely different MCV in the upper limbs in affected members. Bradley⁶ grouped his cases according to MCV in the upper limbs into hypertrophic (<25 m/s), intermediate (25-45 m/s) and neural (>45 m/s). Harding and Thomas⁴ found it impossible to accept such classification because there were kinships with both the intermediate and the hypertrophic type. In spite of the occurrence of both types in the same kinship,^{5,8-10} surprisingly the same authors^{4,7} accept the division between the hypertrophic and neural type made by Dyck and Lambert^{1,2} at 45 m/s in the median nerve and now set at 38 m/s.

More evidence of the inadequacy of MCV as a means for the genetic classification of Charcot-Marie-Tooth disease may come from data on Refsum's disease. Indeed, in recessively inherited disorders it is common to find that the expression of the disease is similar between, and especially within, families; but minor differences, which do not warrant different classification, are not unusual. Thus, if Refsum's disease would ever present with widely different MCV in affected

individuals of different kinships, or more importantly within the same kinship, such differences would be considered "minor variations" and would not warrant separate classification. In most patients with Refsum's disease MCV is substantially reduced.¹¹ However, Ulrich *et al*¹² have found MCV of 45 m/s in the ulnar nerve of a patient but few details were given. In a further case studied in depth by Sahgal and Olsen,¹³ MCV was 40 and 45 m/s in the ulnar and median nerves respectively. Barolin *et al*¹⁴ reported in detail the clinical features of two sisters with Refsum's disease where the MCV in the median nerves of case 1 were 45 and 50 m/s. In these latter three cases the diagnosis was supported by phytanic acid estimation. Thus Refsum's disease may present with normal or only slightly reduced MCV. In addition, the sister of case 1, that is case 2, had median nerve MCV of 23 and 27 m/s.

In our view, the above data on Charcot-Marie-Tooth disease and Refsum's disease cast serious doubts on the value of MCV as a means for "genetic" classification.

PEDRO SALISACHS

Neurological Service

Residencia Sanitaria de la Seguridad Social
Badalona, Barcelona, Spain

LESLIE J FINDLEY

The National Hospital for

Nervous Diseases

Queen Square, London

MONTERRAT CODINA

Neurological Service

Hospital de la Santa Cruz y de San Pablo
Barcelona, Spain

JOSE M MARTINEZ-LAGE

Department of Neurology

Universidad de Navarra

Pamplona, Spain

Address for correspondence: P Salisachs,
Paseo de Gracia 62, Barcelona-7, Spain.

References

- Dyck PJ, Lambert EH. Lower motor and primary sensory neuron diseases with peroneal muscular atrophy. Part 1 (Neurologic, genetic and electrophysiological findings in hereditary polyneuropathies). *Arch Neurol* 1968;**18**: 603-18.
- Dyck PJ, Lambert EH. Lower motor and primary sensory neuron diseases with peroneal muscular atrophy. Part 2 (Neurologic, genetic and electrophysiological findings in various neuronal degenerations). *Arch Neurol* 1968;**18**: 619-25.
- Salisachs P. Charcot-Marie-Tooth disease associated with "Essential tremor". Report of 7 cases and a review of the literature. *J Neurol Sci* 1976;**28**:17-40.
- Harding AE, Thomas PK. The clinical features of hereditary motor and sensory neuropathy. Types I and II. *Brain* 1980;**103**:259-80.
- Salisachs P, Codina A, Gimenez-Roldan S, Zarranz JJ. Charcot-Marie-Tooth associated with "essential tremor" and normal and/or slightly diminished motor conduction velocity. *Eur Neurol* 1979;**18**:49-58.
- Bradley WG. The nosology of peroneal muscular atrophies: Clinical, electrophysiological and pathological aspects. In: Serratrice G, Roux H, eds. *Peroneal atrophies and related disorders*. New York: Masson Publishing USA, 1979:3-14.
- Thomas PK, Calne DB. Motor nerve conduction in peroneal muscular atrophy. Evidence for genetic heterogeneity. *J Neurol Neurosurg Psychiatry* 1974;**37**:68-75.
- Myriantopoulos NC, Lane MH, Silberbert DH, and Vincent BL. Nerve conduction and other studies in families with Charcot-Marie-Tooth disease. *Brain* 1964;**87**:589-608.
- Davis CJF, Bradley WG, Madrid R. The peroneal muscular atrophy syndrome. (Clinical, genetic, electrophysiological and nerve biopsy studies.) *J Genet Hum* 1978;**26**:311-49.
- Brust JCM, Lovelace RE, Devi S. Clinical and electrodiagnostic features of Charcot-Marie-Tooth syndrome. *Acta Neurol Scand* 1978;**56**:Suppl 68: 1-42.
- Refsum S. Refsum's disease. In: Vinken PJ, Bruyn GW, DeJong JMBV, eds. *System disorders and Atrophies Vol. 21*. Amsterdam: Elsevier, 1975:181-229.
- Ulrich J, Esslen E, Regli F, Bishoff A. Die Beziehungen der Nervenleitgeschwindigkeit zum histologischen Befund an peripheren Nerven. *Dtsch Z. Nervenheilk* 1965;**187**:770-86.
- Sahgal V, Olsen WO. Heredopathia atactica polyneuritiformis. (Phytanic acid storage disease.) A new case with special reference to dietary treatment. *Arch Intern Med* 1975;**135**:585-7.
- Barolin GS, Hodkewitsch E, Horfinger E, Scholtz H, Berneheimer H, Molzer B. Klinisch-biochemische Verlaufsunter-suchungen bei Heredopathia atactica polyneuritiformis (Morbus Refsum). *Fortschr Neurol Psychiatr* 1979;**47**:53-66.

Thomas replies

Sir: Salisachs *et al* have raised some interesting questions. Essentially two points are being made. The first is that

the estimation of motor nerve conduction velocity is not a fully satisfactory way of separating the different genetic disorders that present clinically as Charcot-Marie-Tooth disease. With this I would entirely agree. The second is that the proposed separation of Charcot-Marie-Tooth disease into two or more genetically distinct types has lost credibility. With this I would not agree.

As there appears to be some difficulty in the interpretation of the available evidence, a brief recapitulation is necessary. Amongst cases diagnosed clinically as peroneal muscular atrophy are patients with distal denervation atrophy in the limbs and without sensory involvement, either clinically or electrophysiologically. These can be designated *hereditary distal spinal muscular atrophy*.^{1,2} Probably both autosomal dominant and autosomal recessive inheritance occurs.² The remaining cases display additional sensory involvement, sometimes only detectable by nerve conduction studies. These can be designated *hereditary motor and sensory neuropathy (HMSN)*.^{3,4} If median motor nerve conduction velocity in the index cases from such families is plotted against the values obtained in affected relatives, there is a highly significant positive correlation.⁵ This is strongly suggestive of genetic heterogeneity and supports the view, originally advanced by Dyck and Lambert,^{1,6} that there are two genetically different forms of the disease, one (type I) with markedly reduced nerve conduction velocity, the other (type II) with velocities within the normal range or only modestly reduced. The value of 38 m/s chosen by Harding and Thomas⁵ as a dividing line was purely empirical; it gave the best separation between the type I and II clusters in that particular series. It was evident in that study that complete discrimination could not be obtained between families whatever value was taken. Nevertheless, the number of cases misclassified was small.

The median nerve has been chosen for estimates of motor conduction velocity rather than the peroneal or tibial nerves in view of the frequency with which the small foot muscles are totally or almost totally denervated.⁷ It is of interest that using sensory conduction velocity in the sural nerve as a discriminator, Buchthal and Behse⁸ obtained complete separation between hypertrophic (type I) and neuronal (type II) cases; related patients had similar conduction velocities. The two groups thus distinguished were the same