psychiatry services; (e) early referral from nursery/infant school for children with remediable problems such as attention deficit hyperactivity disorder, dyslexia, and severe behavioural problems; (f) effective antibullying strategies in schools; and (g) strategies for prevention of teenage pregnancies.

The school health service as a whole has a potentially crucial role in the development of the above strategies. (In this context it is extremely worrying that in many areas school health services are currently under threat.) However, considerable resources will also be needed for health visiting, social services, child psychiatry, and education to reverse the low morale and near despair that years of underfunding have caused. Hopefully this will allow the professionals to recharge their batteries to the extent that they can tackle these problems effectively on a population-wide basis. It is essential that multiagency responses are coordinated so that identification of problems by health visitors, school doctors, etc can lead to effective intervention.

Important and innovative work by Davies *et al* has shown that it is possible to achieve significant improvements in families in areas of high deprivation in London.¹⁶ This programme involved extra training and supervision of health visitors and school doctors and did not require major new resources. Extending programmes like this on a nationwide basis would seem a practical way of beginning to tackle the major task we are considering.

Finally, society and professionals should face up to the fact that not all parents can respond to professional intervention to a degree sufficient to meet their children's needs. The Kempes' concept of "the untreatable family" is relevant here.¹⁷ Society and social workers accept the need to remove severely battered or sexually abused children from their natural families for good. However, society finds it harder to accept that there is a far larger number of children who suffer significant harm from neglectful parenting to their detriment and to the future detriment of society. Most of these children never even get on to an at risk register, let alone have a protection/nurture plan drawn up. Child A in the Bulger case is a dramatic example. All the features of his emotional deprivation were well known to professionals for several years before the murder yet no action was taken. There is ample evidence that the condi-

tions associated with poor parenting are becoming more widespread.¹⁸ There are strong hints that our politicians are at last waking up to the central importance of good parenting, as evidenced by the formation of the All-Party Parliamentary Committee on Parenting, and the recent document on parenting from the Labour Party.¹⁹ However, unless this leads to a coherent strategy supported by adequate resources, we seem doomed to continue current policies of "too little, too late".

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Genetic aspects of Charcot-Marie-Tooth disease

Historical perspective and nomenclature

In 1886 Drs Charcot and Marie of France and Dr Tooth of England described patients with an inherited form of peroneal muscular atrophy, characterised by a progressive weakness and atrophy of distal muscles, usually originating in the feet and lower legs and progressing to the hands and forearms—a disorder now known as Charcot-Marie-Tooth (CMT) disease. Early literature attested to the existence of several distinct disorders in addition to CMT disease, including Dejerine-Sottas syndrome (DSS) and Roussy-Lévy syndrome, but histopathological evidence combined with the advent of electrodiagnostic testing and molecular investigation have demonstrated that these syndromes are clinical variants of CMT disease.

The term CMT disease is now applied to a range of hereditary peripheral neuropathies, with a population prevalence of approximately one in 2500, which are able to be differentiated at several levels. None the less, the noso-

logy surrounding CMT disease remains confusing and is further confused by the term hereditary motor and sensory neuropathy (HMSN), introduced to describe a broad range of neurological disorders with both motor and sensory involvement.

Classification of CMT disease

NERVE CONDUCTION STUDIES AND PATHOLOGY

A major differentiating factor between the different forms of CMT disease is identified by electrophysiological examination and nerve pathology. The combined strengths of these assessments allow the subdivision of CMT disease into two major groups, termed CMT disease type 1 and type 2 (CMT1 and CMT2).^{1 2}

CMT1(HMSN1) is the more common of the two and characterised by diffusely low nerve conduction velocities (NCVs), typically <38m/s, and the appearance of "onion bulbs" on peripheral nerve biopsy due to demyelination

Table 1 Dominant type 1 and 2 CMT neuropathies. Where known, the genetic location, gene responsible, and genetic defect are indicated

Peripheral neuropathy	Clinical features		Inheritance*	Genetic location	Gene	Genetic defect
	Nerve pathology	NCVs				
CMT1A	Demyelinating/onion bulbs	Reduced	AD	17p11.2	PMP22	Duplication/point mutation
CMT1B	Demyelinating/onion bulbs	Reduced	AD	1q21-q23	P ₀	Point mutation
CMT1C	Demyelinating/anion bulbs	Reduced	AD	Unknown	Unknown	Unknown
CMT2A	Axonal	Preserved or slightly reduced	AD	1p35-p36	Unknown	Unknown
CMT2B	Axonal	Preserved or slightly reduced	AD	3q13-q22	Unknown	Unknown
CMT2C	Axonal	Preserved or slightly reduced	AD	Unknown	Unknown	Unknown
CMT2D	Axonal	Preserved or slightly reduced	AD	7p14	Unknown	Unknown
CMTX1	Demyelinating/onion bulbs/axonal	Reduced	XLD	Xq12-q13	Cx32	Point mutation
DSS	Hypomyelinating/onion bulbs	Severely reduced	AD	17p11.2	PMP22	Four copies PMP22/point mutation
			AD	1q21-q23	P ₀	Point mutation
			AD	8qter	Unknown	Unknown
HNPP	Demyelinating/tomaculi	Reduced	AD	17p11.2	PMP22	Deletion/point mutation

*AD = autosomal dominant; XLD = X linked dominant.

and remyelination of the nerve. CMT2 (HMSNII) on the other hand is characterised by normal or near normal nerve conduction velocities and a decreased number of myelinated axons. While there is no evidence of demyelination and remyelination in CMT2, there are signs of marked axonal degeneration.

Patients with Dejerine-Sottas syndrome (HMSNIII) have markedly reduced NCVs¹ and at peripheral nerve biopsy demyelination and onion bulb formation, similar to that in CMT1, is found in addition to evidence of hypomyelination.

CLINICAL FEATURES

The two major forms of CMT disease (CMT1/CMT2) are clinically very similar, with both motor and sensory nerve function impaired. The distal muscle weakness described above may be obvious from an early age as an abnormality of gait or clumsiness in running. Other typical features include weakness at the ankle, steppage gait, and the characteristic *pes cavus* deformity of the foot. Generally, the clinical features of DSS overlap with a severe CMT1 phenotype with patients demonstrating a chronic and progressive motor and sensory neuropathy, but with an onset usually in infancy or early childhood.

Hereditary neuropathy with liability to pressure palsies (HNPP) describes a neuropathy which causes nerve palsies and sensory dysfunction following minor nerve trauma. These palsies dissipate but a slowly progressive neuropathy is evident in patients. Nerve pathology demonstrates the typical demyelination and remyelination observed in CMT1 in addition to multiple sausage shaped focal thickenings (tomaculi) of the myelin sheath.³

Molecular basis of CMT disease

The clinical heterogeneity of CMT disease is paralleled at a genetic level, with autosomal dominant and recessive and X linked dominant and recessive families documented. Recent molecular investigations have given further insight into the heterogeneity of CMT disease and, in some instances, allowed the localisation of defective genes (table 1).

CMT1

CMT1 is acknowledged as the most common form of these peripheral neuropathies and consequently genetic linkage studies have focused predominately on these families, resulting in the identification of three subgroups of families, each with a distinct genetic locus.⁴ In each of these groups the disorder is transmitted in an autosomal dominant manner. The first subgroup, CMT1A, maps to chromosome 17p11.2 and is caused, in the majority of

cases, by a duplication of 1.5 Mb DNA, encompassing the *peripheral myelin protein 22* (PMP22) gene. The duplication is caused by unequal crossing over via two repeat sequences located at the proximal and distal end of the duplicated segment. This duplication event associated with CMT1A accounts for 70–85% of CMT1 cases. The reciprocal product of this crossover (deletion of a copy of PMP22) has been shown to be the molecular defect in the majority of HNPP cases.³ Point mutations within PMP22 may also account for a small proportion of CMT1 or HNPP cases, rather than duplication or deletion. A proportion of the remainder of CMT1 cases is accounted for by point mutations in a second myelin protein, *peripheral myelin protein zero* (P₀), which maps to 1q21-q23. This locus has been designated CMT1B. Heterozygous mutations within either of these genes have been identified in DSS patients, leading to DSS now being classed as a severe CMT1 variant.⁴

In addition CMT1 families shown not to be linked to either the CMT1A or CMT1B loci indicate that a third CMT1 gene (CMT1C) exists. No candidate region has yet been identified in these patients, but the identification of a DSS locus on chromosome 8⁵ leads one to speculate that this may represent the CMT1C locus.

CMT2

Genes associated with the axonal form of CMT disease have, to date, been assigned to at least three loci.⁶ Again, in each group the mode of inheritance is autosomal dominant. CMT2 has been mapped on the basis of linkage studies to chromosomes 1p35-36 (CMT2A), 3q13-22 (CMT2B) and 7p14 (CMT2D). A fourth CMT2 form, distinguished clinically on the basis of diaphragm and vocal cord weakness, in addition to an axonal neuropathy, has also been reported. This group, designated CMT2C, has been shown to be genetically distinct from CMT2A and CMT2B.

CMTX1

Clinically, X linked dominant CMT disease resembles the CMT1 phenotype—reduced NCVs and a demyelinating pathology. However, expression of the disease in carrier females is variable ranging from asymptomatic with normal NCVs to disabling manifestations with reduced NCVs.

Linkage studies placed the X linked dominant CMTX locus in a 1 cM interval at Xq12-13.⁷ Several candidate genes from this region were proposed and sequence changes were identified in the coding region of *connexin32* (Cx32) in seven out of eight CMTX patients.⁸ The demonstration of Cx32 expression in the peripheral nerve⁸ and identification of additional mutations in other CMTX families,⁹ confirmed Cx32 as the causal gene in this form of CMTX, designated CMTX1.

Figure 1 Schematic representation of the distribution of the myelin proteins PMP22, P_0 , and Cx32. PMP22 and P_0 are both transmembrane proteins located in compact myelin. Cx32, also a transmembrane protein, is located in the non-compact portion of the myelin. The tetrameric arrangement of the P_0 extracellular domains is shown, and the extracellular heterophilic interaction of P_0 and PMP22 and the homophilic P_0 interaction are depicted by asterisks. The double headed arrow depicts the hypothesized movement of metabolites through Cx32 between the myelin layers.

OTHER CMT DISEASE LOCI

The recessive forms of CMT disease have received less attention than the dominant forms due, in part, to the observed heterogeneity and subsequent difficulties in defining a clinical phenotype. Several distinct loci have been indicated by linkage studies, but there is currently no evidence to suggest that any of the genes involved in CMT1 or CMTX1 are responsible for either X linked or autosomal recessive cases of CMT disease.

Schwann cell biology

The CMT disease genes identified to date are expressed in Schwann cells, which associate with axonal elements and wrap layer after layer of themselves around the axon to form the myelin sheaths, thereby enhancing NCVs.

SCHWANN CELL PROLIFERATION AND DIFFERENTIATION

Proper Schwann cell development and myelination necessitates Schwann cell proliferation and differentiation, events which have been shown to be induced by axonal contact—an effect mimicked by raised cAMP levels.¹⁰ Recent evidence has attributed this mitogenic effect of axons to a family of Neu differentiation factors.¹¹ Following association with axonal segments, Schwann cell differentiation, that is the expression of myelin genes such as P_0 , PMP22, and Cx32 occurs. However, the key factors involved in the timing of their expression are unknown.

Interestingly PMP22 and Cx32 are expressed in both neural and non-neural cells, facilitated by alternative promoters.^{12–13} Each promoter drives the expression, although not exclusively, of a particular transcript in different cell types. In vitro studies of PMP22 gene expression have shown that both neural and non-neural transcripts are induced to an equal extent by an increase in cAMP. Yet in vivo, myelination is allied with the upregulation of the neural transcript, out of proportion to the non-neural form.¹² The intrinsic factors involved in this selective control are as yet undefined, although transcription factors similar in effect to *Krox-20* and *Oct-6*, which have been suggested to have a role in early myelinogenesis,¹¹ may be involved.

The functional significance of these multiple promoters is unclear but conceivable that they are indicative of alternative functions—perhaps one being related to cell growth in early development, and a second in myelin structural integrity of mature Schwann cells.

FUNCTION OF THE MYELIN PROTEINS

The myelin proteins MBP, MAG, PMP22, P_0 , Cx32 all play a part in the maintenance of myelin integrity (fig 1), but for the sake of brevity in this article only those associated with CMT disease to date are discussed here. P_0 is a major integral myelin membrane protein, traversing the membrane once, and mediates membrane adhesion in the concentric myelin wraps. The adhesive properties of the protein are attributed to the extracellular domain of P_0 which forms a tetrameric array that interlocks with similar arrangements in the opposing membranes, and a homophilic cytoplasmic interaction.¹⁴ P_0 is also thought to partake in a heterophilic interaction with the transmembrane protein PMP22 via the L2/HNK-1 epitopes of their glycosidic links.¹⁵ The suggested role of these proteins in the compaction of myelin has been validated by the generation of various knockout mouse models that demonstrate poor myelin compaction, accompanied by axon degeneration and signs of demyelination.^{16–18}

In addition to its structural role it has also been suggested that PMP22 plays a part in cellular growth, primarily due to its down regulation after nerve damage.¹⁹ Whether this is directly related to a cell growth phenomenon or the return to a “dedifferentiated” state of the cell is unknown. However, the role of PMP22 in cellular growth must still be considered, especially in view of the alternative transcript that predominates in non-neural cells.

The gap junction protein Cx32 has been localised to the paranodal regions and Schmidt-Lantermann incisures of myelin,⁸ and believed to function as a channel for the transport of electrolytes and metabolites between the myelin wraps of an individual cell. This trafficking of molecules is also considered to extend to the axon.

Effect of myelin gene defects at the phenotypic level

OVEREXPRESSION OF *PMP22*

The most common genotypic defect in CMT disease is the duplication of the *PMP22* gene and its subsequent overexpression. On peripheral nerve biopsy these patients typically show evidence of demyelination and remyelination, onion bulb formation, and Schwann cell proliferation. Mouse models of the CMT1A phenotype have shown that overexpression is indeed involved, and demonstrate that with an increasing copy number of *PMP22* the effects are exaggerated and the phenotype more severe.^{20, 21} In these cases, it is hypothesised that myelination is initiated, but a breakdown in the process occurs, leading to the continued demyelination and remyelination typical of CMT1. This breakdown in the homeostatic control may be caused by the inherent overexpression of *PMP22*, which prevents the cells from differentiating further and in turn, lead to the apoptotic-like cells observed by Fabretti *et al.*²² Alternatively, the hypothesised increased proportion of *PMP22* within the cell membrane may upset protein stoichiometry and hence the structural integrity of the myelin, leading to its degeneration. Both hypotheses would account for the observed Schwann cell proliferation as macrophage mediated myelin degeneration has been shown to have such a mitogenic effect.²³ That no effects are noted in non-neural cells is interesting. Perhaps the effects of this overexpression are not detrimental to the cell, or alternatively, a functionally analogous protein compensates.

UNDEREXPRESSION OF *PMP22*

The exaggerated phenotype observed with increasing copy number is conversely duplicated, with a decreasing copy number. Knockout mouse models of *PMP22* have shown that the double copy knockout model is more severely affected than the heterozygous mouse.¹⁸ Although no patients with the deletion of both *PMP22* copies have yet been observed, a similar effect would be envisaged.

POINT MUTATION WITHIN THE MYELIN GENES

The effect of this type of defect in *PMP22* appears to be more severe than overexpression of the gene, both in human and animal models. Mutations of the *P₀* gene also appear to result in a severe phenotype. Even within this class, a spectrum of phenotypes is observed and considered to be due to the effect of the mutation—whether a loss of, or dominant negative gain of, function is afforded by the corresponding mutant protein, which in turn yields further phenotypic heterogeneity depending on the actual site of the mutation.

The mechanisms by which the defects in *PMP22* and *P₀* lead to characteristic CMT1 phenotypes will be similar to that described above. *Cx32* defects, on the other hand, have been shown to result in improper gating abilities of the connexin hemichannels,²⁴ theoretically leading to deficiencies in intracellular transport of metabolites, and in turn to Schwann cell degeneration and possibly to the observed axonopathy evident in CMTX1 patients.

In contrast to coding region defects of myelin genes, the first evidence of mutations within the promoter sequences (of *Cx32*) has been reported.²⁵ One of these mutations is thought to affect the rate of transcription initiation, while the second may create a new splice site motif or alternatively, a new translation start codon. However, the actual effect of these and similar promoter mutations requires further investigation.

Molecular diagnosis and prospects for the future

The molecular diagnosis of the peripheral neuropathies is a complex procedure and its success depends on various fac-

Key messages

- The duplication of a 1.5 Mb DNA fragment encompassing the *PMP22* gene on chromosome 17p11.2 is associated with over 70% of CMT1 cases
- Point mutations of the *PMP22*, *P₀*, and *Cx32* genes are also associated with the CMT1 phenotype
- *PMP22* and *P₀* encode myelin proteins which have important roles in the compaction of myelin. *Cx32* encodes a gap junction protein which is considered to allow trafficking of metabolites and secondary messengers between the non-compact layers of myelin. Murine models have validated the hypothesised roles of these proteins
- CMT disease is extremely heterogeneous, with at least eight additional loci identified. No genes have as yet been identified at these loci

tors including knowledge of family history, availability of local clinical testing, and the resources of the diagnostic laboratory. Where possible, clinicians should provide full clinical details including nerve conduction velocities and a detailed family history. Unless there is evidence to suggest a type 2 phenotype, *PMP22* duplication testing is the initial screen in CMT disease diagnosis as it accounts for over 70% of CMT1 cases. If no duplication is observed and there is no recorded male to male inheritance in the patient's family history, then *Cx32* screening follows as this represents the second most common genetic defect in CMT disease to date. Individuals referred with no obvious family history would be investigated likewise.

Mutation screening of *P₀* then *PMP22*, is the natural next step for patients shown to have no *Cx32* defect and/or no observed duplication. However, due to time and monetary constraints of diagnostic laboratories, combined with the somewhat low detection rate, these screens are often only performed within research programmes.

Now that the molecular basis of several neuropathies has been elucidated, research based on this new knowledge can aid in understanding the actual pathogenic mechanisms. Although to date, there is no effective treatment for alleviating the symptoms of CMT disease, these and similar studies will undoubtedly accelerate progress towards the goals of therapeutic medicine. Indeed, a canine model has shown that focally transplanted glial cells are capable of myelinating areas of the central nervous system,²⁶ a situation comparable to the focal lesions observed in multiple sclerosis, thus inferring hope for the future in the treatment of multiple sclerosis and other disorders of myelination.

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