

The CMTA Report

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A resource for information on Charcot-Marie-Tooth disease (Peroneal Muscular Atrophy or Hereditary Motor Sensory Neuropathy), the most common inherited neuropathy.

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Leading the Way in CMT Research

By **ANN LEE BEYER,**
Chairman and President

Because of YOUR generous support, the CMTA has become the world leader in fostering and supporting CMT research. During the last decade there have been more advances in CMT research than in the previous one hundred years, as a result of our efforts.

Our strength lies in our ability to bring CMT clinicians and researchers together for scientific meetings. Although we are a small and relatively young organization, we have already sponsored two international symposia on CMT disorders. Given the number of significant breakthroughs and publications that occurred after these meetings, we know that the CMTA is a major player in CMT research.

We are also one of the very few organizations that fund CMT research. Of particular importance are the genetic breakthroughs. It is now known that there are at least seventeen genetic causes of CMT, and the locations of many more have been identified. These discoveries have led to the development of diagnostic tests for several types and subtypes of CMT, not only providing many patients with a firm diagnosis, but also giving family members information about their risk of inheritance.

At the same time, significant progress is being made in understanding the molecular biology (what goes on in the structure and development of the nerves) of CMT, as well as

the clinical manifestations of our disease (see poster info, page 8).

In spite of the advances, however, research is still in its infancy and much about CMT remains a mystery—making accurate diagnosis difficult and hindering the search for better treatments and a cure.

Continuing our role as a world leader in fostering and supporting CMT research, the CMTA has initiated two ground-breaking programs: The CMT North American Database, which was launched in 2001, and The North American CMT Consortium, the first meeting of which will take place in London, Ontario March 7th-8th, 2003.

Thanks to a challenge grant from the Buuck Family Foundation, the CMTA Database project was put into effect in 2001, and is one of our most exciting research projects to date. The purpose of the database is to put together a standardized collection of clinical, genetic, and family information about a large number of people with all types of CMT. Having this information will provide clinicians and

researchers with a better understanding of the complete range of symptoms that accompany CMT, making it easier to diagnose and develop treatments. Only when we can fully understand CMT—in all of its complexities—can we develop treatments or look for a cure.

In addition, the Buuck Family Foundation has also presented us with a challenge grant to establish the CMT North American Consortium.

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Continuing our role as a world leader in fostering and supporting CMT research, the CMTA has initiated two ground-breaking programs:
The CMT North American Database and The North American CMT Consortium

The CMTA.... Living our Mission

Mission Statement:
To improve the quality of life for people with CMT and to find a cure.

Vision Statement:
A world without CMT.

LEADING THE WAY

(Continued from page 1)

The goal of this annual meeting is two-fold: to foster dialogue and collaboration between CMT researchers and clinicians in North America, and to hold a joint meeting every third or fourth year with our European and Australian Counterparts. The Europeans and Australians are in the process of developing their own CMT databases, so the amount of information available to CMT researchers and clinicians will be incredible.

The Buuck Family Foundation has generously provided the seed money for the first database year. Their challenge to us is to raise \$200,000 to cover expenses for years two and three.

However, their challenge is really a double challenge. The information gained from the databases and the consortium meetings is going to generate more research proposals. Our task will be to show the Buucks that we care enough to also raise the research money to support the grants that emerge from these new programs.

Can we do it? With your support, absolutely!

Even though our \$35,000 postdoctoral research projects have accounted for many advances in CMT, they are very small grants,

If anyone has any fundraising ideas that they would be willing to share, or if anyone would be interested in running a golf tournament, please call the office at 1-800-606-2682 and speak to the Executive Director, or Dick Sharpe for golf tournaments.

indeed. Members of our Medical Advisory Board tell me that we are going to need to be able to fund larger grants, and that we will need an infusion of several million dollars to get to the point where clinical trials might become possible.

All of us on the CMTA Board of Directors are affected by CMT. We want a cure as much as you do. Everyone on the board contributes to the financial support of the CMTA. Some make significant contributions and hold fundraisers, too.

Treatments or cures are still many years away, and they will not come directly from large pharmaceutical companies. The designation of "rare" or "orphan disease" relegates CMT to the bottom of their list—even though it affects up to 200,000 people in the United States, alone.

They will probably come from small startup neuro-genetics companies, but we have to raise enough money to fund the research studies that will provide the impetus for these firms to get involved in CMT research.

Please join us in our mission to cure CMT. Without your continuing generous financial support, treatments or cures will not happen. We are all in this together, and together we will make a difference. Please give generously so we can continue our work.

The CMT North American Database....an Update

When the CMT North American Database was established, the governing body decided on goal numbers of enrollees. For the first year, the goal was to have 250 patients entered in the database at Indiana University. For the second year, they hoped the total would be 500 and for the third year, they hoped to achieve 1000 names in the database.

As of May 13, 2002, Raven Lewis was pleased to report that 132 names are entered, with their forms being completed and verified. 114 patients have completed forms and are pending with one or more details of their applications not yet verified. That totals 246 entries for the first year, just 4 patients short of the goal. That is excellent, but anyone who has not yet completed the form is asked to do so. As the first year ends, it's important that patients remain committed to filling out the survey form and becoming part of this important effort.

If you have not yet requested a database packet from the CMTA office, please do so by calling 1-800-606-2682. There is some effort required to complete the survey, but the benefits to the CMT community far outweigh the effort.

CMT NORTH AMERICAN DATABASE FAMILY HISTORY QUESTIONNAIRE

Date: _____ How did you hear about the database? _____
 Local genetic testing and a packet was sent to the referring physician from Indiana University
 CMT International
 CMT Assoc Canada
 Wayne State University Website
 MDA Website
 Other: _____

To complete this questionnaire, one person in the family is identified as the SOURCE PERSON. This person must have Charcot-Marie-Tooth disease (CMT). All other persons in the family are identified in terms of their relationship to the SOURCE PERSON (i.e., all questions will be asked about the SOURCE PERSON's siblings, parents, etc.). The source person may not be the person who is completing the questionnaire and therefore we ask information about the person who fills out the questionnaire. If other family members are completing a questionnaire there may be more than one SOURCE PERSON in a family.

Please complete the questionnaire as thoroughly as possible. Please do not let this fact that you cannot answer some questions in that some portions do not apply to you, keep you from answering the questionnaire. We are interested in any information you can provide. For all names that are listed, please use their maiden names.

Person completing this family history questionnaire:
 Name: First _____ Last _____
 Address: _____
 City: _____ State: _____ Zip: _____
 Daytime #: _____
 Sex: M F Other _____
 Date of Birth: _____
 Living: Yes No

SECTION A: Information about the SOURCE PERSON

Name: First _____ MI _____ Last _____
 Address: _____
 City: _____ State: _____ Zip: _____
 Daytime Phone #: _____
 Date of Birth: _____
 Living: Yes No

If deceased, date and cause of death: _____
 Ethnic Origin, please check: American Indian Asian Black
 Hispanic White Other, please describe: _____

Spouse of Source Person: First _____ MI _____ Last _____
 Date of Birth of Spouse: _____
 Living: Yes No
 If deceased, date and cause of death: _____

CMTA Launches North American CMT Consortium

The first meeting of the newly formed North American CMT Consortium will be held March 7th and 8th, 2003, at the Spencer Conference Centre, London, Ontario, Canada. The two-day symposium will feature presentations by North American CMT investigators on molecular biology, genetics, neurophysiology and the clinical manifestations and issues of CMT.

The consortium concept is based on the successful European model and its purpose is to foster collaborations among clinicians and researchers doing different types of CMT research. The consortium will meet annually at a central location in North America. The cost of the meeting will be minimized by having the researchers pay for their own lodging, meals and travel. Because of that, CMTA research funds will not be used to support these meetings.

The CMTA will receive abstracts from all investigators wishing to present their work and will collate those abstracts into a book to be distributed to attendees. One person each year will be invited from outside North America to give the plenary lecture at the beginning of the meeting. This year, a representative of the European consortium will be invited to open the session.

Every third year, an International meeting, combining the North American consortium, the European consortium and all "national" CMT organizations, like the CMTA, the Australian group and others, will be held, with expenses being paid by the investigators. It is projected that the next international meeting will be hosted by the European Consortium in two years.

Dr. Angelica Hahn and Dr. Michael Shy, members of the CMTA's Medical Advisory Board, are the organizers and hosts of the first North American meeting. The establishment of the CMT Database at Indiana University was instrumental in paving the way for the collaboration of this consortium.

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Members who are current with their dues are considered "active."
If you are unsure as to whether you are current with your member dues, please call the office at 1-800-606-CMTA.

	QTY	COST	TOTAL
Charcot-Marie-Tooth Disorders: A Handbook for Primary Care Physicians		active members \$15 inactive members \$20	
Membership Dues		\$35	
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CMT Facts I <input type="checkbox"/> English <input type="checkbox"/> Spanish		active members \$3 inactive members \$5	
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CMT Facts III		active members \$5 inactive members \$7	
CMT Facts IV		active members \$8 inactive members \$10	
A Guide About Genetics for the CMT Patient <i>No shipping and handling on this item only.</i>		active members \$4 inactive members \$5	
CMTA Canvas Tote Bag		\$10	
CMT Informational Brochure <input type="checkbox"/> English <input type="checkbox"/> Spanish		FREE	
Physician Referral List: States: _____		FREE	
Letter to Medical Professional with Drug List		FREE	
Contribution to CMT Research <i>10% will be applied to administrative expenses.</i>			
Shipping & Handling <i>Orders under \$10 add \$1.50, orders \$10 and over add \$3.00</i>			
TOTAL			

Check payable to the CMTA (US Residents only).
Foreign residents, please use a credit card or International Money Order.

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A copy of the official registration and financial information may be obtained from the Pennsylvania Department of State by calling, toll-free, within Pennsylvania, 1-800-732-0999. Registration does not imply endorsement.

Research Prospects in Charcot-M

Between 18 months and 2 years ago, the eminent British neurologist and neuromuscular scientist, Dr. Peter K. Thomas, provided this very insightful discussion of where we are now with CMT and where we should be heading, for the use of our Medical Advisory Board. It has been crucial in the way we have planned our actions and in the areas we have supported, and since it has not been improved on and is still very pertinent, we are honored to reprint it in our newsletter. Many of the things he forecast have occurred and he (with local authors) has published an elegant description of the complex dysmorphic variety of CMT found in Balkan gypsies. The genes for HMSN Lom and a number of CMT2 genes have been described; a special session of the European (Italian) Society of Myology was devoted to CMT, including our work with laryngeal involvement. The European Consortium has had several meetings describing the new research and we are planning our own North American Consortium next year. To help our understanding of progress of disability and the natural history of the various forms of CMT as well as to facilitate research, the National Database has been established and supported heavily by CMTA. An additional therapy we may need to consider in the future is the use of stem cells. In fact, we should work hard to stop stem cell research being shelved and setting research on new treatments back years or even decades. —Robert E. Lovelace, MD, FRCP

By PETER K. THOMAS, MD

The opportunities for effective research into CMT disease are now greater than at any time. This is the result of detailed clinical analysis in combination with molecular genetic and neuropathological studies and the use of naturally occurring mutations and induced transgenic models in animals. The following areas have been selected as those of greatest promise, although many other avenues could be included.

AUTOSOMAL DOMINANT TYPE 1 CMT DISEASE

Charcot-Marie-Tooth disease 1A (CMT1A) is due either to point mutations in the gene for peripheral myelin protein 22 (PMP22) or to a segmental duplication on chromosome 17p11.2 leading to the presence of an extra copy of the PMP22 gene. The latter is by far the most common form of CMT disease and has been shown to be due to over-expression of the gene.

An important question that requires solution is the normal function of PMP22. It is known to act as a growth arrest protein and to be involved in cell differentiation and maintenance. PMP22 is also known to be present, in relatively low concentrations, in myelin, where its function is still uncertain. Which function is implicated in the causation of CMT1A is not

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Charcot-Marie-Tooth Disease

established. The best opportunity for investigating the normal function of PMP22 lies in animal models. Spontaneous mouse mutants with point mutations in the PMP22 gene are available, Trembler and Trembler-J (Tr and Tr-J) and models have been produced in mice and rats, either gene knockouts or by the insertion of extra copies of the PMP22 gene into the animal genome. A demyelinating neuropathy is produced. In the Tr mouse, cell biological studies have indicated abnormal trafficking of PMP22 in Schwann cells, the cells that produce myelin, but the role of PMP22 in the causation of the demyelination is still uncertain.

The disorder hereditary neuropathy with liability to pressure palsies (HNPP) is usually due to a segmental deletion on chromosome 17p11.2 resulting in a loss of one copy of the PMP22 gene. A particular feature in the nerves of patients with this condition is the presence of sausage-like myelin swellings (tomacula). These are not specific for this disorder, although they are particularly numerous in HNPP.

Charcot-Marie-Tooth disease 1B (CMT1B) is due to mutations in the gene for myelin protein zero (P_0). Here it is easier to envision the reason for the demyelination, as P_0 constitutes the major protein of myelin. By homophilic interaction (i.e., linkage between opposing P_0 molecules), it is responsible for the formation of the major dense line of myelin.

Although demyelination is the most dramatic feature in the peripheral nerves in CMT1A and 1B, accounting for the marked slowing of nerve conduction, it is not responsible for the disability experienced by the patients which is the result of axonal loss. Thus, patients can have generalized slowing of nerve conduction, indicating widespread demyelination, but at the same time have no disability. Weakness is associated with loss of axons, indicated by the finding of evidence of denervation on electromyography. The cause of this axonal loss is one of the most pressing questions requiring solution. It is important not only for CMT disease, but also for other demyelinating neuropathies, both inherited and acquired. One possibility could be a lack of trophic support for axons provided by Schwann cells. Nevertheless, treatment (see later) might be achieved by preventing demyelination or by the provision of appropriate growth factors.

DEJERINE-SOTTAS DISEASE

This title has been given to patients with a childhood onset of a severe mixed motor and sensory neuropathy in which the pathology combines hypomyelination (i.e., abnormally thin myelin sheaths) with axonal loss. Nerve conduction velocity is severely reduced. Although formerly thought to be of autosomal

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AND BY SCIENTISTS WHO RECEIVED GRANTS FROM THE CMTA

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RESEARCH PROSPECTS IN CMT

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recessive inheritance, it is now clear that most cases are the result of de novo (i.e., new) dominant mutations in the genes for PMP22 and P₀.

X-LINKED CMT DISEASE

This disorder again involves a combination of demyelination and axonal loss and has been shown to be due to mutations in the gene for connexin 32. Connexins are molecules that provide channels referred to as gap junctions for the movement of small molecules between adjacent cells or, in Schwann cells, probably between the portions of the cell outside and inside the myelin sheath. Again, the reason for the axonal loss is a major question for solution.

TYPE 2 CMT DISEASE

In Charcot-Marie-Tooth disease type 2 (CMT2) nerve conduction velocity is relatively well preserved. The disorder is primarily the result of loss of axons in the peripheral nerves, followed later by loss of the parent cell bodies. Both autosomal dominant and autosomal recessive varieties exist and the gene loci for three autosomal dominant forms have been found, although the

responsible genes have not been identified. Attempts to establish the nature of the genes are being undertaken in several laboratories. Once achieved, the findings should provide indications as to the mechanism of axonal loss.

Occasional families with mutations in the P₀ gene resemble CMT2 in that nerve conduction velocity is only modestly reduced and the changes on nerve biopsy indicate axonal loss with little associated demyelination. It is important that mutations in a gene coding for a major myelin protein can at times lead mainly to axonal loss, indicating the close association between Schwann cell function and the maintenance of axonal integrity.

OTHER RESPONSIBLE GENES

Mutations in the early growth response gene 2 (EGR2) have been shown to result in a range of phenotypes (congenital hypomyelination neuropathy, Dejerine-Sottas disease and a Charcot-Marie-Tooth picture). Recently, the gene for hereditary motor and sensory neuropathy Lom (HMSNL) has been identified, although the findings have not yet been published. This is an autosomal recessive demyelinating disorder in which a Charcot-Marie-Tooth phenotype is combined with deafness. Elucidation of the mechanism of the neuropathy in these condi-

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tions will provide further insights into the control of myelination. Additionally, the genes encoding several of the autosomal recessive forms of CMT disease, including ganglioside-induced differentiation-associated protein-1 (GDAP1) form 4A and L-periaxin (4F), have been indentified.

'COMPLEX' CMT DISEASE

There have been reports of patients with the CMT phenotype in association with additional features such as optic atrophy, pigmentary retinopathy, palmar-plantar keratosis, etc. A complex disease termed the congenital cataracts facial dysmorphism neuropathy (CCFDN) syndrome has recently been described in Balkan gypsies. These disorders are likely to involve novel genes and their elucidation may well illuminate disease mechanisms in CMT disease as a whole.

SUPERIMPOSED INFLAMMATORY NEUROPATHY

Some patients with CMT disease who show acute deterioration have been found to respond to treatment with corticosteroids. It has been proposed that in such cases there is a superimposed autoimmune inflammatory neuropathy resembling chronic inflammatory demyelinating polyneuropathy (CIDP), a chronic variant of the Guillain-Barre syndrome (GBS). This phenomenon has so far not been adequately explored. It has recently been shown that antibodies to PMP22 are present in a proportion of patients with GBS and CIDP and that inoculation of PMP22 into experimental animals produces a neuropathy, experimental autoimmune neuropathy (EAN), that is a good animal model for the GBS.

TREATMENT

So far the treatment of CMT disease has been restricted to the provision of orthotic appliances, connective surgery and supportive measures. Advances in molecular genetics have now opened up exciting prospects for more fundamental treatment which will initially have to be explored in animal models. The following are the two most important areas:

Gene therapy for CMT1A

As this disorder is most commonly due to excessive gene expression, measures have to be devised to reduce this. As already mentioned, transgenic animal models are now available with a demyelinating neuropathy related to the intro-

duction of extra copies of the PMP22 gene into the mouse genome. The over-expression could be repressed by the delivery of antisense oligonucleotides, by DNA constructs for the expression of antisense mRNA, or by ribozymes to the Schwann cells.

Prevention of axonal degeneration

On the assumption that axonal degeneration in demyelinating CMT disease is the result of a lack of growth factor support by Schwann cells, growth factors or DNA constructs expressing growth factors could be provided by inoculation into the target organ, i.e. muscles. The growth factors would then be taken up by motor axons and translocated back to their parent cell bodies by retrograde axonal transport. Prevention of axonal loss could be studied either in Tr or Tr-J mutants or in transgenic animals. Suitable growth factors for study would be brain-derived nerve growth factor (BDNF) or insulin-like growth factor 1 (IGF1) or glial-derived neurotrophic factor (GDNF).

SUMMARY

A selection of suitable projects for investigations can be listed as follows. Some are likely to produce results in the short term; others, such as establishing the cause for axonal loss in CMT disease, are likely to be more long-term, but are clearly vital for understanding CMT disease and devising effective treatment.

1. Investigating the normal function of PMP22 in Tr and Tr-J mutants and in PMP22 knockout and transgenic mice.
2. Investigating the treatment of demyelinating CMT disease by genetic manipulation in transgenic animal models of CMT1A.
3. Establishing the cause of axonal loss in demyelinating CMT disease by the use of animal models.
4. Trials of growth factors for preventing axonal loss in animal models.
5. Seeking novel genes for other forms of demyelinating CMT disease.
6. Establishing the genes responsible for type 2 CMT disease.
7. Characterizing complex CMT syndromes and identifying the responsible genes.
8. Immunological studies in patients with a possible inflammatory neuropathy superimposed on CMT disease.

Spreading the Word about CMT...

On the Road with President/Chairman, Ann Beyer

The period from the middle of April through the middle of May was a very busy time.

In mid April, I flew to Denver to set up and staff a booth at the American Academy of Neurology meetings, where, along with distributing information on CMT and the CMTA, I had the opportunity to attend our Medical Advisory Board meeting and some of the sessions and speak with a number of researchers and clinicians.

The flyers that were distributed about our first annual North American CMT Consortium meeting generated a great deal of interest and excitement. Even though the meeting is ten months away, we already are receiving registrations.

THE POSTER SESSIONS

At the American Academy of Neurology and other meetings, researchers have two venues for delivering reports on their research—poster or oral presentations. The advantage of presenting in a poster session is that the researcher gets the opportunity to talk about his or her work in one-on-one conversations with other attendees.

This year, there were a number of posters that dealt with various aspects of our disease. One of the topics for presentation and discussion addressed possible treatments, others addressed CMT1, CMT1B, CMT2, CMTX, and HNPP.

Dr. Victoria Lawson explains her poster presentation to Ann Beyer at the AAN meetings.



Several of the poster presentations have significant implications for us. To keep you informed about the most up-to-date information on CMT, I have included a copy of the poster titles, the authors' names, the objectives and conclusions of the studies, as well as a brief, user-friendly explanation of the studies. These excerpts are taken from the abstract supplement (*Neurology* 58 April 2002 Suppl 3) from the American Academy of Neurology meeting.

The first poster on the list has particular significance for all of us affected by CMT, because it offers hope that, one day, when researchers gain a more complete understanding of the molecular biology of CMT, nerve regeneration may indeed become a reality. I put this first, because as we all know, potential treatment options for CMT are rarely discussed in CMT research.

Impaired Regeneration in Trembler Mice:

Effects of Neurotrophin-3 Treatment.

Zarife Sahenk, Lei Chen, Inga Kakabadze, Columbus, OH.

Purpose: To determine the effects of the PMP 22 point mutation causing the Trembler J (Tr-J) phenotype upon axonal regeneration and associated myelination, and whether or not neurotrophin-3 (NT3) improves this process or correlates with the RNA expression levels of NT3 and TrkC during regeneration.

Conclusions: Peripheral nerve regeneration in Tr-J is severely impaired. This impairment is associated with decreased levels of TrkC expression in the distal stump, which might play a role in defective regeneration. NT3 treatment improves regeneration (p.A375).

The next four studies show that your research dollars do make a difference. All of them have been supported by grants from the CMTA. They also demonstrate some of the complexities of Charcot-Marie-Tooth disease.

The *Disease Severity and MPZ-Mediated Adhesion in CMT1B* poster provides a clear example of what researchers and clinicians are up against, as it shows that while myelin protein zero (MPZ) can cause CMT1B, it is also responsible for Dejerine Sottas—a severe recessive form of CMT that appears in infancy.

In addition, CMT1B can mimic CMT2. Some patients who appear to have CMT2 because their nerve conduction velocities are normal or near normal, actually have a milder form of CMT1B. Why this occurs is not yet understood.

Disease Severity and MPZ-Mediated Adhesion in CMT 1B.

Agnes J Ascadi, Karen M. Krajewski, Detriot, MI, Mena Scavena, Wilmington, DE, Richard A. Lewis, John Kamholz, James Y. Garbern, Michael E. Shy, Detroit, MI.

Objective: To utilize genotype-phenotype correlations in patients with mutations in the major myelin protein zero (MPZ) to determine how mutations cause neuropathy.

Conclusions: Our results suggest that mutations which severely disrupt the extracellular domain's ability to form cis and trans interactions necessary for adhesion prevent myelin compaction and cause severe disease in infancy. Mutations which permit compaction, even if they subsequently disrupt adhesion in a limited fashion, cause milder neuropathies, including the so-called CMT2 forms of the disease (p.A377).

Like other types and subtypes of CMT, HNPP has not been defined well. A *Phenotypic Study of Hereditary Neuropathy with Liability to Pressure Palsies* fits in beautifully with Maureen Horton's article on page 12.

A Phenotypic Study of Hereditary Neuropathy with Liability to Pressure Palsies.

Jun Li, Karen M. Krajewski, Michael E. Shy, Richard A. Lewis, Detroit, MI.

Objective: To prospectively evaluate the phenotypic spectrum of hereditary neuropathy with liability to pressure palsies (HNPP).

Conclusions:

1. Our HNPP patients all have a similar phenotype, most easily explained by focal damage to nerves or plexus.
2. We have not seen isolated carpal tunnel syndrome (CTS) in our HNPP patients clinically or electrophysiologically. We, therefore, do not recommend screening for the PMP-22 deletion in patients with isolated CTS.
3. Preventing or minimizing focal trauma or compression to susceptible nerves may prove effective in managing patients with CTS. Correlations with other laboratory tests will also be discussed (A375).

Motor Unit Number Estimation in Charcot-Marie-Tooth Disorder.

Victoria H. Lawson, A. Gordon Smith, Mark B. Bromberg, Salt Lake City, UT.

Objective: Demyelinating Charcot-Marie-Tooth disorder (CMT) is thought to cause distal predominant weakness as a result of axonal loss. We sought to quantify the extent of axonal loss in the proximal and distal upper extremity of patients with demyelinating (CMT1) and axonal (CMT2) inherited neuropathy using a technique

of motor unit estimation (MUNE). MUNE was correlated with strength measurements from the hand muscle from which estimates were derived. Electromyographic data were gathered from the same hand muscle. MUNE, EMG data and strength measurements were compared to data obtained from control subjects.

Conclusions: As hypothesized, distal and proximal axonal loss occurs in CMT, but is greater distally and in the axonal subtype. The larger ratio obtained in CMT2 subjects probably represents the greater relative distal axonal loss in CMT2, confirming this to be a length-dependent axonopathy. The correlation between ADQH and ADQH MUNE is significant but not as robust as expected. The absence of evidence for significant proximal reinnervation in CMT1A may be due to sampling bias or may reflect a defect in reinnervation (p.375-376).

Motor unit number estimations are a way to look at how many nerve fibers are going to a given muscle.

The following CMTX studies are extremely important for families that may have the Connexin 32 mutation.

There has been a long-held assumption that women with X-linked diseases are generally asymptomatic carriers or mildly affected. The *Women with CMTX* study shatters this premise, as it clearly reveals that females with CMTX can be more severely impaired than affected male family members. It also reports that there is a yet unexplained wide range of variability in these women, and proposes that in families where male-to-male transmission is absent, Cx32 mutations should be considered.

Women with CMTX

Karen M. Krajewski, Richard A. Lewis, Jun Li, James Y. Garbern, John A. Kamholz, Michael E. Shy, Detroit, MI.

Objective: To describe the phenotypes of women with CMTX.

Conclusions: Females with Cx32 mutations typically develop clinically significant peripheral neuropathies that may be more severe than their affected male family members. As with males, their disease correlates more with axonal loss than demyelination. Unlike males, their disability does not correlate with age. While skewed X-inactivation or allele-specific interactions in Schwann cells expressing mutant Cx32 may contribute to disability in females, Occam's razor suggests that one single mechanism is unlikely to explain the variability in the phenotype of affected women. Cx32 mutations should be considered in the differential of females with inherited

(continued on page 10)

CORRECTION

In the last issue of the newsletter, the American Association of Acupuncture and Oriental Medicine was listed with an incorrect phone number. They can be reached now at 1-888-500-7999 or 610-266-1433. You can also access their information by going to their website at www.aaom.org. At the website, you can type in your zip code and find out the names of certified acupuncturists in your area. (Please remember that the CMTA does not endorse any form of alternative medicine and provides these details as information only.)

SPREADING THE WORD

(Continued from page 9)

neuropathies in the absence of male-to-male transmission in the kindred (p. A376-377).

The following CMTX case report of two patients may seem a little frightening, both for travelers and skiers, as it points out that CMTX patients may be at risk of “developing an acute, transient, neurological syndrome when they travel to places of high altitudes and return to sea level.” However, it is not thought that this happens regularly.

Transient CNS White Matter Abnormality in X-Linked Charcot-Marie-Tooth Disease.

Michael E. Shy, Karen M. Krajewski, James Y. Garbern, Detroit, MI, Timothy F. Hoban, Ann Arbor, MI, John Kamholz, Detroit, MI, Kenneth Fishbeck, Bethesda, MD, Hank L. Paulson, Iowa City, IA.

Objective: To demonstrate transient CNS abnormalities in patients with Charcot-Marie-Tooth type X (CMTX).

Conclusion: These two cases suggest that CMTX patients are at risk for developing an acute, transient, neurological syndrome when they travel to places at high altitudes and return to sea level. The syndrome is characterized by profound symmetrical ataxia, weakness and dysarthria. CMTX mutations probably cause CNS dysfunction by reducing the number of functioning gap junctions between oligodendrocytes and astrocytes, making both cells more susceptible to abnormalities of intercellular exchange of ions and small molecules in situations of metabolic stress (p.A376).

All of the above studies also point out the need for more research.

THE MEDICAL ADVISORY BOARD MEETING

While there, I also attended the CMTA Medical Advisory Board meeting. We are very fortunate to have a very committed group of members on this board, and they have been quite busy.

Dr. Tatiana Foroud, from Indiana University, and Dr. Michael Shy, of Wayne State, presented a program and chaired a lively discussion on the CMT North American Database.

Dr. Jack Petajan, University of Utah Medical School and Dr. Lisa Baumbach, University of Miami, have completed their review of the Physicians' Handbook, and have recommended several new chapters.

Dr. Angelika Hahn, Department of Clinical Neurosciences, London (Ontario) Health

Science Center, has made all the arrangements for the CMTA's first annual CMT North American Consortium meeting, which will take place in London, Ontario in March of 2003.

Dr. Gareth Parry, who has been on loan to New Zealand for the last several years, has put together a Task Force that will develop criteria for establishing CMTA Centers of Excellence. Their report will be ready to present at the CMT North American Consortium meeting in Canada, next March.

Dr. Florian Thomas, St. Louis University, is heading up the grant review committee.

The North American Consortium was also on the agenda and received very positive feedback.

We were very pleased to see Dr. Irena Hausmanowa-Petrusewicz, from Warsaw, who thanked us again for awarding a CMTA Fellowship to Dr. Andrez Kochanski. She reported that Dr. Kochanski is a first-rate neurologist/geneticist and has just published a paper on CMT 1B.

SUPPORT GROUP VISITS

On my way to the neurology meetings, I stopped in Lexington, Kentucky, and Wheat Ridge, Colorado, to talk to our Support Groups about our present programs, the state of CMT research, why it's in the state it's in, and our CMT North American Database and Consortium programs.

It was a pleasure to be able to meet so many of our members. Our Support Groups are one of our most important assets in our community outreach program, and our leaders are doing an outstanding job. I am thankful for the many excellent suggestions and ideas for newsletter articles, extending the CMTA's community outreach program, patient needs, and fundraising, all of which will be addressed at our next board meeting.

And last week, one of our members, Kim Salzberg invited me to attend a meeting of Welcome Wagon and present an overview of CMT to her group in Garden City, NY, because the CMTA was the recipient of their philanthropic efforts for 2001-2002.

The next morning, it was down to the CMTA office to spend a few days with our executive director and staff reviewing and discussing our programs. In addition, we also discussed a strategic planning session which will take place at our next board meeting, and what changes the implementation of this plan might mean for our staff.

Although a bit hectic, all in all it was an exciting and rewarding few weeks.

Electromyograms...

A Standard Test for CMT

Editor's Note: Electromyograms, or EMGs are often the first test done to determine if someone has CMT. This article explains why and how the test is done. The information was provided by MedicineNet, doctor produced information for patients.

An electromyogram (EMG) is a test that is used to record the electrical activity of muscles. When muscles are active, they produce an electrical current. This current is usually proportional to the level of the muscle activity. An EMG is also referred to as a myogram.

EMGs can be used to detect abnormal muscle electrical activity that can occur in many diseases and conditions, including muscular dystrophy, inflammation of muscles, pinched nerves, peripheral nerve damage (damage to nerves in the arms and legs, i.e., CMT) amyotrophic lateral sclerosis (ALS), myasthenia gravis, disc herniation, and others.

An EMG is most often performed when patients have unexplained muscle weakness. The EMG helps to distinguish between muscle conditions in which the problem begins in the muscle and muscle weakness due to nerve disorders. The EMG can also be used to detect true weakness, as opposed to weakness from reduced use because of pain or lack of motivation.

There are two types of EMG: intramuscular EMG and surface EMG (SEMG). Intramuscular EMG (the most commonly used type) involves inserting a needle electrode through the skin into the muscle whose electrical activity is to be measured. Surface EMG involves placing the electrodes on (not into) the skin overlying the muscle to detect electrical activity of the muscle. Intramuscular EMG is the "classic" form of EMG and the one discussed here.

For an EMG, a needle is inserted through the skin into the muscle. The electrical activity is detected by this needle (which serves as an electrode). The activity is displayed visually on an

oscilloscope and may also be displayed audibly by a microphone.

Since skeletal muscles are often large, several needle electrodes may need to be placed at various locations to obtain an informative EMG.

After placement of the electrode(s), the patient may be asked to contract the muscle (for example, to bend the leg). The presence, size and shape of the wave form (the action potential) produced on the oscilloscope provide information about the ability of the muscle to respond to nervous stimulation. Each muscle fiber that contracts produces an action potential. The size of the muscle fiber affects the rate (how frequently an action potential occurs) and the size (amplitude) of the action potential.

No special preparation is needed for an adult patient. For infants and children, however, the physical and psychological preparation depends on the child's age, behavior and prior experience. (For instance, has the child been traumatized by another medical or dental procedure?) Pediatric facilities are trained to help parents prepare their children for this procedure.

An EMG can produce discomfort at the time the needle electrodes are inserted. They feel like shots (intramuscular injection), although nothing is injected during an EMG.

Afterwards, the muscle may feel a little sore for up to a few days. But EMGs remain one of the most dependable early tests for CMT.



An EMG is most often performed when patients have unexplained muscle weakness.

The word "electromyography" looks dauntingly long, but it is made up of three parts: "electro" + "myo" + "graphy". "Myo" is from the Greek meaning muscle and "graphy" comes from the Greek "grapho", meaning to write. So, electromyography is literally the writing (recording) of muscle electricity.

(Editor's note: This is the final installment in the article on types of HNPP.)

Understanding HNPP Phenotypes, P

By MAUREEN HORTON, RN

POLYNEUROPATHY RESEMBLING CMT PHENOTYPE OF HNPP

Megan, 26, was the third generation of her family diagnosed with CMT. Her great uncle was diagnosed with CMT when he was overseas during WWII. He walked into a doctor's office, in Japan, for some other ailment and the doctor told him he had CMT based on the symptoms he exhibited. Her great uncle's two sons, her grandmother, mother, uncle, first cousin, Megan herself, and her daughter all show the same symptoms, to varying degrees. None of them ever had DNA testing. And most of them had been seen at different MDA clinics over the years, and have always been diagnosed with CMT. Now the fourth generation was showing the disease. Megan's, 2-year-old daughter, Amy, began developing the family symptoms—unsteady gait, twisting ankles, high arch, hammer toes, really fat feet, “pigeon toes”, and no reflexes in the ankles or knees. Megan wanted to know for sure, so she had the DNA test done on Amy. Amy's DNA test came back positive for HNPP.

Jim, 35, also had CMT. Or so he thought. He had lived with it for most of his life. While at the MDA clinic, seeing a new neurologist, he mentioned a growing problem. To shave in the morning, he had to lean his hand on the sink, in order to stabilize himself. And the hand that he was leaning on kept going to sleep. Since he had never had the DNA test done, nor had any family members, his doctor ordered the test. It came back positive for HNPP.

Mike had been diagnosed with HNPP years ago. He had learned to live with the pressure palsies. In his late 40's, he began having increased symptoms. Over the course of a year, he developed foot drop in both feet and eventually needed AFOs. Fine-motor activities were becoming harder to do. Muscle fatigue was becoming a huge problem and he was forced into early retirement. His neurologist, who understood HNPP, told him that this was his disease progressing. While he had been a classic phenotype of HNPP, he now would be considered to have the polyneuropathy resembling CMT phenotype of HNPP.

Polyneuropathy refers to many nerves simultaneously involved. With the nerves of both the arms and legs involved, CMT is certainly a polyneuropathy. The polyneuropathy of CMT is always bilateral (both sides) and largely symmetrical (equal on both sides). CMT symptoms are generally considered to be permanent and slowly progressive. Given the descriptions of both a polyneuropathy and of CMT, one could conclude that when a person has neurological problems involving both sides of his body and one side is pretty much as involved as the other side, AND testing or symptoms indicated HNPP, AND there are signs of CMT (hammer toes, high arches, etc.), then the person is considered to have the polyneuropathy resembling CMT phenotype of HNPP. And one would be correct. Partially. The individual may or may not have (or be aware of) the pressure palsies of HNPP. And he may or may not have signs of CMT. Some people never develop the episodes of weakness and numbness, but simply develop progressive weakness and atrophy of the feet and then the hands.

Obviously, there has to be some way to tell the two diseases apart. And there is. Actually, there are four key ways for the physician to distinguish HNPP from the CMT phenotype of HNPP: the history; the EMG; DNA testing; and if needed, a nerve biopsy. During the ‘history’, when the patient is asked about the problem (When did it start? How often does it happen? etc.) The physician may ask or the patient may volunteer information about intermittent numbness and/or weakness or of arms or legs going to sleep for more than a few minutes. This is suggestive of pressure palsies, and should be noted, especially if the patient has a generalized neuropathy. Secondly, the EMGs look quite different. In CMT there is widespread conduction slowing. In HNPP, conduction is slowed across common entrapment sites, such as the knee, wrist and elbow (there can be significant slowing across the elbow and normal conduction below the elbow). DNA testing, which is seen as the ultimate way to confirm the diagnosis, will be positive in 70-80% of individuals with HNPP. If the DNA test is negative, a nerve biopsy may be needed to confirm the HNPP diagnosis. The biopsy would show sausage-like swellings of myelin sheaths called ‘tomacula’ in HNPP.

Given the similarities of the two diseases, it is no wonder that researchers are recommending that at least one person in each family have the

art II

genetic blood test done to confirm the diagnosis. Once the diagnosis is confirmed in one family member, then any other family members who develop symptoms are presumed to have the same disorder. Many physicians feel it is imperative to correctly diagnose the disease in the family. CMT is usually a more severe disease than HNPP. And treatments, especially surgery, which may be indicated for CMT, may be contraindicated for HNPP.

CONFLUENT MONONEUROPATHY MULTIPLEX (CMM) PHENOTYPE OF HNPP

Ted, a 65-year-old man, noticed that he tended to drag his left foot and toward the end of the day his foot would slap on the ground. He had first noted the weakness a few months earlier and felt that it was slowly getting worse. He had noticed no weakness on the right or in his hands and had no numbness. When he was examined, the doctors noticed more widespread weakness involving the hands and feet on both sides, although in the feet, the weakness was much worse on the left. He also had mild loss of feeling in both feet and his ankle reflexes were absent. As far as he knew, no other member of his family had nerve problems. He himself had never had episodes of numbness or weakness prior to this. Ted had EMG studies and was diagnosed with an inflammatory nerve disorder known as CIDP. Treatment was planned but a nerve biopsy was ordered and this showed tomacula, a finding highly suggestive of HNPP. Genetic testing confirmed the diagnosis.

Mononeuropathy refers to disease of a single nerve. Instead of 'disease of a single nerve', it may also be called an individual nerve lesion. Carpal tunnel syndrome, involving the median nerve, in one hand is an example of mononeuropathy. Mononeuropathy multiplex refers to disease in two or more nerves in separate locations. Carpal tunnel syndrome in both hands, though it is more often called bilateral (both sides) Carpal tunnel syndrome is technically an example of this. Carpal tunnel syndrome in one hand and cubital tunnel syndrome, involving the ulnar nerve, in the other arm is also an example of mononeuropathy multiplex.

Like the polyneuropathy that resembles the CMT phenotype, patients with confluent mononeuropathy multiplex have permanent symptoms and signs and they tend to be moderately to severely involved. While CMT is symmetrical, CMM is not. CMM is asymmetrical or not equal on both sides. Though both sides may have problems, one side is significantly worse.

It is not unusual for a person to have small injuries to individual nerves which are ignored at the time they develop because the symptoms are so minimal. However, with time—and this may be years, even decades—the effects of these small injuries merge together to form a confluent (means flowing or coming together) pattern of neuropathy, involving two or more nerves, which closely resembles a polyneuropathy. But in other cases, the nerve injuries are more significant and not ignored. They just do not go away and may get progressively worse. While there is a clear-cut evidence of injury to individual nerves, there is also an overall pattern of many nerves involved, in a non-symmetrical pattern.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is as an acquired neuropathy which may evolve this way. Since both CIDP and HNPP cause demyelination and both have a confluent mononeuropathy multiplex pattern, they can be confused, particularly if there is no overt family history of neuropathy. The two disorders can be distinguished based on the nerve biopsy. It is very important that these two disorders not be confused since CIDP is treatable. On rare occasions the CMM pattern may develop very rapidly and become very severe, including respiratory failure, and may be misdiagnosed as Guillain-Barré syndrome, another inflammatory disease of nerves.

THE OLIGOSYMPOMATIC GROUP (FORMERLY PHENOTYPE) OF HNPP

John knows that things are not quite right. Too much of anything and he develops weakness or numbness. But it never lasts more than a few minutes. His legs frequently go to sleep, but he knows it is because of sitting the way he does. Other family members are that same way. No big deal. If it gets any worse he will mention it to his doctor next time he goes in.

(continued on page 14)



VISIT OUR HOMEPAGE

at

www.charcot-marie-tooth.org

HNPP

(Continued from page 13)

Laura has mild Carpal tunnel syndrome.

Kathy agreed to be part of a family study for HNPP. She had no symptoms at all. Testing showed no ankle reflexes and the nerve conduction study showed slowing across her elbow and wrist.

All three of the above individuals represent the Oligosymptomatic group of HNPP. Oligosymptomatic means few symptoms. By far, this is the largest group of people with HNPP. It is believed that the majority of people with HNPP (80-90%) are either undiagnosed or incorrectly diagnosed, and those numbers include the Oligosymptomatic group.

In this phenotype, there is a wide range of symptoms, which are mostly mild and episodic. Mild and more permanent problems such as a mild carpal tunnel syndrome are also included in this group. Some people deny having any symptoms, even though they carry the gene

(Researchers studying families frequently discover abnormalities in the EMGs of these people despite having no symptoms). In others, the symptoms may be so mild that they may be ignored.

Currently, individuals with classic pressure palsies lasting less than 24 hours are classified here. Oligosymptomatic individuals may notice that an arm or leg stays asleep a bit longer (a few minutes) in some of their family or that it happens a bit more often than in other people they know. It may be brushed off as just something unique to their family. They may mention it to a doctor, only to be told that everyone's arms and legs go to sleep from time to time.

This group many also have a family member or two that develop neurological symptoms that are thought to be something else: back problems; carpal tunnel syndrome; Bell's palsy (a temporary facial paralysis), small stroke, etc. Most of these other neuropathies, just listed, would be considered "acquired", meaning that they developed later in life and are not hereditary. So, making the connection to an inherited disorder would be difficult. For individuals and families with few or no symptoms, they usually discover that they have HNPP when more symptoms develop in themselves or another family member is identified as having HNPP.

Anyone studying HNPP quickly learns that the symptoms of HNPP are almost as varied as the number of individuals with the disease.

OTHER SYMPTOMS

There are other symptoms which people with HNPP are reporting (Note: This does NOT mean that everyone with HNPP will develop these symptoms.) Many of these are typical symptoms of anyone who has a generalized neuropathy. And for the most part, it is those with more severe symptoms who are reporting them. Symptoms reported:

- Fatigue: some mention fatigue and an intense need to sleep at the end of a day of work or of sleeping away the weekend after working all week. Others relate fatigue to activity—the less they do, the less the fatigue and vice versa.
- Pain: Back pain, pain at the sites of entrapment, pain in muscles and following nerve paths. The pain is described as sharp and shooting, dull, deep, aching, etc.
 - Leg/ankle foot swelling.
 - Muscle cramps.
 - Paresthesias (abnormal sensations).
 - Muscle weakness related to activity, improves with rest.

As people with HNPP meet on the Internet, they tend to compare other symptoms and problems which they are experiencing. These problems range from headaches to digestion to bladder problems, etc. It is not yet known if these problems are indeed related to HNPP. More medical studies need to be done. This is not to say that discussions should not continue. But all problems that a person with HNPP is experiencing should be reported to the attending neurologist and to the neurologist involved in any studies in which the person is involved.

Anyone studying HNPP quickly learns that the symptoms of HNPP are almost as varied as the number of individuals with the disease. When and how symptoms begin, where they are located, how they progress, whether there is fatigue, pain or weakness is all over the map. While the majority of those with HNPP do share the symptom of pressure palsies, there is great variance in this symptom alone. Pressure palsies can last minutes to months to as long as a year. They can involve any and all combinations of entire arms, elbows, wrist, hands, fingers, legs, feet, toes, and scalps. Right side and or left side. They can cause varying degrees of weakness or numbness or both. The list of things that cause the pressure palsies is long. This is truly a fascinating disease!

Preventing falls... Especially among the elderly

There are some startling statistics regarding the likelihood of falling once a person reaches age 65. Obviously, the fact of having CMT makes the statistics even more alarming. One third of people living in retirement or assisted-living communities have accidental falls at some point. Those over the age of 75 fall at least once a year. Five percent of all elderly falls result in hospitalization. The result of a fall is not only a wide range of injuries but an emotional as well as functional decline which may result in depression, fear of falling, inactivity and eventual demise. Both injurious and non-injurious falls are associated with a profoundly negative impact on function.

What can be done?

Therapeutic exercise is a useful means of reducing falls among the older population because it helps improve balance, flexibility, strength, endurance and coordination. Improving the patient's range of motion and getting him or her on an appropriate non-traumatic exercise program is key. Patients need to stretch their contractures and improve their range of motion. An aquatic-based program is ideally suited for the elderly individual. Tai Chi has also been shown to improve balance, strength and coordination in persons in residential facilities for the elderly.

Risk factors

- age
- impaired coordination
- visual impairment
- dementia
- cardiac arrhythmias
- neurological disorders
- musculoskeletal disorders
- physical restraints
- sensory loss
- muscular weakness due to aging or illness
- medications
- alcohol
- arthritis
- gait and balance disorders
- postural instability
- inappropriate footwear
- foot disorders

The above list of risk factors for falling was designed to pertain to the elderly, but if you have CMT, see how many of these risks are ones you deal with. The negative impact of falling is true for everyone and each person must do all he/she can to avoid falls. Braces, canes, walkers and other devices (just the simple aspect of being extra careful) can help prevent falls.

Don't be fooled by miracle health claims

"Every year, thousands of consumers—many of them suffering from serious illnesses—fall prey to fraudulent health claims. They spend billions of dollars on unproven, often useless products that not only cheat them out of their money, but may also keep them from getting the treatment they need. Some products may cause serious harm."

So begins the cover letter for a new booklet produced by the Federal Trade Commission (FTC) and the U.S. Food and Drug Administration (FDA). The booklet is entitled, *'Miracle' Health Claims: Add a Dose of Skepticism*.

It was produced to help consumers understand the consequences of health fraud and learn how to identify it. The booklet describes claims that are allowed by federal law in labeling of food and dietary supplements. It discusses the fact that dietary supplements may have drug-like effects and, therefore, may pose a risk to some people.

It also tells how to find out whether the FDA or FTC has taken action against the promoter of a product and how to spot false advertising claims. It points out that people who are overweight or who have serious medical conditions for which there are no treatments or cures are frequent health-fraud targets. In addition, it tells how to report a health product that you believe may be advertised falsely.

To read about the booklet, go to www.ftc.gov/bcp/online/pubs/health/frdheal.htm. To order copies, go to www.ftc.gov/bcp/online/pubs/bulkordr.htm.

Canes and Walking Aids Both

Because of the problems with balance that most people with CMT face, a cane can be a source of reassurance as well as being a literal assistive device. There are many options available, ranging from extremely decorative canes to the very durable, supportive orthopaedic varieties. The important considerations in choosing a cane are fit and function.

A study on canes sponsored by the American Association of Retired Persons found that 85% of respondents considered a cane with a T-shaped handle or pistol grip more comfortable than the crook-handle model. The study also indicated that two-thirds of the regular users developed back pain because they were using a cane that was not the right height.

In general, the length of the cane should be equal to the distance from your wrist to the floor. To measure, you should wear comfortable shoes, stand straight with your arms at your side, and measure the distance from your wrist to the floor. A yard stick works well.

If you are using a cane for weight-bearing, the cane should be in the hand opposite your weak side. For example, if you have a knee or hip problem on the right side, the cane goes in the left hand. The cane and weak leg should take a step together so that some of the weight is taken by the cane.

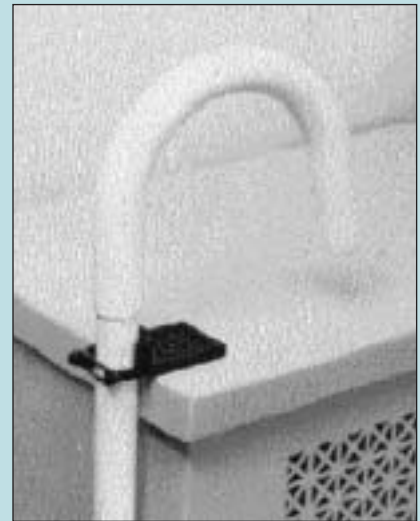
Using a cane in the winter requires some planning. To help prevent falls, make sure the tip on your cane is in good shape. One that is worn down is likely to slip on ice, snow or any wet surface. Use the widest tip possible for more surface coverage. For greater balance, consider using two canes during winter walks. Wear good footwear. Even with a cane, your feet can slip on snow or ice.

Samples of some canes are shown below. They come from a variety of sources such as Canes and Such, who can be reached at www.canesandsuch.com or by calling 1-888-383-CANE; House of Canes, at www.houseofcanes.com or by calling 1-888-458-5920 or Ableware, at www.ableware.com

SHE CANERY AND THE CANE VALET FROM ABLEWARE



She Canery is an assortment of women's hand decorated canes in floral and other patterns and clear-coated to protect the pattern.

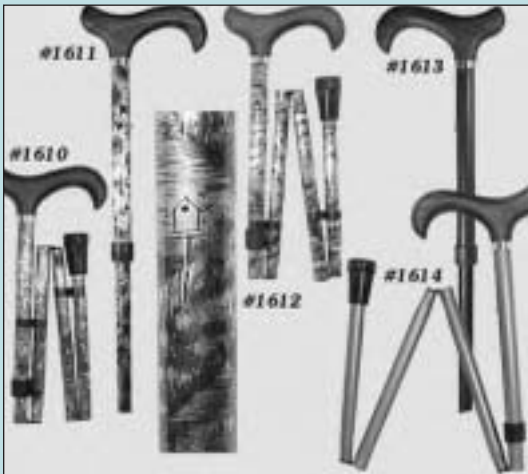


The cane valet holds a cane to the table edge, with a small plastic fitting that mounts on the cane and will hold it to a table top when not in use. The piece snaps onto the cane and slides up or down to contact the top or bottom of the table.

Decorative and Functional

FOLDING AND TELESCOPING CANES FROM HOUSE OF CANES

Folding canes are amazing...canes that open with just a flip..and are handy to put away when not in use. They weigh approximately 14 oz.and can fold to just 12 inches. Telescoping canes do not fold and their shortest length is 27 inches.



ORTHOPEDIC CANES FROM CANES AND SUCH



The Fisher handle spreads pressure evenly across the palm and the Surefoot and quad base canes are shock-absorbent and provide optimum support. Many different handles can be combined with various bases.

Support Group News

■ Kentucky/Southern Indiana/Southern Ohio

The April 13th meeting was excellent because Ann Beyer, Chairman and President, shared her knowledge of the efforts by the CMTA to develop solutions for CMT and the necessity of finding funds to keep the program active and growing. The real solutions lie in being able to fund grants for research that will determine the causes and a cure for CMT. There were 13 attendees and would have been more except for the bad weather. The next meeting will be July 13, 2002.

■ Minnesota—Benson

The April meeting was attended by 12 people, including two new members. The subject of the meeting was bracing. Those who wore braces gave their thoughts and the information that professionals have provided them. A new member bravely showed his feet to the group to see if anyone had the same challenges as he does. They did and a valuable exchange of ideas followed. The goal of this meeting was to provide new information and to give people a positive attitude about what they can do for themselves.

Packets for the North American Database were received and will be given to new members whenever they attend a meeting.

■ New York (Westchester County)/ Connecticut (Fairfield)

The support group is pleased to announce that it has two new support group leaders, Diane Kosik and Beverly Wurzel. After years of service to the group and the CMTA, Kay Flynn is stepping down as leader. Information on how to contact the new leaders is found on the support group contact page.

Ann Beyer addressed the Kentucky support group on April 13th.



New support group leaders Diane Kosik and Beverly Wurzel stand behind outgoing leader Kay Flynn.

■ New York—Horseheads

At the last support group meeting, a physical therapist/rehab specialist talked about "Exercising with Limitations." Group Leader Angela Persimino narrates this story: "As the meeting began, one of the regular members, Bob Chandler, was not present. This was surprising because he is very faithful. However, about half an hour later, he arrived. He explained that he saw a young woman outside a stopped car along the highway. HE stopped to check on her. He took the woman, a 6-month-old infant and a male passenger to the police station for help. Bob uses a cane for ambulation 99% of the time and has quite a bit of trouble with his CMT. I thought it was great that he went out of his way to help someone else in trouble." He had also made a cane, as a surprise, for another of our members because he doesn't like to see him waiver when he walks. Such a nice guy!"



CMTA Support Groups

Arkansas—Northwest Area

Place: Varies, Call for locations
Meeting: Quarterly
Contact: Libby Bond, 501-795-2240
E-mail: charnicoma57@yahoo.com

California—Berkeley Area

Place: Albany Library, Albany, CA
Meeting: Quarterly
Contact: Ruth Levitan, 510-524-3506
E-mail: rulev@pacbell.net

California—Los Angeles Area

Place: Various locations
Meeting: Quarterly
Contact: Serena Shaffer,
 818-841-7763
E-mail: CMT_losangeles@yahoo.com

California—Northern Coast Counties (Marin, Mendocino, Solano, Sonoma)

Place: 300 Sovereign Lane,
 Santa Rosa
Meeting: Quarterly, Saturday, 1 PM
Contact: Freda Brown, 707-573-0181
E-mail: pcmobley@mac.com

Colorado—Denver Area

Place: Glory of God Lutheran Church
 Wheat Ridge
Meeting: Quarterly
Contact: Marilyn Munn Strand,
 303-403-8318
E-mail: mmstrand@aol.com

Kentucky/Southern Indiana/ Southern Ohio

Place: Lexington Public Library,
 Northside Branch
Meeting: Quarterly
Contact: Robert Budde,
 859-255-7471

Massachusetts—Boston Area

Place: Lahey-Hitchcock Clinic,
 Burlington, MA
Meeting: Call for schedule
Contact: David Prince, 978-667-9008
E-mail: baseball@ma.ultranet.com

Michigan—Flint

Place: University of Michigan,
 Health Services
Meeting: Quarterly
Contact: Debbie Newberger/
 Brenda Kehoe,
 810-762-3456

Minnesota—Benson

Place: St. Mark's Lutheran Church
Meeting: Quarterly
Contact: Rosemary Mills, 320-567-2156

Mississippi/Louisiana

Place: Clinton Library, Clinton, MS
Meeting: Quarterly
Contact: Flora Jones,
 601-825-2258
E-mail: flojo4@aol.com

Missouri/Eastern Kansas

Place: Mid-America Rehab Hospital,
 Overland Park, KS
Meeting: First Saturday bi-monthly
Contact: Lee Ann Borberg,
 816-229-2614
E-mail: ardi5@aol.com

Missouri—St. Louis Area

Place: Saint Louis University Hospital
Meeting: Quarterly
Contact: Carole Haislip, 314-644-1664
E-mail: c.haislip@att.net

New York—Greater New York

Place: NYU Medical Center/
 Rusk Institute, 400 E. 34th St.
Meeting: Monthly
Contact: Dr. David Younger,
 212-535-4314,
 Fax 212-535-6392

New York—Horseheads

Place: NYSEG Meeting Room, Rt. 17
Meeting: Quarterly
Contact: Angela Piersimoni,
 607-562-8823

New York (Westchester County)/ Connecticut (Fairfield)

Place: Blythedale Hospital
Meeting: Monthly, Saturday
Contacts: Diane Kosik, 914-937-2013,
 Beverly Wurzel,
 914-783-2815
E-mail: ladydismiles@aol.com or
 craneomat@frontiernet.net

North Carolina—Archdale/Triad

Place: Archdale Public Library
Meeting: Quarterly
Contact: Ellen (Nora) Burrow,
 336-434-2383

North Carolina—Triangle Area (Raleigh, Durham, Chapel Hill)

Place: Church of the Reconciliation,
 Chapel Hill
Meeting: Quarterly
Contact: Susan Salzberg,
 919-967-3118 (evenings)

Ohio—Greenville

Place: Church of the Brethren
Meeting: Fourth Thursday,
 April–October
Contact: Dot Cain, 937-548-3963
E-mail: Greenville-Ohio-CMT@
 woh.rr.com

Oregon/Pacific NW

Place: Portland, Legacy Good Sam
 Hospital, odd months
 Brooks, Assembly of God
 Church, even months
Meeting: 3rd Saturday of the month
 (except June and Dec.)
Contact: Jeanie Porter, 503-591-9412
 Darlene Weston, 503-245-8444
E-mail: jeanie4211@attbi.com or
 blzerbabe@aol.com

Pennsylvania—Philadelphia Area

Place: University of PA, Founders
 Building, Plaza Room A
Meeting: Bimonthly
Contact: Amanda Young,
 215-222-6513
E-mail: stary1@bellatlantic.net



WRITE TO US!

Pat Dreibelbis, Editor

The CMTA Report

CMTA

2700 Chestnut Pkwy.

Chester, PA 19013

The CMTA reserves the right to edit letters for space.

Ask the Doctor

Dear Doctor:

I have seen reference to the potential need for foot/ankle surgery in some cases of CMT. Are there specific indicators or contraindicators for this surgery? What outcome should an adult patient (age 45) with moderate to severe ankle-turning expect from the surgery? Is the surgical procedure specialized, or would it be considered fairly routine for an orthopaedic doctor who specializes in foot problems? Is there a specific resource doctors can be referred to, or is there a list of doctors in the U.S. who specialize in this surgery?

The doctor replies:

Surgery should only be done if there is a need and a benefit. The outcome should be a frank discussion between the patient and the surgeon. Before surgery is done, there is an “informed consent” that a surgeon gives to the patient and all questions need to be answered so that the patient knows what exactly is going to be done, the expected results, the problems, complications, difficulties and benefits. Alternative measures need to be discussed. This is essentially universal practice in the USA.

Medical doctors do not consider operating on CMT patients to be routine surgery for any orthopaedic surgeon. There are some orthopaedic surgeons who have had special training in foot and ankle surgery via fellowships and who specialize and possibly even limit practice to foot and ankle surgery in most major US cities. Because of the variability and the ongoing weakness, each case has to be assessed individually and surgery planned carefully.

Dear Doctor:

I am 43 years old and have CMT. I am having pain in the knee. The doctor said my CMT is pulling my kneecap to the side and that is what is giving me the pain. What can be done for that?

The doctor replies:

I trust that the doctor who gave this person the advice is one who knows CMT. Generally, unless the CMT starts in childhood, the quadriceps, the muscle that pulls the kneecap to the side, is usually not affected. The inquiring person also did not state whether this person was male/female (females have a tendency to have this problem more frequently), height/weight and whether it is on one side or both. Also, knowledge of the muscle grading (how strong the muscles are) in both lower extremity, including knee, ankle and foot would be useful.

However, there may be deformity in the knee caused by arthritis or other disease of the knee joint, even unrelated to CMT disease. That would cause pain. Then, there is reason for quadriceps to pull the kneecap to the side and the treatment for that is to take care of the underlying problem.

Dear Doctor:

Are there any negative side effects to taking Gabitril for a mood disorder with my CMT? I notice the side effects listed are dizziness and balance problems, which is already problematic with CMT.

The doctor replies:

It comes down to the risk/benefit ratio. Anticonvulsants (some of which have been noted to have mood-altering efficacy) such as tiagabine (Gabitril) are notorious for side effects, e.g., dizziness and drowsiness. These side effects are also present with the conventional antidepressants. CMT patients are, therefore, confronted with a dilemma, the feeling of well-being associated with these medications vs. the fear of falling down and injuring themselves.

Dear Doctor:

I was recently diagnosed with CMT following referral to an orthopedist for multiple stress fractures in my foot. I have osteoporosis (-3.5) and began Fosamax treatment. I am now experiencing pain in my legs particularly my right leg (which had the stress fractures of the foot). Sometimes I feel like needles are all over my legs, numbness in my right leg, and a low-grade ache in my right leg about two inches above my ankle. Sometimes my hands hurt a little. I have never experienced these pains before. I am losing muscle in my hands. Could Fosamax have a neurotoxic effect? If so, could I use Evista?

The doctor replies:

Non-estrogenic medications to treat osteoporosis have their fair share of adverse effects:

- (1) alendronate: arthralgia (joint pain); bone pain; musculoskeletal pain; myalgia (muscle pain)
- (2) risedronate: arthralgia; myalgia
- (3) raloxifene: muscle cramps; myalgia

The patient needs to discuss her symptoms with her neurologist, so that together they can best decide on the appropriate therapy for her.

The Herb of the Month: Ginseng

By **BRUCE A. CRISTOL, PharmD**

When one thinks of ginseng, images of human-shaped roots come to mind. In fact, the Chinese named the root “shen-seng,” which when translated into English means “man-root.” Botanists refer to plants in terms of genus and species. As regards ginseng, an example would be *Panax quinquefolium* L. (otherwise known as American ginseng). The name *Panax* is derived from the Greek word meaning “all healing.” Seven species and varieties of ginseng are distributed around the world. People of Asian descent believe that Korean ginseng is the highest quality available.

Probably the most widely recognized plant in the traditional medicine market, ginseng has been known as a medicinal for more than 2000 years. Over the millennia ginseng has been used in the treatment of asthenia (general fatigue and muscular weakness), atherosclerosis (cholesterol deposits within large and medium-sized arteries), blood and bleeding disorders, colitis, and to relieve the symptoms of aging, cancer and senility. There are reports that the root raises mental and physical capacity, and exerts a protectant effect against experimental diabetes, neurosis, radiation sickness and some cancers. It is advocated today because of its alleged “adaptogenic effect” (stress-protective) due to the saponin content of the root.

Saponin glycosides (a combination of a sugar and non-sugar molecule) are said to be the active component of the root, although many more minor components have been isolated and

identified. The active ingredient concentration is based on the species, age of the root, location, season and curing method. Since it is extremely difficult to extract more than a minute quantity of the active compound, the entire root is used in herbal preparations.

The current view of ginseng is that it may provide the following benefits to individuals: (1) reducing stress; (2) lowering cholesterol; (3) lowering blood sugar; (4) resisting infection; (5) having an estrogen-like effect on women; (6) increasing strength, endurance and mental acuity. Side effects have included: (1) nervous excitation; (2) difficulty concentrating with long-term use; (3) elevated blood pressure; (4) insomnia; (5) vomiting; and (6) headache. Diabetics should be alert to the blood-sugar-lowering effects of ginseng.

It is important to re-emphasize the following: (1) ginseng is not considered a “drug” by the U.S. Food and Drug Administration (FDA). Therefore, the buyer should be aware of commercial preparations, such as extracts, solutions, capsules, tablets, sodas and teas, which may not contain the active ingredient and may be adulterated with Western medications and other herbs; (2) there are drug-herb interactions which have been uncovered in the past several years which the patient should be aware of.

If ginseng were to be classified as a drug by the FDA, standardized dosage forms could possibly be assured. However, the patient can become aware of the drug-herb interactions reported in the medical literature. They are classified as follows:

Drug interactions with Ginseng	Result of interaction	Comments
Warfarin (Coumadin)*	Increased coagulation	Warfarin dose may need to be increased or ginseng discontinued
Digoxin (Lanoxin)	Falsely elevated digoxin blood levels suggesting toxicity	Noted only with Siberian ginseng (<i>Eleutherococcus senticosus</i>)
Phenelzine (Nardil)	Headache, tremor, manic episodes	
Blood pressure medications	Increased blood pressure	
Estrogen products	Augmented estrogenic effects, e.g. vaginal bleeding	

* Concomitant use of warfarin, heparin, aspirin, NSAIDs (e.g. naproxen; ibuprofen, etc.) should be avoided.

REFERENCES:

DerMarderosian, Ara. The Review of Natural Products. *Facts and Comparisons* 1999.

Fugh-Berman, Adriane. Herb-drug interactions. *The Lancet* 2000; 355: 134-138.

Miller, Lucinda. Herbal Medicinals: Selected Clinical Considerations Focusing on Known or Potential Drug-Herb Interactions. *Archives of Internal Medicine* 1998; 158: 2200-2211.

GIFTS WERE MADE TO THE CMTA

IN MEMORY OF:

George Allison
James Wallingford

John Connelly
Peter Bell
Mr. & Mrs. Robert Burns
Marilyn Dobbins
Donald & Mary Graham
John & Rosanne Herrinton
Harold & Carol Jackson
Mollie Leonelli
Penwork Group

Elvin Fondren
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Brad Freezman
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Marah Griffith
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Paul & Julie Cavanaugh

Jeanette Reilly
Patricia Davis

IN HONOR OF:

Justin Stolte
Colleen Becker

CMTA Remembrances

Your gift to the CMTA can honor a living person or the memory of a friend or loved one. Acknowledgment cards will be mailed by the CMTA on your behalf. Donations are listed in the newsletter and are a wonderful way to keep someone's memory alive or to commemorate happy occasions like birthdays and anniversaries. They also make thoughtful thank you gifts. You can participate in the memorial and honorary gift program of the CMTA by completing the form below and faxing it with your credit card number and signature or mailing it with your check to: CMTA, 2700 Chestnut Parkway, Chester, PA 19013.

Honorary Gift:

In honor of (person you wish to honor)

Send acknowledgment to:

Name: _____

Address: _____

Occasion (if desired):

- Birthday Holiday Wedding
 Thank You Anniversary Other

Memorial Gift:

In memory of (name of deceased)

Send acknowledgment to:

Name: _____

Address: _____

Amount Enclosed: _____

Check Enclosed VISA MasterCard

Card # _____

Exp. Date _____

Signature _____

Gift Given By:

Name: _____

Address: _____

Letters to the Editor

Dear CMTA,

I appreciated your sending me a few copies of The CMTA Report. My membership check and application are enclosed.

It has taken me a long time to get in contact with you. I have CMT and had triple arthrodesis surgery on both feet plus transplantation of large toe tendons in 1957. The surgeon never mentioned CMT, muscular dystrophy or neuropathy and I therefore always thought it was just a birth defect. I eventually got directed to the MDA through the Jerry Lewis fundraising. I went to the University of Michigan and was directed by them to the Neuropathy Association. Never once was I told about the CMT clinic at Wayne State University, located only 15 miles or so away.

Your association was mentioned in the last issue of the Canadian newsletter and that's how I finally got to your "door."

—A.W. DeWitt, MI

Dear CMTA,

I would like to thank Steve O'Donnell for swimming for CMT and ask him to consider other swimmers and swimmers with CMT joining in the effort next year!

—D.H.

Dear CMTA,

I was thrilled to see the article about Steve's upcoming swim. I think it is fantastic. I am also a CMT patient who loves to swim. I go weekly to a local pool and swim a good 30-45 minutes. My husband (no CMT) swam the Bay in 1996. It was a fabulous experience for both of us. We love swimming together, but this was a chance for him to excel. He took his time and made the swim in 3 1/2 hours. He was a swim instructor many years ago and is athletic. Even so, the Bay swim was a real challenge! We are both 50 years young this year, but feel and act much younger.

My CMT has progressed a lot the last 7 years or so. My hands are thin and weak, so I use fins in the pool. My legs are weak, but I am building them up with flippers and a light weight-lifting program. Balance is a challenge, but a positive and grateful attitude is key.

I wish Steve much success and many blessings, especially on June 16th.

—I.A.

Dear CMTA,

My admiration for Steve O'Donnell is unlimited and also for his family. My grandson, age 9, lives in Los Altos, CA, and has CMT. We are very proud of what he has accomplished so far. Good luck to you, Steve.

—B.R.

Dear CMTA,

Last year, while visiting my dentist, I encountered an interesting situation. Prior to the dental work I was having done, my dentist suggested nitrous oxide to calm my nerves. Unfortunately, that didn't happen. Shortly after receiving the inhalation of nitrous oxide, I began to experience muscle spasms, first in my arms and then in my legs. The spasms lasted for hours. It wasn't a painful experience, but it certainly was annoying. I wouldn't recommend this type of medication to anyone with CMT.

—P.T.

Dear CMTA,

I want to thank you for responding to my emails so many times and so quickly. I live in Spain, where it is much harder to find information, and you were so good as to mail me the information you have printed in Spanish. Although I read English, it was a big help to have the chance to read more information about CMT in Spanish than I could find anywhere in Spain.

I am joining your association and am happy to have found such good and timely help.

—P.R., Spain

Dear CMTA,

After struggling for years with painful feet and legs, I have finally been diagnosed with CMT. After reading about it in your packet of information, I'm surprised that I have only been diagnosed at age 62. It's obvious to me that my two children both suffer from the same problems and I'm just glad that they will get help while it might still make a difference.

Thank you for sending me your newsletter and brochure. I took them to my doctor, who was happy to find out you existed.

—M.N., MT

The CMTA Report

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The opinions expressed in the newsletter are not necessarily those of the Charcot-Marie-Tooth Association. The material is presented for educational purposes only and is not meant to diagnose or prescribe. While there is no substitute for professional medical care for CMT disorders, these briefs offer current medical opinion that the reader may use to aid and supplement a doctor's treatment.

MEDICAL ALERT:

These drugs are toxic to the peripheral nervous system and can be harmful to the CMT patient.

Adriamycin
Alcohol
Amiodarone
Chloramphenicol
Cisplatin
Dapsone
Diphenylhydantoin (Dilantin)
Disulfiram (Antabuse)
Glutethimide (Doriden)
Gold
Hydralazine (Apresoline)
Isoniazid (INH)
Megadose of vitamin A*
Megadose of vitamin D*
Megadose of vitamin B6* (Pyridoxine)
Metronidazole (Flagyl)
Nitrofurantoin (Furadantin, Macrodantin)
Nitrous oxide (chronic repeated inhalation)
Penicillin (large IV doses only)
Perhexiline (Pexid)
Taxol
Vincristine
Lithium, Misomidazole, and Zoloft can be used with caution.

Before taking any medication, please discuss it fully with your doctor for possible side effects.

*A megadose is defined as ten or more times the recommended daily allowance.



What is CMT?

- ... is the most common inherited neuropathy, affecting approximately 150,000 Americans.
- ... may become worse if certain neurotoxic drugs are taken.
- ... can vary greatly in severity, even within the same family.
- ... can, in rare instances, cause severe disability.
- ... is also known as peroneal muscular atrophy and hereditary motor sensory neuropathy.
- ... is slowly progressive, causing deterioration of peripheral nerves that control sensory information and muscle function of the foot/lower leg and hand/forearm.
- ... causes degeneration of peroneal muscles (located on the front of the leg below the knee).
- ... causes foot-drop walking gait, foot bone abnormalities, high arches and hammer toes, problems with balance, problems with hand function, occasional lower leg and forearm muscle cramping, loss of some normal reflexes, and scoliosis (curvature of the spine).
- ... does not affect life expectancy.
- ... has no effective treatment, although physical therapy, occupational therapy and moderate physical activity are beneficial.
- ... is sometimes surgically treated.
- ... is usually inherited in an autosomal dominant pattern, which means if one parent has CMT, there is a 50% chance of passing it on to each child.
- ... Types 1A, 1B, 1X, HNPP and EGR-2 can now be diagnosed by a blood test.
- ... is the focus of significant genetic research, bringing us closer to answering the CMT enigma.

The CMTA Report

Information on Charcot-Marie-Tooth Disorders from the Charcot-Marie-Tooth Association



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