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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.

EMAIL CMTA AT:
CMTAssoc@aol.com

CMT Research: Status 2000

By ANN LEE BEYER

Since its inception the CMTA has had a deep commitment to promoting research that would lead to better diagnosis, treatments and eventually a cure for CMT. Although there are not yet cures for CMT, as you are aware, there has been more progress towards this end in the past 10 years than in the preceding 100 years. All of the known causes of CMT have been discovered in the last 10 years—as far as research goes, a very short time indeed. This being said, there are several obstacles which are impeding the rate of CMT-related research.

CMT, like many orphan or rare diseases, still remains something of a mystery.

One obstacle is rates of funding for CMT-related research. CMT is a relatively rare disease, which, although just as common as multiple sclerosis or Lou Gehrig's disease, is not usually life threatening. Therefore public and scientific interest in finding a cure for CMT is not as high a priority as it is for some of these "more severe" disorders. This is why a most important part of living our mission has been and continues to be educating and creating interest in CMT, particularly to those in the medical and research communities. More awareness leads to better care and also generates hope that better diagnosis, improved treatments and a cure will become a reality.

Another obstacle is the realization that although great progress has been made in CMT-related research, an actual cure for the disease will take time, in part because of the complex nature of the disease. While the gene defects causing many forms of the condition are known, the mechanisms by which these mutations cause disease are not. Gene therapy for all inherited diseases is in its infancy. This technology will take time to become a safe standard of care for treatment. However, this was not even being intensely studied 10 years ago. To make this approach and others a reality, it will take the effort of organizations such as the CMTA.

MAKING CMT KNOWN

The CMTA is working to make CMT a known entity. Because of the pressing need for identifying the genetic causes of still unknown forms of CMT and the need to develop a treatment and eventually a cure, we are working hard to educate and generate interest in CMT in the medical and research communities. We do this in several ways.

First, we provide information about CMT through our brochure, *What Is CMT?*, our newsletter, *The CMTA Report,* the *CMT Facts* series, and a CMTA Web Site that provides up-to-date information on CMT. We also communicate through the distribution of our physician's handbook, *Charcot-Marie-Tooth Disorders: A Handbook for Primary Physicians*.

In addition, we disseminate information by staffing a booth at major medical and health-related conferences, where we distribute our publications, and have an attention-drawing display that provides up-to-date information about CMT and the work of the CMTA. In addition, a booth also provides a setting for establishing face-to-face contact and conversa-

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You can help raise awareness too by calling the CMTA office and asking Pat or Edna to send you some brochures which you can, in turn, give to physicians who treat you and members of your family. In addition, you can buy a copy of our Physician's Handbook and give it to your primary caretaker. Not only will you be spreading the word about CMT but this will help you receive better care.

CMT RESEARCH: STATUS 2000

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tion with health care professionals, keeping CMT in the minds of the many attendees who carry out clinical and research work and can aid in our crusade to find a cure for Charcot-Marie-Tooth sufferers.

One of our most important allies in the effort to make CMT known is our actively involved CMTA Medical Advisory Board *(see list of current members on page 17)*. These clinicians and researchers are deeply committed to living out the CMTA Mission and Vision, and devote countless hours to pursuing the cause of CMT. Though their work, publications, and the papers they deliver at various meetings they create awareness and stimulate interest in CMT. Thanks to their efforts we have the *Physician's Handbook* to distribute, and thanks again to their efforts it is now in the process of being updated. In addition, it is because of our Medical Advisory Board that we are able to sponsor research conferences.

RESEARCH: THE ROAD TO TREATMENT AND CURE

In our short existence we have already sponsored two International Research Symposia. These conferences serve a number of purposes.

Each international conference on CMT has prompted a surge of research activity.

The main concern is bringing clinicians and researchers in CMT together, so that they can share their knowledge and theories about CMT. This dialogue, in turn, not only adds to the attendees' own knowledge and understanding of our disease, but also stimulates a flow of ideas that often results in new ways of thinking about it. Another expected outcome is that the papers and publications that follow will make colleagues more aware that CMT is a serious disease that warrants extended research interest and funding.

In 1976, before the founding of the CMTA, Dr. Georges Serratrice, who is now a member of the CMTA Medical Advisory Board, organized the First Conference on CMT in Marseille, France. The second, the Arden House Conference, held in 1987, was sponsored by the CTMA in conjunction with Columbia University, just four years after the CMTA was established. A Third International Conference on CMT Disorders, co-sponsored by the CMTA with the New York Academy of Sciences, took place in 1998 in Canada.

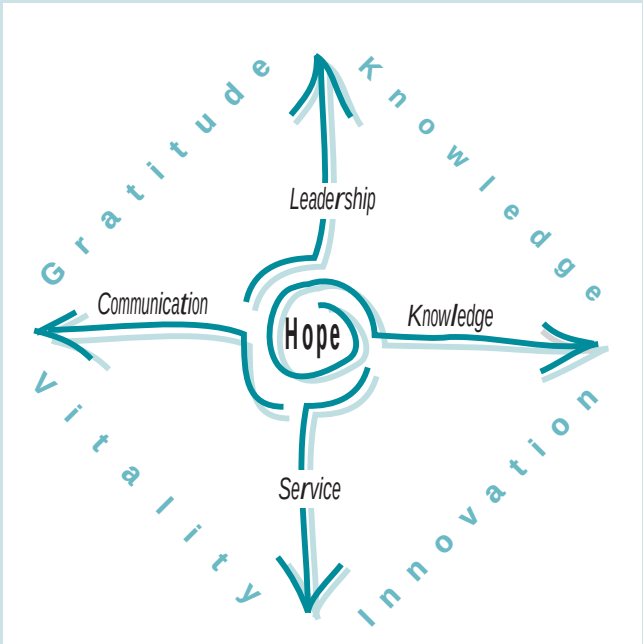
Our Mission, Our Values

THE CMTA'S MISSION STATEMENT:

To improve the quality of life for people with CMT

THE CMTA'S VISION STATEMENT:

Dedicated to generating hope



The Arden House Conference was very successful. During the eleven-year period following this conference, much headway was made in unraveling the mystery of CMT, particularly in understanding the genetics, pathology, and molecular biology of our disorder. Until these processes are more fully understood, therapies to arrest, reverse or cure CMT cannot be developed.

When the Arden House Conference was convened, it was known that there were several types and subtypes of CMT, but not all had been identified. In 1987, although gene mapping research was in its infancy, genetic research was taking place in two types of CMT, and it was believed that a genetic defect on chromosome 1 was responsible in the majority of CMT families. However, the genes responsible had not yet been identified. At the same time, researchers were working hard to map the location of the gene in X-linked CMT.

In the Introduction of the book that came out of the Third International Conference, "Charcot-Marie-Tooth Disorders," published by the New York Academy of Sciences in 1999, there is an excellent overview of the state of CMT research today as well as some promising areas for future therapies. It was written by the editors, Drs. Michael E. Shy and John Kamholz of Wayne State University in Detroit, and Dr. Robert E. Lovelace of Columbia University, New York. Dr. Shy, who is a Member of our Medical Advisory Board, and Dr. Kamholz are both clinicians and researchers in CMT. Dr. Lovelace is a Professor of Neurology, one of the founders of the CMTA, and chairman of the CMTA Medical Advisory Board. Much of the research information that appears below has been taken from this Introduction.

GENETIC BREAKTHROUGHS

The interval between the Second and Third Conferences was probably the most prolific period in the history of CMT research. During this time a number of significant breakthroughs occurred, the majority of them in CMT type1. CMT1 is the most prevalent type of CMT and a demyelinating (involving loss of the fatty nerve sheath) form of the disease. *(See Figure 1.)*

I believe that knowledge and understanding of CMT will increase exponentially, as a result of the Third International Conference. In fact, the work being done in CMT research

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	QTY	COST	TOTAL
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Membership Dues		$35	
SPECIAL OFFER FOR ACTIVE MEMBERS ONLY: CMT Facts Series (I-IV)		*active members* $16	
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CMT RESEARCH: STATUS 2000

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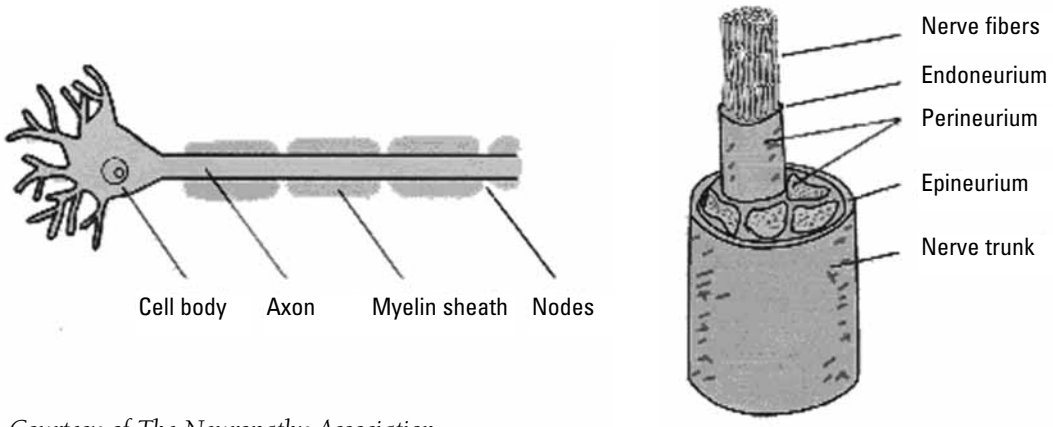
now indicates that this is already happening. A summary of some of the advances reviewed at this conference is listed below.

- In 1990, about two years after the Arden House Conference, a major breakthrough occurred when CMT1A was mapped to chromosome 17. (A chromosome is a structure in the nucleus of every cell containing genes or genetic material that determines the characteristics of that cell. In the case of ova and sperm, their crucial genes govern the development of all the cells and body systems.) *(See Figure 2.)*
- In 1991, another significant breakthrough occurred when the gene, peripheral myelin protein, or PMP22 gene, was identified. It is now known that an overexpression of PMP22 is associated with demyelination in CMT1. Genes carry the chemical messages of heredity—they constitute a blueprint of our bodies. *(See Figure 2.)*
- In 1992, it was found that CMT1A was caused by a duplication of a gene on chromosome 17.
- It was also learned that CMT1B, is caused by mutations in a gene, the P_0, or myelin protein zero gene.
- In 1996, it was found that point mutations in the Krox 20 or EGR2 gene, a transcription factor, which can turn other genes on and off, leads to a previously unknown, and less common form of CMT1. Transcription factors may be extremely important not only in the future of genetic research, but also in research strategies in affected individual patients.
- It was also during this period, that researchers found that CMT1X, a dominant disorder, is caused by point mutations in another gene, the Connexin 32 gene.
- The cause for hereditary neuropathy with a predisposition to pressure palsies (HNPP) was discovered and shown to be a deletion of the same region on chromosome 17 that is duplicated in CMT1A.
- Many cases of the more severe form of CMT called Dejerine-Sottas syndrome were shown to be caused by mutations in the PMP22, P_0, or EGR2 genes.
- Another important breakthrough during this period, was the discovery that the degeneration that takes place in CMT1 is due, not to demyelination, as was previously believed, but rather to secondary axonal involvement. This is what gives rise to the disabling atrophy and muscle weakness occurring progressively as affected patients age.
- To further demonstrate the rapid progress of genetic research in CMT, just this May, the genetic cause of one of the forms of CMT4 (recessive CMT) was identified and

FIGURE 1: THE PERIPHERAL NERVE

Nerves are like wires; they carry electrical impulses. The outside covering of this "wire" is made of myelin which acts as insulation to help impulses travel quickly. In demyelinating forms of CMT, the myelin sheath breaks down and interferes with the ability of the nerve to function.



Courtesy of The Neuropathy Association.

Diagnostic blood tests are now available for CMT1A, CMT1B, HNPP, and CMT1X.

shown to be a "phosphatase" which probably regulates the cell biology of certain myelin proteins.

DEVELOPMENT OF GENETIC TESTS

The above advances paved the way for development of genetic tests for several clinical types (called phenotypes) of this disorder. The significance of the above research becomes quite evident in the diagnostic blood tests that are now available for CMT1A, CMT1B, HNPP, X-linked CMT, and as of last year, the recently discovered form caused by the Krox 20 or EGR gene. In addition, prenatal tests for CMT1A and others have also been developed. The development of genetic blood tests is extremely important in that they provide the definitive answer about the type of CMT one has. Interestingly, through genetic testing it has been found that a number of people who were diagnosed as having CMT1 in pre-genetic testing days, really have HNPP. Similarly patients with chronic inflammatory demyelinating polyneuropathy (CIDP) are being rediagnosed as having HNPP. Genetic tests not only identify the type of CMT that is in a family, but they also provide information for family members about how CMT is inherited. As we develop therapies for different types of CMT, accurate genetic diagnosis (genotype) will be extremely important. Correlations between phenotypes and genotypes are important areas for future clinical CMT research.

Although the genes that cause CMT2 have not yet been identified, recent studies have narrowed in on the chromosome regions where the genes are located. Within the next few years these genes are certain to be identified. The forms of CMT2 comprise almost one third of the total CMT cases.

This will lead to genetic tests for the various types (or phenotypes) of CMT2.

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CMTA Hosts the First Annual Golf Outing

On August 14, 2000, the first annual golf outing to benefit the Charcot-Marie-Tooth Association will be held at the Sands Point Golf Club in Sands Point, Long Island, New York. The outing is being organized by CMTA Treasurer Richard L. Sharpe and association member, Robert Kleinman.

Mr. Kleinman's firm, AFA Protective Systems, Inc., the country's oldest central station fire and burglar alarm company, established in 1873, is underwriting the basic cost of the outing so that the profits can help find a cure and assist those with CMT. AFA Protective Systems has offices located throughout the East Coast.

Six to eight volunteers have already signed on to help with checking in the participants, giving out the "goody bags" and measuring the distance to the pin in the "shoot-out."

The event will take place on Monday, August 14th at the exclusive Sands Point Golf Club with a limited field of 18 foursomes. The golf course is known for its challenging and sporty layout and the culinary offerings of its outstanding Chef Dominick. The cost of the outing is $1,800 per foursome or $500 per individual with all ticket proceeds benefitting the CMTA.

The golf outing has a unique format, with a limited field and prizes being awarded to nearly 30% of the field. There will be no raffles, solicitations or other distractions to diminish the true golfing experience.

This fundraiser is the first of its kind to benefit the CMTA, but other successful fundraisers have included the West Chester Broadway Theater event, the Teddy Bear Auction, the Songfest in Oklahoma and an early golf benefit in which support group leader Mary Jane King played to raise money for the association.

For more information about this event, call Richard Sharpe at 1-800-606-2682.

New CMT Genetics Booklet Produced

By KAREN KRAJEWSKI, MS, Wayne State University

The genetics of CMT can be extremely confusing for people to comprehend. Often people are not even aware of what and how much is known about this topic. Soon there will be a booklet available through the CMTA that explains the genetics and genetic issues surrounding CMT. This booklet was written by myself and another genetic counselor to help explain this complex disease to patients. The genetics of CMT is complicated even for those who are "the experts." In the booklet, we have tried to give basic information about genetics and how it relates to CMT. We have also used many illustrations that will explain the information presented. We struggled as we wrote to make the information simple enough so that it is understandable to most, yet detailed enough so it will be useful.

After a diagnosis of CMT, people are often not provided with information about the genetics of this condition and how it may affect other family members. The majority of people with CMT have probably never interacted with a genetic counselor. Genetic counselors are trained to educate and support people who have inherited conditions. The inherited nature of CMT makes it very challenging when a person's diagnosis or care requires information from other family members. Health care issues are usually matters that are kept private and not something that are discussed in detail in many families. The idea about talking about health issues with distant family members is foreign to many. It can be extremely awkward to ask distant relatives for information about their health care. Many people are concerned about the chance that their children will be affected and want to know what testing can be done. Because CMT can be caused by a number of different genes, and because many of these have yet to be identified, testing is not always straightforward. Genetic testing can also be frustrating because sometimes test results do not give a simple "yes" or "no": answer. They may in fact create more questions than answers. The combination of this booklet and genetic counseling can provide patients with a clear understanding of their disease.

Our CMT clinical study at Wayne State University is the largest of its kind in the country and we have had the privilege of evaluating individuals from all over the world. As the genetic counselor and clinic coordinator, I have had the opportunity to interact with most of the people who come to visit us. We hope that this booklet will be a benefit to individuals and families with CMT.

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RESEARCH QUESTIONS AND FUTURE DIRECTIONS

As with the genetics breakthroughs, the above advances in molecular biology have provided important insights into the pathology of CMT. Every piece of this puzzle we put together adds to the body of knowledge about CMT, and opens doors that will provide further answers.

Some of the research questions generated by these advances are:

- What is the role of peripheral myelin protein, PMP22, in the development of CMT1A? How does making a little extra PMP22 so severely damage the myelin and nerves. There are clearly many intermediate levels including promoter genes and transcriptions factors before the final affected nerve is reached.

- How does demyelination occur on the peripheral myelin region of the nerve via the above gene products? Biopsies of a peripheral nerve, such as the sural (located in the calf of the leg), show the damage caused by the defective overexpressed PMP22 in CMT1A. These do not show how this damage occurs. Exactly how this process takes place is the $64,000 question!

- Why do different mutations on the same PMP22, P_0, or EGR2 gene cause different severities of disease, some of which are mild and others quite severe?

- Why is the PMP allele on chromosome 17, called HNPP, sometimes different (lesser severity and relapsing-remitting course) from the more severe CMT1A reduplication at the same location?

- It is now known that in CMT1 the degeneration that takes place is due to secondary axonal involvement rather than demyelination. What is the relationship between Schwann cells, that make myelin, and axons? This leads to another research question:

- How do mutations in Schwann-cell myelin cause axonal degeneration?

- How does neuropathy occur in the majority of CMT1B cases, which are caused by P_0 or peripheral protein zero gene, and have an unusual late childhood onset and less severe demyelination?
- CMTX studies show that in many instances of CMTX onset occurs in late childhood and demyelination is less severe. How does the abnormality take place?
- Why in some myelin-protein P_0 mutations associated with CMT2, with slight slowing of nerve conduction velocities, is there "significant" axonal involvement?
- Why in CMTX where nerve conduction is slightly reduced are axons damaged?
- Why is there variability in disease severity within the same family?

Three other research questions relating to the "here and now" are:

- What are the effects of toxic medications and even pregnancy on the speed of progress of Charcot-Marie-Tooth disease?
- How may it be prevented or reversed?
- How can we slow down or prevent the "axonal" atrophy or weakness in individual patients?

Answers to these questions will unlock the mystery that is CMT, and lead us further on the road to the development of treatments to "stabilize," "reverse," or treat CMT.

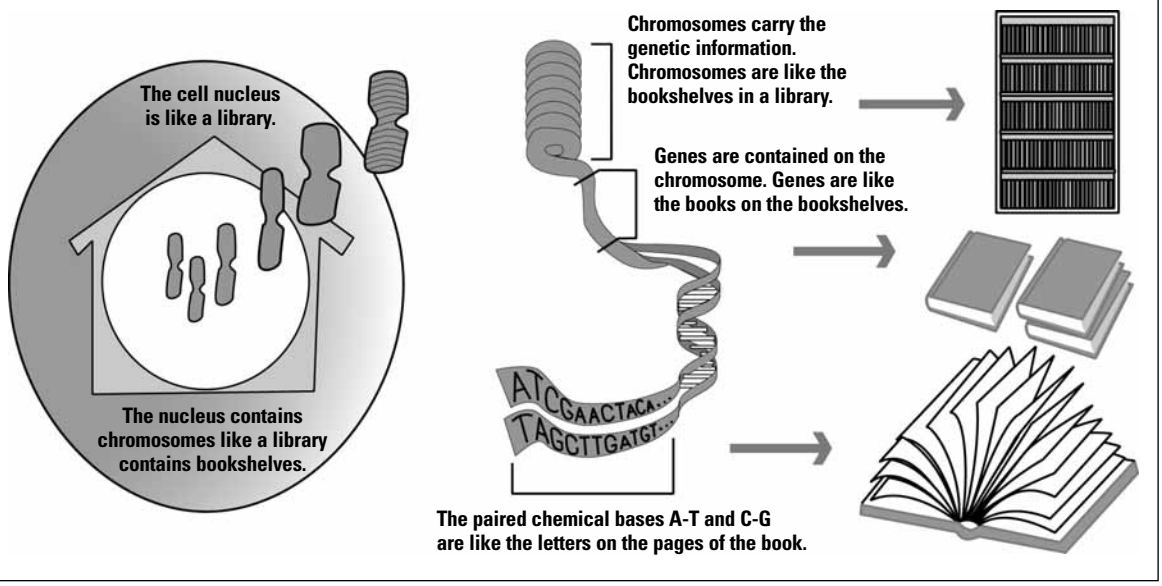
Answers to research questions will lead us to the development of treatments for CMT.

TREATMENT AND CURE

Although research is taking place in gene therapy for CMT, it is not ready to be tried in humans. However, it may offer hope in the future. Some research that seems promising includes:

- The use of growth factors or trophic factors to prevent motor neuron and nerve degeneration, and finally hinder or reverse atrophy and weakness.
- Using pieces of viruses to introduce therapeutic genes into Schwann cells, nerves, or muscle.
- Genetically altered T cells to introduce genes into the peripheral nerve.
- Alteration of promoter genes and transcription factors to slow progress in CMT or even reverse disease progression.
- Developing pre-implantation therapies to ensure children will not have CMT.
- Developing better orthotics and other rehabilitation aids to enable individuals with CMT to maintain their independence.

FIGURE 2: GENES AND CHROMOSOMES



The History of CMTA-Funded

By PAT DREIBELBIS

Editor's note: In this, our research issue of the newsletter, it seems only appropriate to remind our readers of the many grants that have been issued since the CMTA began funding research only five years ago. Here is the breakdown, by year.

1995

Three Summer Student Grants

The first grant was made to Erasmo Perera under the direction of Dr. Lisa Baumbach at the University of Miami to study genetic anticipation in CMT1A. The hypothesis of the study was that an increasing severity of presentation within a family is associated with DNA rearrangements which disrupt a number of normal genes in the CMT1A duplication region of chromosome 17, giving rise to different disease manifestations.

The result of this grant was a furthering of the study of anticipation and the use of a Clinical Severity Scoring System which evaluates a person's disease course over time based on a neuropathic deficit score.

A second summer research grant was made to Steve Sepal working with Dr. Carol Oatis at Beaver College in Glenside, PA. The study was entitled "Moderate Resistance Exercise: Its Effect on Patients with Charcot-Marie-Tooth Disease." The study tested the improvement of functional capacities and strength of patients using moderate exercise.

The study had too few subjects, so a suitable comparison between the control group and the study group could not be made. Some study subjects did report mild improvement in balance and walking capacity after the exercise regimen.

The third summer research grant was made to Dr. Harohito Sago, under the direction of Dr. Roger Lebo at the University of CA, San Francisco, to study "Preimplantation Diagnosis of CMT1B." The purpose of the study was to develop a diagnostic test for mouse Trembler J and human CMT1B point mutations.

The study showed that preimplantation diagnosis could make in vitro fertilization an option for couples who wanted to assure that their children did not have CMT. This study studied only type 1B gene mutations.

Dr. Lisa Baumbach (right) has mentored several CMTA fellows including Mary Ellen Ahearn (left).

1996

Anita Harding Charcot-Marie-Tooth Association Postdoctoral Fellowship

The first $35,000 grant was awarded to Dr. Peter Denton, working with Dr. Jeffrey Vance at Duke University in Durham, NC. Dr. Denton's study involved mapping and identifying the CMT2a gene. CMTII is the second most common form and is neuronal, in which the axon of the nerve is affected, rather than the myelin sheath.

The most exciting result of this first postdoctoral study was that Dr. Vance's laboratory received a National Institutes of Health grant, based on the success of Dr. Denton's CMT2 work.

1997

Armington Research Fellowship of the Charcot-Marie-Tooth Association

Dr. Agnes Jani of Wayne State University, Detroit, MI, received the first Armington Research Fellowship to study under Dr. Michael Shy and Dr. John Kamholz. The project focused on gene therapy in an animal model of CMT1. The goal of the project was to use the techniques of molecular biology to correct the genetic defect in CMT1B Schwann cells and thus, to lessen the clinical effects of the disease in patients. Dr. Jani uses P_0 (zero) knockout mice which develop a severe demyelinating neuropathy in "childhood" and mimics CMT1B. She has developed an adenoviral vector to

Research

introduce the missing P_0 gene into the mice and thus, remyelinate the peripheral nerves of the mice.

Having learned that weakness and loss of sensation in demyelinating forms of CMT is caused by secondary damage to the nerve itself rather than damage to the myelin, they are changing the focus of gene therapy to introduce genes for growth factors into nerves to prevent the disintegration of the axon.

Four Summer Student Grants

A grant was made to Mr. Spencer Blackman, working with Dr. Lisa Baumbach, at the University of Miami, continuing the investigation of genetic anticipation in CMT1A that was funded in the summer of 1995. Different disease manifestations among kindreds are believed to be linked to rearrangement of DNA in the CMT1A duplication region of chromosome 17p11.2.

One of the most important outcomes of Spencer Blackman's study was the discovery of a unique polymorphism in intron 3 of PMP22 which seems to be responsible for two severely affected, unrelated CMT patients of African-American heritage.

A second grant was made to Dr. Eleni Zamba of the Cyprus Institute of Neurology, who worked under the mentorship of Dr. Lefkos Middleton. She collected families with CMT2 and recessive CMT for evaluation aimed at identifying additional genes and proteins involved in causing CMT.

Dr. Eleni Zamba returned to Cyprus having worked in the EMG and nerve conduction laboratories of Dr. Dale Lange at Columbia University, NY. She has since been able to participate in the identification of autosomal recessive and autosomal dominant forms of CMT2 in Europe.

The third grant recipient was Dr. Odile Dubourg, working with Dr. Pierre Bouche at the Hospital de la Salpetriere in Paris, France. He studied 210 patients to classify the families according to motor nerve conduction velocities and modes of inheritance in order to develop a strategy for diagnosis based on those two pieces of evidence.

Dr. Dubourg concluded from his studies that the 17p11.2 duplications should be tested first in all patients with a median nerve conduction velocity below 30 m/s. When nerve conduction velocities are above 30, both the connexin 32 mutation and the 17p11.2 duplications should be considered.

Twenty-five research grants have been awarded by the CMTA in the years from 1995 to the present.

The final recipient was Jeffrey Bonneville from the University of Health Sciences, St. Johns, Antigua. Mr. Bonneville developed a survey which was mailed to 1,000 CMT patients and 2,500 members of the American Board of Certified Orthotics and Prosthetics. The survey studied the types of orthotics in use by CMT patients and the level of understanding of orthotics by those patients.

As a result of the orthotics study, recommendations were made that articles on orthotics should be published to help educate the CMT population on orthotic management and terminology. Further, education is recommended for orthotists so that CMT is recognized as a diagnostic group.

1998

Armington Research Fellowship and Two Other $35,000 Grants

The 1998 Armington Research Fellowship was awarded to Dr. Lawrence Reiter, working with Dr. James Lupski at Baylor College of Medicine in Houston, TX. His project is entitled "An EST Approach to the Identification of CMT Candidate Genes." EST (expressed sequence tags) is a novel approach for characterizing expressed genes by partial DNA sequencing. Dr. Reiter hopes to create an EST library in order to identify other genes that may be responsible for peripheral nerve disorders.

Dr. Reiter succeeded in sequencing some cDNAs and found some of the genes he expected, like PMP22 and MPZ. However, he experienced some technical difficulties with the vector and host bacterial strain of the library. The work is ongoing so that the library can be completed.

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CMTA-FUNDED RESEARCH

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The second $35,000 grant from the Charcot-Marie-Tooth Association went to Dr. Mary Ellen Ahearn of the University of Miami, working with Dr. Lisa Baumbach. They are studying genetic anticipation in families with CMT1A. Some of their goals are to evaluate the possible rearrangement of DNA at chromosome 17 and to evaluate the incidence of a new polymorphism in the African-American CMT population, with possible connections to disease severity.

Dr. Mary Ellen Ahearn's work revealed the need for a much larger sampling of African-American CMT families in order to understand the unique polymorphism found in about 35% of the study group. The polymorphism has never been found in a Caucasian patient. The study is ongoing and looks to discover whether the polymorphism affects disease severity.

The final $35,000 grant, the Buuck Family Research Grant, was awarded to Dr. Agnes Jani to continue her work using molecular biology techniques to correct the genetic defects of CMT1B Schwann cells and lessen the clinical effects of the disease.

Four Summer Student Grants

A grant was awarded to Dr. Elif Yosunkaya, working with Dr. Roger Lebo, at Boston University, Center for Human Genetics. Her study was titled "Fetal Gene Therapy of Peripheral Neuropathy" and used small laboratory animals with multiple fetuses and short gestation periods to study the delivery of genes to fetal nerve cells that migrate during development.

Dr. Yosunkaya's work during the summer allowed gene therapy in fetuses to move one step closer to reality.

Dr. Jeffrey Vance (center) of Duke University has been a significant contributor to Type II research.

Another grant was presented to Ms. Julie Cole, working with Dr. Gareth Parry, at the University of Minnesota to study "Phenotypic Variability in Hereditary Neuropathy with Liability to Pressure Palsy (HNPP)." The study followed a large family (50 members) with varying symptoms related to HNPP.

Ms. Cole's study revealed the variety of symptoms possible within a single family with HNPP, including significant pain, paresthesias (numbness or tingling), episodes of weakness, and fasciculations (spontaneous, irregular contractions of a muscle, apparently at rest.)

A third grant was given to Jennifer Anderson, working with Dr. Margaret Pericak-Vance, at Duke University. Her study was entitled "Search for Genetic Modifiers for Charcot-Marie-Tooth Type IA." The study seeks to identify the clinical variability with pedigrees and to discover if there is a genetic factor that modifies the major gene effect.

Jennifer Anderson's work determined that there was no correlation between motor nerve conduction velocity and gender, gender of transmitting parent, age of onset, age at exam or disease duration. They are continuing to search for a modifying gene that might account for pronounced clinical variability.

The final grant was presented to Chandra Wan, working with Dr. Howard Hillstrom, at the Pennsylvania College of Podiatric Medicine, Temple University. Ms. Wan's study was entitled "Efficacy of Conservative Support and/or Realignment Based Therapies for Managing the CMT Patient." The study compares the use of MAFOs (molded ankle-foot orthoses) and NPFOs (in-shoe neutral-position foot orthoses) with regard to success in managing foot and ankle malalignments.

Chanda Wan's project found that improvement in walking speed, step length, stride length and pelvic tilt angle all improved with molded ankle-foot orthoses. However, a larger sample size is recommended to improve the statistical data.

1999

Armington Research Fellowship and Two Other $35,000 Grants

The first grant was given to Dr. Ken Inoue, working in the Baylor College of Medicine, Department of Molecular and Human Genetics, with Dr. James Lupski. His study is entitled "Large-Scale DNA Sequencing of Entire 1.5-Mb CMT1A Duplication/HNPP Deletion Region."

In part, the study seeks to identify new genes contained within the 1.5-Mb region that

continued on page 22

Why Support CMT Research?

By ANN LEE BEYER

Like its predecessor, the Third International Conference on Charcot-Marie-Tooth Disorders was a defining moment in the history of the CMTA. In light of the major breakthroughs that occurred in genetics, molecular biology, and gene therapy during the ten-year period between conferences, the conveners of this conference wanted an interdisciplinary conference. Geneticists, molecular biologists, and clinicians, who do not usually meet with one another to share and discuss their findings and theories about CMT, actually came together and talked to one another about their work. An interdisciplinary approach made for an incredibly exciting conference, where one could almost reach out and touch the energy that was generated

The first goal has been met. The conference was a success. CMT has finally been placed on the international research map, and gained the attention and respect of the research community. The proceedings have been published in a volume, Charcot-Marie-Tooth Disorders, by the New York Academy of Sciences (Volume 833), which can be found in major research institutions, medical schools, and leading universities throughout the world.

Today more and more scholarly papers on CMT are being accepted by major medical and research journals. In addition to research, communication is essential to fully understand and correlate our advances (genetics, therapy, surgery etc.) This October, we are booked to have a full day workshop on CMT at the annual senior neurology (American Neurology Association) meeting in Boston. A first! The purpose of this meeting is to report on and discuss advances in CMT. The morning will be reserved for CMT Fellows who will present their cutting-edge CMT research, the afternoon for senior researchers. We are working to make this day a great success and to repeat it on an annual basis. We also believe it is of utmost importance to have international meetings on CMT every three years.

The second goal of the conference, which was to foster collaboration and interdisciplinary research projects, is up to us. With the knowledge that has been gained from this conference, we can now begin to encourage and fund these projects. In the coming years, as a result of the Third International Conference, many more breakthroughs will occur. However the future of CMT Research is up to us.

Research is and will continue to be vitally important, not only for our generation, but especially for the generations to follow, our children and grandchildren. It is very painful and extremely frustrating for parents to see their children, and then grandchildren, develop a disease that can, and most likely will, affect their ability to live a normal life.

When I had my children, I did not know that I carried a hereditary disease. Consequently I never went through the anxiety parents tell me they have experienced of worrying about whether any of their children would have CMT. Or the guilt that so many report they feel because their children did indeed inherit it.

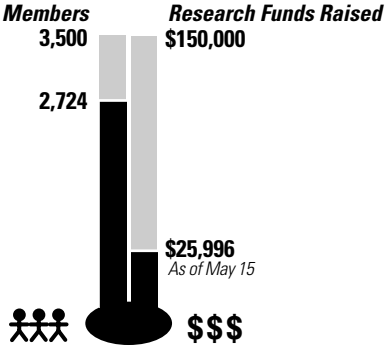
Neither did I have to make the decision not to have children, as people I know have done. Some because they did not want their children to go through the pain and suffering they have experienced. Others because they did not want to pass down a hereditary disease.

However, I find that I am anxious about my grandchildren. As they grow and develop, I find myself looking at their feet, watching their gait, feeling very uneasy when some of them walk a little later than I think they should. At the same time, I also hope that my fears are groundless. That just maybe they've escaped it. However, the reality is that CMT will continue to show up in future generations unless each of us makes a concerted effort to work towards a cure now.

*Every Dollar **You** Contribute Brings Us Closer to A Cure.*

Our Research Fundraising Goals as of May 15, 2000:

Our research fundraising has just recently begun, so the numbers are low. We hope to report on great additions to the research fund in our next newsletter.



Educating and Generating Interest at Medical Conferences

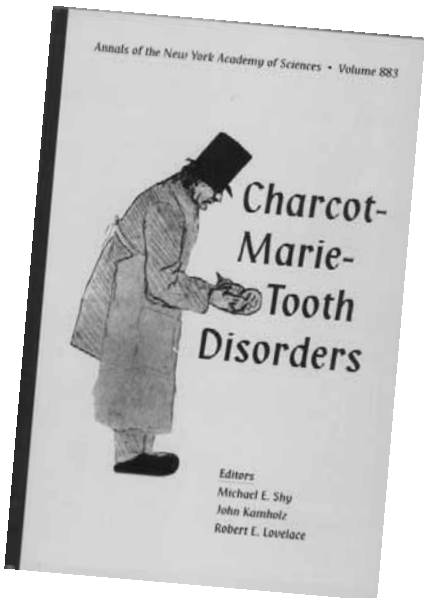
By ANN LEE BEYER

As part of our commitment to educate and generate interest in CMT in the medical and research communities, in 1999 we had booths at four major annual medical conferences. In April we represented the CMTA at the 2nd World Congress in Neurological Rehabilitation, in Toronto. A few days later, we staffed a booth at the American Academy of Neurology, also in Toronto. In October, we attended the American Neurological Association in Seattle and then went to the American Society of Human Genetics in San Francisco.

CMT generated a great deal of interest at the 2nd World Congress in Neurological Rehabilitation. It was the first time we were invited. Many people stopped by our booth, talked to us about CMT, put their names on the CMTA mailing list, took our literature, bought *Physician's Handbooks* and even came back to sit, talk and ask questions about CMT.

At the American Academy of Neurology meeting, CMT was mentioned in the opening address, another first. Not only was CMT mentioned in the opening address, but three posters on CMT research were presented during the Poster Session—an important part of the conference. In addition, the poster submitted by Dr. Agnes Jani from Wayne State University, one of the CMTA-funded researchers, was voted one the ten best posters of the conference.

At the American Academy of Neurology Meeting in Seattle, advance copies of the Proceedings of the Third International Conference showed off the work of the CMTA.



As we were getting ready to attend the American Academy of Neurology Meeting in Seattle, we learned that the proceedings of the Third International Conference on Charcot-Marie-Tooth Disorders, with the wonderful drawing of Charcot—which is instantly recognized by every neurologist—on the cover, had just been published. Luckily we were able to get advance copies to proudly show neurologists the work the CMTA has been carrying out, and also to encourage them to order it.

We also held a meeting of the CMTA Medical Advisory Board, where Dr. Valerie Street, a CMTA-funded researcher, presented a paper on her work. Among other things, the Medical Advisory Board established two committees, one to revise the Physician's Handbook, and another to explore the possibilities of establishing a North American Consortium for CMT Research. In addition, new members were appointed to the Neurotoxic Drug Committee, and a discussion was held on the need for research on the drugs included on the CMTA's neurotoxic list. It was also decided that any study would have to include herbal medicines, as well as tranquilizers.

For the past few years several members of our Medical Advisory Board had been telling us that the CMTA needed to have a booth at the American Society of Human Genetics meetings. In 1999 we finally made it, and were very surprised, delighted and gratified at the interest in CMT. What drew the most attention was a poster we had made on the dangers of taking Vincristine, a drug used to treat cancer, and one of the drugs contraindicated when there is CMT in the family. This is a subject you will be hearing more about.

During the year 2000 we will be promoting awareness of CMT at six conferences: the American Academy of Neurology Meeting in San Diego, where a Medical Advisory meeting will take place; the American Physical Therapy Association in Indianapolis; the Neuropathy Association in Branson, MO, where board member Ardith Fetterolf has been invited to speak; the American Association of Human Genetics which takes place In Philadelphia; the Podiatric Association also in Philadelphia, and the American Neurological Association in Boston, where a one-day Forum for Young CMT Researchers as well as a "State of the Art Symposium on CMT Research" will take place.

Thanks to a benefactor, the CMTA will have a new booth for these conferences, in our teal and white colors, with velcro-backed panels that we can change or add to, depending on the focus of conference. We are very excited about this booth, as it will draw attention to CMT.

GIFTS WERE MADE TO THE CMTA IN HONOR OF:

Mrs. Betty Berris
Barbara & Robert Bernstein

Cathy Brooks
Janice & Kenneth Dunham

Stephanie DiCara
Marlene & Carol Prestiano

Joseph Fulmino
Showtime Networks, Inc

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Mike Twigg
Dave Aldersley

Daniel Weingarten
Absecon Nursery School

Minna Wurtzburg's Birthday
Sis & Joseph Lelewer

GIFTS WERE MADE TO THE CMTA IN MEMORY OF:

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Kay & William Conlee

Cleo Belz
Bob Belz

Ralph H. Binford
Margaret Binford
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Mr. & Mrs. Robert Kleinman

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Ralph A. Hall
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His U.S. family

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Sheri Sach's Mother
Social Workers of Childrens' Hospital of San Diego

Larry Smith
Mona Smith

Annabelle Warren
Elizabeth Coryell

VISIT OUR HOMEPAGE
at
www.charcot-marie-tooth.org
The site was provided through the generosity of
MindSpring

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:_____

_____

Updates on Current CMTA-Funded

Large-Scale DNA Sequencing of Entire 1.5-Mb CMT1A Duplication/HNPP Deletion

By KEN INOUE, M.D., Ph.D., Baylor College of Medicine, Department of Molecular and Human Genetics

The purpose of this project is to obtain the DNA sequence data of the entire CMT1A duplication/HNPP deletion region on chromosome 17 and search for new genes which may be related to the phenotypic variability of CMT1A and HNPP. These data will give us important information to study the genomic complexity of this critical region.

As the initial step, we have generated a collection of large genomic DNA fragment clones called PAC (P1 artificial chromosomes) and BAC (bacterial artificial chromosomes) that cover this 1.5-million base-pair region as a map to work with. Using these PAC and BAC clones, we can isolate certain portions of the entire human genome as a clone for further analysis. To construct this collection of DNA fragments to be aligned in the correct manner representing their arrangement in the genome (this is called contig), we selected multiple sequence tagged sites (STSs, short DNA sequences that work as check points or milestones) in this region and used them to screen the PAC and BAC libraries. We selected 55 PAC and BAC clones with at least two-fold coverage of this region.

After the completion of this contig construction, we collaborated with Dr. Bruce Birren at Whitehead/MIT Genome Sequencing Center and started large-scale sequencing of this region. Since Dr. Birren's group utilized an independent method and approach to construct their contig of this region, we could compare and collate our data to generate a better map. Thirteen clones that minimally tile the entire region were selected for sequencing. Shotgun libraries (smaller pieces of DNA made by chopping up each PAC and BAC clone) were constructed and they were sequenced utilizing automated DNA sequencers at Whitehead/MIT Genome Sequencing Center, followed by computer-based assembly of raw data into contiguous large sequences. More than 90% of this region was completely sequenced

CMT Research at the University of Utah

By MARK BROMBERG, M.D., Ph.D, University of Utah, Department of Neurology

Our program received a research award from the CMTA for Victoria Lawson, M.D., to study correlations between the number of motor units innervating a muscle and muscle strength. Our hypothesis was that weakness in CMT1A is due to denervation (loss of motor neurons) and not to slow conduction. Our research plan was to compare motor unit counts between subjects with CMT1A and CMT2 with the hope of showing that for a given level of strength there would be roughly equal numbers of motor units.

Our progress to date has been to explore different motor unit estimation techniques in patients with CMT. Hypertrophic nerves make it difficult and uncomfortable to stimulate the nerve with percutaneous stimulation in CMT1A, and we are focused on a different technique. So far, we have gathered data on CMT1A and CMT2 patients. We have also expended a considerable degree of effort in building a manipulandum to measure the strength of finger abduction. Accordingly, we had to contract with a local biomedical engineering company and we have tried a number of prototypes and now have a working manipulandum. We have also collected data on normal individuals to determine the range of normal strength and to access test-retest variability.

SCHOLARSHIPS

The President's Committee on Employment of Individuals with Disabilities has developed programs designed to ensure that the disability community will have highly educated, knowledgeable leaders in the years to come.

One program is designed to help individuals with disabilities attend college and graduate school. Several companies and organizations have agreed to sponsor scholarship programs, coordinated through the President's Committee.

NIKE offers a $2,500 scholarship for individuals with disabilities who plan to major in sports, recreation management, sports marketing, or sports medicine in college. Nordstrom sponsors five $2,000 scholarships for individuals with disabilities who are planning on majoring in business.

The ELA Foundation is sponsoring a $2,000 award for women who are planning to attend graduate school, and who are hoping to eventually "change the face of disability in their life work."

To file an application, visit the President's Committee web site at www.pcepd.gov and choose the "scholarship" link.

Research

and the remaining portion will be completed soon.

We have already identified at least 15 genes in this region and they are under characterization by various molecular biological techniques. These data will enable us to further evaluate yet uncharacterized genes as candidates for modifiers of the phenotypic complexity of CMT1A and related disorders. A paper describing this study is under preparation and will be submitted for publication soon.

We have also performed other studies partially supported by the CMTA fellowship. One is a study of the molecular basis of duplication of the proteolipid protein gene leading to a myelin deficiency of the central nervous system called Pelizaeus-Merzbacher disease. This study was published in *Annals of Neurology* (1999;45:624-632). The other one is an identification of a mutation in a myelin-specific transcription factor gene, SOX10, in a patient with myelin deficiencies in both central and peripheral nervous systems, accompanied by Waardenburg-Hirschsprung disease. This study was also published in *Annals of Neurology* (1999;46:313-318). The latter will be further expanded to understand the molecular basis of the regulation of myelin genes by SOX10, which is supported by the CMTA fellowship for the coming year.

While we were working on motor unit estimation in CMT, we encountered a large family with nerve conduction findings supporting CMT type 2. Dr. Lawson has expended a considerable effort in verifying the pedigree and contacting as many symptomatic and asymptomatic individuals as possible and performing detailed clinical and electrophysiologic evaluations. In parallel with the clinical evaluations, we are investigating the genotype for this family through Dr. Kevin Flanigan's laboratory at the University of Utah. At this time, linkage analysis is in progress and no specific genetic information is available. An abstract on the CMT type 2 family has been submitted to the ANA.

Dr. Lawson will continue her efforts with motor unit number estimation in both CMT1A as well as type 2 patients.

Linkage and Candidate Gene Analysis of Two Families with Charcot-Marie-Tooth Neuropathy Type 1C

By VALERIE STREET, M.D., University of Washington

We are studying two large multi-generation families that have CMT Type 1. These two families do not have an alteration in the three genes [peripheral myelin protein (PMP-22) on chromosome 17, myelin protein zero (MPZ) on chromosome 1, or early growth response 2 gene (EGR2) on chromosome 10] previously shown to underlie CMT1. These two families have been designated as CMT1C and may have alterations in the same gene or two different genes. Discovery of the gene(s) causing CMT1 in these two families will enhance our understanding of the basic processes controlling myelination and nerve function.

To determine the location of the CMT1C gene(s), we are using a genetic linkage and mapping approach. We are checking approximately 400 neighborhoods spread across the 22 different human chromosomes. [We have already eliminated the X chromosome as the home for the CMT1C gene(s), because the disease in both families can be passed from a father to his son.] We have analyzed approximately 60 of these 400 neighborhoods in one of the CMT1C families. This analysis indicates that the CMT1C gene in this family does not reside at any of these 60 areas on chromosomes 14, 19, 20, 21, or 22. Therefore, we are continuing to analyze the remaining 340 locations, selecting those areas that are known to be gene-rich or hold a promising candidate. Once we have discovered which neighborhood the gene resides in, we will refine our genetic map by narrowing the gene location to a few addresses within the neighborhood. The gene at each address will then be analyzed in members from the two families to look for alterations in the DNA sequence or copy number. This final mutational analysis will allow us to reveal the gene causing CMT1C in each family.

I would like to thank the CMTA and my mentors, Drs. Phillip Chance, Thomas Bird, and Bruce Tempel for providing me with this research opportunity. It has been particularly rewarding to pursue a CMT-causing gene alteration given that I have CMT Type 1A.

Medicare Patients' Rights

(This information was provided from a publication of the Office of Services for the Aging.)

MEDICARE 2000

1. The Original Medicare Plan
2. The Original Medicare Plan with a Supplemental (Medigap) Insurance Policy. Ten standardized Medigap policies are designed to supplement Medicare's benefits and help fill the gaps in Medicare coverage, such as deductibles and co-insurance.
3. Medicare + Choice. These are managed care plans that have contracts with Medicare. These are generally HMOs and PPOs (Preferred Provider Organizations.)

WHAT IS MEDIGAP?

There are private insurance policies which are designed to help pay for some Medicare gaps and offer some coverage that Medicare does not pay for, such as partial reimbursement for prescriptions.

With a Medigap policy, you have the freedom to go to any doctor anywhere in the United States and as often as you need. You do not need a Primary Care Physician and you can see any specialist without a referral.

There are 10 policies sold which are standardized for easy comparison shopping. All policies are called Plan A through Plan J. Plan A is the least expensive and the least comprehensive. Plan J is the most expensive and the most comprehensive. The letter designations cannot be changed and neither can the combination of benefits. The ONLY difference in the policies from one company to another is the price. **Research the prices of Medigap policies...the price difference can be quite significant.** Comparisons of competing Medigap insurance companies showed Plan A costing $55.00 from one company and $134.75 from another.

Not everyone needs a Medigap policy. If you belong to a Medicare HMO or are on Medical Assistance, you don't need Medigap insurance.

MANAGED CARE PLANS

A Managed Care Plan is a group of doctors, hospitals and other health care providers (Network Plan Providers) who have agreed to provide care to Medicare beneficiaries in exchange for a fixed amount of money from Medicare every month. Beneficiaries must have Part A and Part B of Medicare to use this plan. One type of Managed Care Plan is an HMO (Health Maintenance Organization). HMOs may offer additional benefits such as preventive care, hearing care, dental care, vision care and prescription coverage. Medicare HMOs are still Medicare!

PREFERRED PROVIDER ORGANIZATIONS (PPOs)

A PPO is a managed care plan that has a network of providers from whom enrollees can get all covered care, but they also have the option of going outside the network of providers. PPOs are not HMOs because you do not need a primary care physician or a referral to see a specialist. For out-of-network providers, there is a deductible and a 20% co-insurance up to an annual maximum.

MEDICARE PATIENTS' RIGHTS

As a Medicare beneficiary:

- You have the right to receive emergency care if you believe the problem may cause your health serious danger without immediate care. You never need prior approval for emergency care anywhere in the United States.
- You have the right to appeal a denial of payment or denial or reduction of service under the original medicare plan or an HMO.

APPEALING SERVICES THAT ARE REDUCED OR DENIED

- If the services you are receiving are reduced or denied, you have the right to an expedited decision by calling the HMO member benefit department and stating that "I am calling to request an expedited 72-hour decision because I believe that my health could be seriously harmed if my services are reduced or cut."

DISABILITY RESOURCES

There is a new gateway to disability information on the Internet called the Disability Resources Monthly Guide to Disability Resources on the Internet. It helps people with disabilities, family members and service providers find the best information online. Thanks to a generous grant from the Bell Atlantic Foundation, the web site has a new address at www.disabilityresources.org.

- Include a letter from your physician noting the urgent need for the services. The health plan is obligated to process the 72-hour review and is not permitted to turn down a request when it is supported by a physician.
- Be certain to record the name of the person with whom you spoke and the date and time of the call.
- Put your request in writing. Keep a copy for yourself and mail the original to the HMO by registered mail, return receipt requested.

PEER REVIEW ORGANIZATION (PRO)

A PRO ensures that Medicare patients receive necessary and good quality medical care. Each state has its own PRO.

You have the right to receive all the hospital care that is necessary for the treatment of your illness. Your discharge date should be determined solely by your medical needs, not by Medicare payments. If you believe you are being discharged too soon from the hospital, request a review by PRO.

STEPS TO REQUEST A REVIEW:

- Call PRO—the hospital must honor the request by a patient for a review.
- Contact the hospital administration and immediately tell them, "I'm too sick to leave; I want a PRO review of my case."
- The patient will be required to sign a document called a Hospital Notice of Non-Coverage, but there is NO liability.
- The PRO review process is a Free Process.

ANOTHER HELPER IN THE MEDICAL CARE PROCESS: AN OMBUDSMAN

An Ombudsman (mediator) is a trained individual who can help if you have a concern or complaint about the quality of care or treatment in a long-term service facility, e.g. in a nursing home or personal care home. Ombudsman services are confidential and free.

MDA Home Page Offers "Ask the

TRAEGER THERAPY

A letter to the editor in the last issue discussed the therapy called Traeger Body Works. A woman reported measurable success in moving her toes after a year and a half of therapy. Many people called the office to find out more about the program. Unfortunately, information was difficult to come by. There are not many practitioners of Traeger therapy in the United States. The massage therapy involves a gentle rocking of the body parts in a rhythmic fashion. It is designed to release tension and be very relaxing. If you are interested in the procedure, you must call therapy centers in your area and ask if anyone on staff is certified in Traeger massage therapy.

The Muscular Dystrophy Association web site at www.mdausa.org has section called "Ask the Experts" which is provided for informational and educational purposes. It is not intended to replace or be interpreted as professional advice, medical or otherwise. However, having stated that disclaimer, the section is staffed by medical experts and the section on Charcot-Marie-Tooth contains answers from some of the best known CMT clinicians and researchers in this country. Many of them are members of the CMTA's Medical Advisory Board.

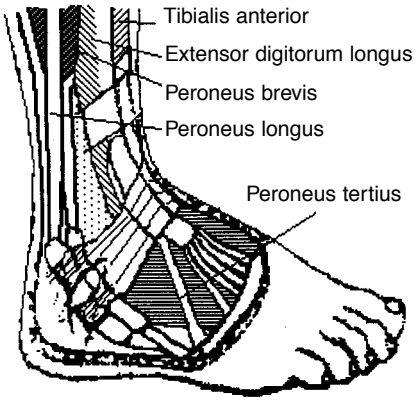
For those of you who do not have access to the Internet, a few of the questions and answers are provided below:

FOOT SURGERY

I have CMT and have seen an orthopaedic surgeon. My heel turns in as is typical of CMT. He recommends a surgery that involves cutting my heel and repositioning it toward the outside to compensate for the inward turn. I am hoping this will help my balance and improve the appearance of my foot. Is this type of surgery unusual? Do you have an opinion about it?

Reply from John Hsu, M.D., F.A.C.S., Clinical Professor, Orthopaedics at the University of Southern California and the University of California, Irvine

The specific surgical operation of cutting the heel bone and repositioning it—(calcaneal osteotomy) to compensate for the inward turn (varus of the heel) is a useful operation, and when done correctly, it helps physically reposition the heel and may also take away some pain, if it is present. It may also improve the appearance of the foot. It is not an unusual operation, when performed by an experienced orthopaedic surgeon, and it will give benefits.



However, the main problem is recurrence of the turning of the heel after the corrective surgery. This may occur if there is muscle imbalance; thus, such an operation needs to be done after full understanding of what muscle forces are working to have pulled the heel into a varus position over time. These muscle forces may need to be rebalanced through other surgical procedures or braced against.

Information as to the age of the patient, the strength of the muscles around the foot and ankle, such as the muscle grading of the peroneal longus, peroneal brevis, anterior tibial, posterior tibial and gastrocnemius soleus is useful in the final decision *(see illustration)*. Also, the medical evaluation should take into account how long the problem has been going on, what type of shoes are being worn, and whether any braces have been tried or are currently being used.

COLD AND HOT FEET

I'm 37 and have Charcot-Marie-Tooth disease (CMT). I have read that many people with CMT experience very cold and/or very hot feet, as I do, but I have never read an explanation as to why this occurs. Can you help me to understand? Is there any treatment or procedure that I can use to alleviate this problem?

Reply from Dr. Carlos Garcia, MDA Clinic Director, Tulane University Medical School, New Orleans, LA

Poor tolerance to cold weather is probably due to the loss of muscle mass in feet and legs. The loss of muscle mass due to nerve fiber loss is the reason for the wasting of the legs and feet in individuals with CMT. Decreased muscle mass decreases the amount of blood that goes to the lower limbs. The circulating blood is what keeps the normal temperature in the tissues. Bones, tendons and joints require less blood. Cold feet and legs are frequent complaints in individuals with CMT. The only treatment is to use leg warmers and decrease exposure of the affected areas to cold weather.

Having hot feet or burning feet is a sign of axonal neuropathy (loss of wiring in the nerves). Involvement of the axons is frequent in CMT. Pain due to the nerve damage in CMT responds to Neurontin (gabapentin), an anticonvulsant. This is a prescription medication that needs to be prescribed, preferably by a neurologist.

Experts"

HNPP QUESTION: PAIN AND FATIGUE

I'm trying to determine how much of the pain and fatigue I've been having is due to HNPP and how much might be caused by other complicating factors (osteoarthritis, degenerative disk disease, prescription medicines). I've just read that intense muscle pain and fatigue may be caused by one of my medications: Pravachol, a cholesterol-lowering drug. (I also take Relafen for arthritis pain, Synthroid, HRT, and occasionally Prilosec for GERD.)

The pain/fatigue problem: after long hours of walking or standing, foot pain becomes intense, leg/calf muscles tire and ache, and movement becomes very difficult. Rest—lying down—eventually relieves the aching/throbbing, but it may take 4 to 6 hours for the symptoms to diminish. Which is more likely the cause of this problem: the medicine or the HNPP?

Reply from Michael Shy, M.D., Wayne State University School of Medicine, Detroit, MI

The natural history of HNPP is not well known so that the question has to be answered based on personal experience, not only with HNPP, but also with patients with various forms of CMT. Pain that is directly the result of CMT or HNPP does occur but is infrequent. Typically this pain consists of burning or a pins-and-needle sensation in the bottom of the feet. However, in CMT, because people often walk abnormally, unusual stresses are put on their ankles, knees and hips. Thus, CMT patients can develop arthritis pain earlier and more severely than patients without CMT. This type of pain usually consists of joint aching or throbbing. The treatments are similar to the treatment of arthritis in general. Whether similar arthritic pain occurs in HNPP is not well known. A reasonable assumption, if walking is abnormal, is that some of these pains may be arthritic. Muscle pain can also be more severe if walking is abnormal because more effort may be required to walk than if the peripheral nerves were functioning normally.

With respect to specific medications, these may be exacerbating some of this pain as well. The best way to approach this possibility is to discuss with your physician the specific needs for each medication and whether alternative medications are available. Only then can one determine the contribution of any individual medication to the pain.

Help Perpetuate the CMTA's Work

REMEMBER THE CMTA IN YOUR WILL. You can give hope to thousands of CMT patients by extending your support of the CMTA's programs beyond your lifetime. Whether your legacy is small or large, you can support our programs of education, service and research by remembering the CMTA in your will.

To make a bequest of cash or other property to the CMTA, your will (or supplemental codicil, if you do not wish to write a new will) should state:

"I give and bequeath to the Charcot-Marie-Tooth Association, a not-for-profit corporation, organized under the laws of the Commonwealth of Pennsylvania, and having its principle office at 2700 Chestnut Parkway, Chester, PA 19013, the sum of $_____ or _____ percent of the rest, residue and remainder of my estate to be used for the (general purposes) or (research fund) of the Organization."

A bequest to the CMTA is fully deductible for estate tax purposes. Additionally, you will be providing hope to CMT patients and family now and in the future. You may wish to learn about other gift-giving opportunities by consulting your attorney, accountant, and/or tax or estate planner.

Taking Stock in the CMTA

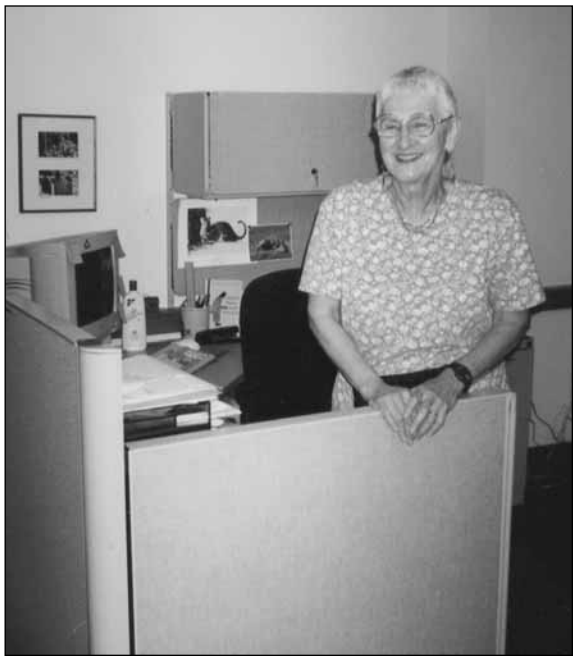
In addition to bequests, it is possible to give gifts of stock to the Association. Stock can be directly sent to the CMTA's account #JH45207-53 at Paine Webber, Incorporated, Two Logan Square, Suite 2400, Philadelphia, PA 19103. DTC #221.

Our broker is Lewis Cohen, who can be reached at 215-972-6841. The Federal ID number for the CMTA is 22-2480896.

CMTA Support Group News

California - Berkeley

Support group leader Ruth Levitan was recently featured in the West County Times in the "Our Neighbors" column. Ruth was pictured in the article with her many awards for the charity fun-runs she did for 18 years before her feet and leg problems forced her to quit. The Berkeley group will not meet in May because of remodeling at the library, but will meet again in July to hear Dr. Richard McCarthy of the San Rafael Kaiser neurology department discuss the EMG machine and how the tests work and what they tell a doctor.



Ruth Levitan, Berkeley support group leader, visited the new offices of the CMTA in what has become her "biannual" trip east.

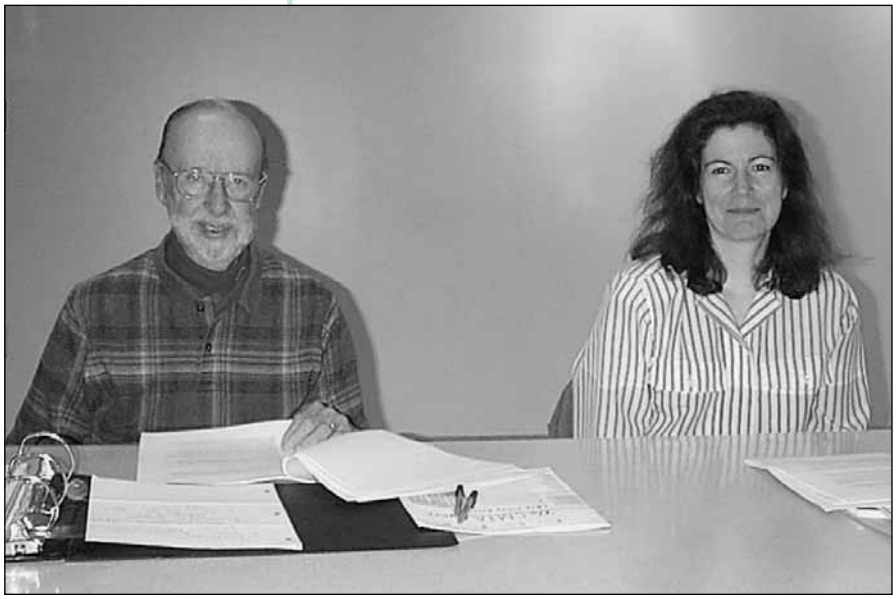
California - Los Angeles

Serena Shaffer reports that the meeting place for the Los Angeles support group changes with each meeting and that they are currently meeting on a quarterly basis, usually on either a Saturday or a Sunday. Please call Serena if you are interested in attending a meeting. See listing on the following page.

Colorado - Denver Area

Sixteen people attended the March 27, 2000, meeting of the support group. Dr. Joel Callahan spoke to the group, giving an overview of CMT and its treatments. He then opened the floor for questions and fielded many queries on all aspects of the disorder. He offered to return at any time and he took the CMTA's brochures to hand out to his patients. The next meeting will be held on May 22.

Bob Budde and recent presenter Dr. Cynthia Smith field questions from attendees.



Kentucky/Southern Indiana/Southern Ohio

The group has changed their meeting location and are now meeting at the Lexington Public Library, Northside Branch, 1727 Russell Cave Road, Lexington, KY. Their last meeting was on April 8, 2000, when they heard a presentation from Dr. Cynthia Smith, a neuropsychologist from the University of Kentucky Neurology Department. She spoke on the effects that a CMT diagnosis has on both the patient and the family.

New York (Westchester County)/ Connecticut (Fairfield)

The Westchester support group, under the leadership of Kay Flynn, has scheduled a meeting in May, with Dr. Victor Ionasescu, noted CMT researcher and member of the CMTA's Medical Advisory Board, who has retired from the University of Iowa and is currently living in Connecticut.

North Carolina - Archdale, Triad

Nora Burrows has scheduled the annual picnic, complete with Bingo and other games for kids and adults, for May 20th. A good crowd attended last year and another large group is expected this year.

CMTA Support Groups

Alabama/Greater Tennessee Valley
Place: ECM Hospital, Florence, AL
Meeting: Quarterly
Contact: William Porter, 205-767-4181

Arkansas—Northwest Area
Place: Harvey and Bernice Jones Center for Families, Springdale
Meeting: 3rd Saturday of each month
Contact: Libby Bond, 501-795-2318
E-mail: charmicoma@netzero.net

California—Berkeley Area
Place: West Berkeley Library
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: SerenaM71@aol.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@home.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

Florida—Boca Raton to Melbourne
Place: Upledger Institute, Palm Beach Gardens
Meeting: Quarterly
Contact: Cynthia Gracey 561-243-0000

Florida—Miami/Ft. Lauderdale
Place: North Broward Medical Center, Pompano Beach, FL
Contact: Al Kent, 954-742-5200 (daytime) or 954-472-3313 (evenings)
E-mail: marbearwld@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: Every other month, the first Tuesday
Contact: David Prince, 978-667-9008
E-mail: baseball@ma.ultranet.com

Michigan—Detroit Area
Place: Beaumont Hospital
Meeting: Three times each year
Contact: Suzanne Tarpinian, 313-883-1123

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: Betty Aultman, 601-825-5626 Julia Provost, 601-825-6482

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: St. Louis University Medical Health Ctr.
Meeting: Quarterly
Contact: Carole Haislip, 314-644-1664

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
Contact: Kay Flynn, 914-793-4710
E-mail: alma622@worldnet.att.net

North Carolina—Archdale/Triad
Place: Archdale Public Library
Meeting: Quarterly
Contact: Ellen (Nora) Burrows, 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

Oregon—Willamette Valley
Place: Brooks Assembly of God Church
Meeting: Monthly
Contact: Regina Porter, 503-591-9412
Maryann DiStefano-Hill 503-585-3341
E-mail: moonglow21@aol.com

Texas—Dallas/Ft. Worth
Place: Harris Methodist HEB Hospital
Contact: Greta Lindsey, 817-281-5190 or
Shari Clark, 817-543-2068
E-mail: jdsbclark@webtv.net

CMTA-FUNDED RESEARCH

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may modify the phenotype of CMT1A and HNPP and to identify other low-copy-number repeat sequences in this region.

A second full-year grant was awarded to Dr. Valerie Street, working with Dr. Phillip Chance, at Children's Hospital and Medical Center in Seattle, Washington. The study is entitled "Linkage and Candidate Gene Analysis of Two Pedigrees with Charcot-Marie-Tooth Neuropathy Type 1C." A genome scan on DNA from two pedigrees with CMT1C will be performed to establish linkage. If the mutation underlying CMT1C in either pedigree maps near a known myelin or other candidate gene, the sequence of that gene will be compared between affected and unaffected family members. (At the request of the recipient, this grant runs from July 1, 1999 through June 30, 2000.)

A third grant was awarded to Dr. Victoria Lawson for her study on "Correlations Between Motor Neuron Loss and Weakness in CMT1A and CMT2." Dr. Lawson is working with Dr. Mark Bromberg of the University of Utah. The study proposes to address the controversy regarding the role of the axon in CMT by applying more sensitive measures of axonal loss to the study of patients with CMT1A and comparing them to patients with CMT2.

Three Summer Research Grants

The first grant was given to Tina Kraljevic of the University of Virginia School of Medicine, working with Dr. Vern Juel. The study entitled "Pregnancy and Exacerbation of Peripheral Neuropathy in Charcot-Marie-Tooth Disease" utilizes a questionnaire mailed to women through the CMTA, as well as random phone interviews of patients with CMT to study the effect of pregnancy on the symptoms of CMT.

Another grant went to Ms. Brooke Tate, working with Dr. Michael Shy, at the Wayne State University in Detroit, MI, on a study entitled "An Analysis of Clincal Phenotypes in CMT2 and CMTX." Her project was to compile data gathered at the CMT Clinic at Wayne State regarding CMT2 and CMTX patients concerning their nerve conduction velocities, quantitative motor and sensory testing, and motor unit analysis. The study should produce a manuscript for publication which can be used to provide a baseline for longitudinal studies in CMTX and CMT2.

The final grant was given to Andrea Robertson, from the Royal Free and University College Medical School, London, England, working with Dr. P. K. Thomas. Her study with the Trembler-J mouse will stress the peripheral nerve by producing nerve degeneration and examining the changes which occur during regeneration, including the capacity for axonal regrowth.

Drs. Agnes Jani and Michael Shy began the on-going research on adenoviral techniques at Wayne State University.

2000

Three $35,000 Full-Year Grants

Dr. Ken Inoue, of Baylor College of Medicine, requested and was granted a continuation of his study from the previous year to also include a characterization of a myelin transcription factor, SOX10, responsible for myelin deficiencies in both the peripheral and the central nervous systems.

Dr. Edgardo Arroyo, working with Dr. Steven Scherer, at the University of Pennsylvania Medical Center, was granted a fellowship to study "The Reorganization of the Axon Membrane in Animal Models of CMT." He will study the localization of several axonal proteins in normal myelinated fibers of rat and mouse peripheral nerve.

The third award was granted to Dr. Emilia Ianakova, working with Dr. Michael Shy at Wayne State University. Her study was entitled "Tissue-Specific Gene Therapy for CMT1." She will study gene therapy by generating replication-defective adenoviral vectors as a means of continuing the work in gene therapy for neuromuscular disorders.

Letters to the Editor:

Dear CMTA,

I read your site on the Internet and was glad to find something written up on CMT. It seems to be an area that not many people understand. I know because I was diagnosed with it about 5 years ago when I was a freshman in high school. It has affected the muscles controlling the dilation of my eyes so much that I cannot drive, or at least, not comfortably, when there is bright sun outside.

—A.C., via email

Dear CMTA,

I wanted to share something with you. About 14 months ago, I started lifting weights 3 times a week. At first, it was very painful and my strength wasn't what it should have been for a man my size. I had tried many times to work through the soreness and pain, but just let it go. I wanted to know if there was any chance to get past it all. I made a promise to myself to keep lifting, no matter what. After over a year, I am still cranking out the workouts at the gym. This is the most amazing part: my strength has doubled in my upper body and even my legs have made a gain.

The two things that seem to have made a difference are getting out of a bad relationship I was in and taking DHEA. My chest has gone from a 48 to 52 and my neck went from 19 to 22 inches while I still weigh the same 275 pounds. I feel amazing. I still have a lot of pain, but now the best thing for the pain is working out. I can go to the gym and make it stop.

CMT can be dealt with. It just takes time and effort. We will never be "normal," but we can be proud of ourselves.

—T.H., via email

Dear CMTA,

This is for anyone interested in the boot for foot drop. We have been successful in designing a sandal that works for foot drop. The woman who was our first client has bilateral foot drop from a failed lumbar back procedure. She has severe neuropathy as a result. She has worn the boot since January and has more feeling in her feet than with her bilateral AFOs. She can feel her foot itching and can feel the cold, which she couldn't with her AFOs.

—Donna Clark, Pedorthist
footman@mail.advertisnet.com

PATIENT/FAMILY CONFERENCE SCHEDULED FOR UTAH

The next patient/family conference on Charcot-Marie-Tooth Disorders will be held on Saturday, August 5, 2000, at the University of Utah, Salt Lake City, UT. The full day conference will feature presentations by neurologists, orthopaedic surgeons, physical therapists and other specialists. Following the now-traditional format, the conference will open with a full-group presentation followed by small group break-out sessions. Lunch will be provided as part of the cost of registration. The day's activities will end at approximately 3:30 PM.

The conference is being arranged by Dr. Victoria Lawson, a recipient of a CMTA $35,000 Research Fellowship and her mentors, Dr. Mark Bromberg and Dr. Jack Petajan.

Registration forms will be mailed to members of the association living in Utah, Arizona, Nevada, Colorado, Idaho and Wyoming. Anyone wishing to attend from another state should call the office at 1-800-606-2682 to receive a registration form.

Cost for the full day will be $45.00 for active members and $55.00 for all others.

For more information, call the office at 1-800-606-2682.

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.

The CMTA Report is published by the Charcot-Marie-Tooth Association, a registered non-profit 501(C)(3) health organization.

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, and HNPP 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

CMTA

2700 Chestnut Parkway
Chester, PA 19013
1-800-606-CMTA

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