FEBRUARY 2002

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:
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The CMTA Awards Three Postdoctoral Grants for 2002

The Charcot-Marie-Tooth Association is pleased to announce the recipients of its $35,000 postdoctoral grants for the current year: Jerome Devaux, PhD, working at the University of Pennsylvania with Dr. Steven Scherer; Raul Perez-Olle, MD, from Columbia University, working with Dr. Ronald Liem; and Gulam Mustafa Saifi, PhD, working with Dr. James Lupski at Baylor College of Medicine.

The first grant is entitled "The Role of Potassium Channels in CMT1." Dr. Devaux will study the demyelinating forms of CMT, which are caused by mutations in the genes encoding proteins expressed by myelinating Schwann cells. Although these gene defects initially affect the myelinating Schwann cells, demyelination and remyelination profoundly affect the organization of the axonal membrane, including the Shaker-type K+ (potassium) channels, Kv1.1 and Kv1.2.

Demyelination and remyelination profoundly affect the organization of the axonal membrane.

In demyelinating neuropathies, Kv1.1 and Kv1.2 are abnormally distributed and more accessible, so that K+ channel blockers will likely have pronounced effects on axonal conduction. The altered organization of the axonal membrane may cause slowing of conduction or conduction block, which may contribute to the disabilities in CMT1 patients as well as to the pathogenesis of neuropathy.

Dr. Devaux will determine the effects of 4-aminopyridine (4-AP) and dendrotoxin (DTX-I) on axonal conduction in the *Trembler* mouse and other animal models of CMT. He believes that if K+ channels contribute to the slowing of axonal conduction in the animal models, then conduction should increase in the presence of 4-AP (which blocks most kinds of K+ channels) and possibly DTX-I (which selectively blocks Kv1.1 and Kv1.2). The relative effectiveness of DTX-I as compared to 4-AP will provide evidence relating to the role of Kv1.1 and Kv1.2 in conduction slowing.

A second grant has been awarded to Dr. Raul Perez-Olle to study "The Effects of Charcot-Marie-Tooth Linked Neurofilament Mutations on Intermediate Filament Formation." Dr. Perez-Olle came to Columbia after receiving his medical degree from the University Rovira & Virgili Medical School in Spain. He had previously done research at the University of Kentucky, New York University, and the National Cancer Institute. He learned about the neurofilament mutations in CMT type 2E and started a study on how those mutations might affect assembly and transport of the neurofilament proteins, and if those effects could be important in the progression of the disease.

He has already constructed vectors encoding the homologous mutations in the rat gene and is now making vectors encoding the mutant human cDNA. His study will investigate how mutations affect neurofilament assembly and organization. His experiments should make important contributions toward understanding this form of the disease.

The third grant of 2002 was awarded to

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The CMTA.... Living our Mission

Mission Statement:
To improve the quality of life for people with CMT.

Vision Statement:
A world without CMT.

So Much Progress, So Little Time...

By VINCENT BERTOLINO, Executive Director

The CMT North American Database will help speed the pace of research for treatment options and a cure.

So much is happening, where do I begin? We've been encouraged by the response to the annual appeal. Two-hundred-thirty-eight of you have given to the appeal so far. Thanks to your generous support we will continue to make progress in the battle against CMT disease. The cure is not here yet, so expect to hear from me again regarding the Spring Research Appeal.

IF EACH FAMILY GAVE . . .

Fill in the blank yourself. There are 150,000 people with CMT who are members of approximately 60,000 families. A board member observed that if each CMT family gave $100 a year to CMT research, that would be $6 million, or more money than the CMTA has raised in its entire existence. How much could you write in on the blank? How much could we invest in CMT research if everyone filled in all he or she could?

GOLF AT "THE CREEK"

For the past three years, CMTA Board Member Robert Kleinman has orchestrated a CMTA golf fundraiser at The Creek Country Club on Long Island. July 22, 2002 will be the date of the fourth annual event. This exclusive program has raised over $120,000 for CMT during its existence and may exceed the $200,000 mark this July. Thank you, Mr. Kleinman!

If you have an inclination to do this kind of fundraiser, call the CMTA office. We have people experienced in managing these programs to help you help our cause and have fun doing it!

BOARD, RESEARCH, AND DATABASE

The Board of Directors meeting in January was hosted by Board Member Phyllis Sanders at her law offices. The board accepted the resignation of Ardith Fetterholf. While her talent may be lost from the board, I believe she will still be an asset to the CMT community. I look forward to continuing to work with you, Ardith, as we strive toward the cure.

The Board voted to fund all three projects reviewed and approved by the Medical Advisory Board. These projects are focused upon gene discovery, protein function, and ion channels in CMT. The discoveries from these investigations may help elucidate some of the causative mechanisms of CMT and point toward a way to intervene in the disease process (see front page article).

The Board also heard Dr. Michael Shy's progress report on the North American CMT Database, which now has over 216 participants. Dr. Shy explained that it is important to have as much information as possible in order for the database to be valuable. Without this level of detail, researchers would be forced to repetitively qualify many people for their studies, making the

CMTA AWARDS GRANTS

(Continued from page 1)

Dr. Gulam Mustafa Saifi to study "The Identification of Novel Genes Associated with Charcot-Marie-Tooth and Related Peripheral Neuropathies." This proposal primarily focuses on identification and characterization of novel peripheral nerve-specific genes that could serve as candidates for the more rare forms of CMT and related peripheral neuropathies. Dr. Saifi hopes to identify PNSE (peripheral nerve specific-enhanced) genes, establish their chromosomal locations, and establish a profile of them. He will then carry out a mutational analysis of these genes and chromosomes in a selection of unrelated peripheral neuropathy cases that have not been associated with mutations in known genes.

The identification of molecular defects leading to CMT and related peripheral neuropathies should lead to better diagnostics. It should also provide insights that will enable doctors to understand the underlying mechanisms leading to such neuropathies. This in turn is expected to lead to better prognosis and the development of more effective therapies.

information less reliable. **To help research by completing a survey, call the CMTA office at 1-800-606-2682.**

Some of the questions that a broad, reliable database can answer are:

1. What are the effects of pregnancy on CMT?
2. What are the risks of certain medications?
3. What is the effectiveness of various surgeries on the person with CMT? What are the long-term effects? Are there common problems that occur?
4. What are the effects of different types of rehabilitation (physical therapy, occupational therapy, foot-ankle braces) on CMT? Are there ways to prevent problems such as food and hand deformities?

These questions require information about large numbers of people with CMT and there are many others that a reliable database will be able to accurately answer, as well.

The funding for the North American CMT Database was guaranteed for the first year by a generous donor. We are now being challenged to fund this powerful project for the up-coming year. Help us meet the Database Challenge. Let's keep the momentum going. The cure depends upon your participation. Complete a survey form and give generously to the research fund when you receive our appeal in March.

PERIPHERAL NEUROPATHY CONFERENCE TO BE HELD IN OREGON

One of our support group leaders, Jeanie Porter, is a committee member of the National Peripheral Neuropathy Conference and will be helping to host their first annual meeting in Tigard, Oregon, from June 21-24, 2002 at the Embassy Suites Hotel. This non-profit group works with the Neuropathy Association. The conference will feature speakers such as Dr. Phillip Chance, University of Washington, leading a break out session on Charcot-Marie-Tooth. Other speakers will discuss diabetic neuropathy, chronic inflammatory demyelinating polyneuropathy, alternative therapies and the dangers of falling. The cost of the conference is $130 and hotel reservations are available at a group rate of $79 per night. For a registration form or more information, call the NPNC at 1-503-259-0461.

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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	
SPECIAL OFFER FOR ACTIVE MEMBERS ONLY: CMT Facts Series (I-IV)		*active members* $16	
CMT Facts I ☐ English ☐ Spanish		*active members* $3 ***inactive members* $5**	
CMT Facts II ☐ English ☐ Spanish		*active members* $5 ***inactive members* $7**	
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 *No shipping and handling on this item only.*		*active members* $4 ***inactive members* $5**	
CMTA Canvas Tote Bag		$10	
CMT Informational Brochure ☐ English ☐ Spanish		FREE	
Physician Referral List: States: _____ _____ _____		FREE	
Letter to Medical Professional with Drug List		FREE	
Contribution to CMT Research *10% will be applied to administrative expenses.*			
Shipping & Handling *Orders under $10 add $1.50, orders $10 and over add $3.00*			
TOTAL			

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Mail to the CMTA, 2700 Chestnut Parkway, Chester, PA 19013

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.

A Guide to Selecting a Physician

"The good physician treats the disease. The great physician treats the patient who has the disease."

— Sir William Osler

Choosing a physician to manage your CMT requires care and thoughtful consideration. Asking the following questions will help:

- What is the physician's reputation? Talk to friends and acquaintances about their experiences. Try to get a feel for the level of medical care, time spent with the patient, and the physician's willingness to interact with the patient. Has the physician treated many people who have CMT?
- What is the physician's location/availability? Considerations include distance from your home, office hours, on-call hours, after-hours and vacation coverage, and hospital privileges. Is the physician's practice accessible to people with disabilities (parking, office entrances, examining tables, restrooms)? Are laboratory and x-ray services or rehabilitation services located in the same or other convenient facility? How long must you wait for an appointment?
- What are the physician's qualifications? Check with your local medical society. You can specify what type of doctor you are looking for by sex, specialty, age, or location. Find out if the doctor is "Board Certified" or "Board Eligible." "Board Certified" means that he/she has several years of training in a specialty after graduation from medical school and has passed a national qualifying examination. "Board Eligible" means that the training has been completed, but not the exam. The local medical society can provide this information; however, these credentials do not guarantee competency. Other qualifications may include medical school or post-graduate specialty training, professional society memberships, and staff membership at well-recognized hospitals.
- Are the physician's services covered by your insurance plan and what are the fees? Ask if there is a "fee for service" office policy. This means that you are asked to pay for your visit at the time of the appointment rather than being billed. Determine if the doctor is a member of an HMO or other group health organization.
- What do you want and/or need from a physician? What is the type of problem you think you have? Do you need an initial diagnosis or ongoing health care management assistance? Are you looking for a generalist or a specialist?

EVALUATING YOUR PHYSICIAN

After your initial visit to the physician, review the following questions to decide if you and the doctor can become "working partners" in your continuing health care management.

- Is the physician's personality compatible with yours? Can you openly discuss your feelings and talk about personal concerns? Do you believe your doctor will stand by you, no matter how difficult your problems become?
- Does the physician seem sincerely interested in you and your unique problems as a patient with CMT? Are your concerns considered seriously? Has your past history been adequately considered? Is the physician interested in you as a whole person—your inner self and your lifestyle, as well as your physical self?
- Is the physician willing to help you learn about your condition? Do you feel at ease asking your doctor questions that may sound "silly?" Does your doctor clearly explain the nature of your condition? Does he/she listen to you and answer all your questions about the causes and treatment of your physical problems or is he/she vague, impatient, or unwilling to answer? Does the physician not only diagnose the problem, but take time to discuss specific treatment options such as changes in lifestyle, referrals for adaptive equipment, or choices in therapy, surgery, or medications?
- Is the physician familiar with the literature available on CMT? Has the physician had sufficient experience and/or involvement with CMT patients for you to have confidence in his/her opinions? Is the physician willing to learn more about the effects of CMT?
- Is your doctor willing to refer you to others? Does your physician utilize the services of other health care professionals needed to manage CMT, i.e., physical and occupational therapists, nurses, brace makers, and/or social service and counseling personnel? Does the physician use a team approach in his/her practice? Will your physician discuss referral to other CMT specialists?
- Is the office staff cordial and attentive to you? Does your doctor answer your letters or telephone calls promptly? Are you generally kept waiting for long periods of time when you have an appointment?

This guide was adapted from Polio Network News; *Summer 2001*

Professionals Working for CMT Patients: Dr. Richard A. Lewis

Editor's Note: Dr. Lewis has written a first person narrative of his journey in medicine to his present position working on the issues surrounding CMT.

I am currently Professor and Associate Chair of Neurology at Wayne State University School of Medicine in Detroit, Michigan. In addition, I am Director of the Clinical Neurophysiology Laboratory and co-Director (with Dr. Michael Shy) of the Neuromuscular Clinic of Harper Hospital.

The path that brought me to my current position took a number of unusual turns. However, the journey has provided me with a broad range of experiences that have been fulfilling and rewarding. I grew up in Jackson Heights, Queens, New York City and graduated from Union College with a B.S.. Having played the violin since the age of 9, I had considered a career in music, but careful reflection on the true nature of my talent suggested that music would best be an avocation. I pursued my career in medicine at the Medical College of Virginia but I had no specific specialty in mind throughout my four years in medical school. It is still not entirely clear to me what the deciding factors were in my decision to become a neurologist. Certainly, my 4th year elective in neurology at Montreal General Hospital with Donald Baxter had a significant impact upon me. It was my first exposure to peripheral nerve disorders and electrodiagnostic medicine. Dr. Albert Aguayo, who has made important contributions to our understanding of CMT, was active there and I was clearly intrigued. In retrospect, I believe my decision to go into neurology was based on subconscious feelings having to do with my interest in the complexities, subtleties, and abstract aspects of the field. To some extent, it was the musical nature of neurology that drew me to it.

Dr. Richard Lewis is a newly appointed member of the CMTA's Medical Advisory Board.

I consider myself to be truly fortunate to have had my neurology residency at the University of Pennsylvania from 1975 to 1978. I had the opportunity to observe and participate in clinical and scientific investigations of demyelinating neuropathies. Throughout my residency, I would "hang out" in the EMG laboratory directed by Dr. Austin Sumner. Drs. Asbury and Sumner stimulated a great deal of enthusiasm about peripheral nerve disease and the dynamic way electrophysiology complements the clinical examination in the diagnosis of peripheral nerve disorders. In addition, they were able to show how there was a link between basic scientific investigation and clinical medicine. While we all can understand how an understanding of basic scientific information pertains to clinical neurology, it is also true that careful evaluation of patients can provide valuable information that can lead to insights into our basic understanding of how peripheral nerves function.

After my residency I stayed at Penn as Assistant Professor, doing clinical neuromuscular disease, EMG, and working in Dr. Sumner's peripheral nerve physiology laboratory. We also worked on animal models of diabetic neuropathy. During these years I was involved in two papers that have become important parts of the literature of the demyelinating neuropathies. The first, reported with Drs. Sumner, Brown, and Asbury, identified five patients with a multifocal disorder that had not previously been recognized. Over the years this has been called the Lewis-Sumner Syndrome and was the precursor of multifocal motor neuropathy. The second paper, authored by myself and Dr. Sumner, showed the differences in nerve conduction studies between acquired demyelinating neuropathies, primarily CIDP, and familial disor-

(continued on page 6)

PROFESSIONALS WORKING FOR CMT PATIENTS: DR. RICHARD A. LEWIS

(Continued from page 5)

ders, CMT 1. The concept that CMT 1 has uniform conduction slowing has become a clinical concept useful in the diagnosis of CMT. Now that we have genetic tests that can pinpoint the specific gene defects in many of the forms of CMT 1, we have had to re-evaluate these concepts, but uniform conduction slowing is present in CMT 1A, some cases of CMT 1B, and a few other disorders.

After a total of 5 years at Penn, I moved to the University of Connecticut to initiate their neuromuscular program and EMG laboratory. I developed an adult MDA clinic and participated in the pediatric MDA Clinic at Newington Children's Hospital. It was there that I learned to appreciate the importance of rehabilitative medicine in inherited neuromuscular disorders. I was involved in the care of a number of patients with CMT and learned about the varied manifestations of the illness and the problems patients had with the disorder.

We have formed a team committed to learning as much as we can about the basic pathology of inherited demyelinating disorders.

After 3 years in Connecticut, I made the decision to devote myself to clinical neurology and moved to Norfolk, Virginia, where I joined a 35-member multi-specialty group. After a few years, I and two other neurologists in the group started our own neurology practice. Although I did general neurology, taking care of patients with headaches, seizures, and strokes, my interest in neuromuscular disease and peripheral nerve disorders in particular persisted. I became director of the MDA clinic in Norfolk and continued to see many patients with CMT. I remember my ten years in Norfolk for the strong friendship I had with my partners and the strengthening of my clinical skills. I feel that it was there that I learned to be a "real doctor".

After ten years in Norfolk, I realized that as much as I enjoyed clinical neurology, I missed the teaching and investigation that was part of the academic world. Call it a "midlife crisis," but I was looking to expand my horizons. I was lucky that Dr. Lisak, one of my mentors at Penn, now chairman at Wayne State University in Detroit, was looking for a neuromuscular person with clinical experience. So, I was able to make the very unusual move from private practice back to an academic position. Somewhat fortuitously, we were subsequently able to recruit Drs. Michael Shy, John Kamholz, and James Garbern, who had been working in Philadelphia on understanding the molecular biologic nature of central and peripheral myelin. Along with Karen Krajewski, who is the genetics counselor and organizational glue of our group, we have formed a team committed to learning as much as we can about the basic pathophysiology of the inherited demyelinating disorders. As such, we have created programs to treat and investigate these disorders. We have developed a multidisciplinary clinic specifically for patients with CMT. As any of you who have visited with us know, we are an eclectic, but enthusiastic group, who enjoy our work. We attempt to give high-quality care to our patients, as well as make careful observations that will extend our knowledge of the disorders that comprise CMT. We anticipate that in the near future we will be able to translate the knowledge we have obtained of the clinical disorder and of the basic science of the neuropathies that has been accumulated from laboratories, into therapeutic trials that will eventually bring substantial improvements to the lives of people with CMT.

I consider myself incredibly fortunate to have had the neurological career and experiences that I have had over the past 25 years. It has brought me together with wonderfully bright, energetic, and committed professionals that has made my work fun and exciting. It has also introduced me to truly special people, patients, and families with CMT. Their ability to overcome the disabilities brought on by these disorders is truly inspirational. This, along with the joys my wife Lynn and children Ben, Rachel, and Briere have provided me, and the pleasure that music has given me over the years, has made my life fulfilling and meaningful.

Our Annual Research Issue

In this, our annual research issue of the newsletter, we announce the recipients of this year's awards and present summaries of the work done last year. These summaries provide information on how your research dollars are advancing knowledge about CMT.

PROGRESS REPORT

"Hereditary Neuralgic Amyotrophy (HNA): Identification and Characterization of the Genetic Defect"

By JAN MEULEMAN

Hereditary neuralgic amyotrophy (HNA) is a rare, autosomal dominant disease. It is a recurrent, focal neuropathy affecting the brachial plexus, a complex structure of intertwined nerves in the shoulder. Patients experience episodes starting with sharp pain and evolving into weakness, paralysis, and wasting of the arm muscles. Although the recovery is usually very good, the episodes are very painful and usually severely limit the person's abilities. For about 5 years now, we have known that the gene causing HNA must be located on chromosome 17q25. Since then, this candidate region has been refined and reconstructed in manageable fragments called clones. Some candidate genes have been screened for mutations; however the gene/mutation causing HNA remains unknown.

The first aim within this CMTA fellowship was to identify new genetic markers, which could then be used to narrow down the region in which we are currently looking for the HNA gene. Refining this region would mean reducing the amount of candidate genes that need to be screened, and therefore speed up the identification of the HNA gene. Using different computer programs, 18 new genetic markers were developed, tested, and analyzed within the HNA families. Unfortunately, the HNA candidate interval could not be refined any further. Nevertheless, analysis of results obtained within this collaborative effort between the University of Washington, University of Antwerp (Belgium), and University Hospital of Muenster (Germany) allowed us to define a priority region within the current HNA candidate region.

The second aim was the identification of new candidate genes. Because we had previously screened most candidate genes within the region, the identification of new genes would be critical in this project. Using a cohort of different gene prediction programs, along with the bits and pieces of genes that are already present in different databases, we created an overview of all known genes/gene fragments within the HNA candidate interval. Meanwhile, I have fully characterized two candidate genes (MGAT5like and KIAA1582) and am currently working on two additional genes, which are thus far only partially known.

The third aim was the mutation analysis of the characterized genes in order to find the gene/mutation causing HNA. This analysis is done by comparing the DNA sequence of the candidate gene in patients and in healthy individuals. The difference can be normal variation, or the mutation we are actually looking for. At this moment, I have finished the two candidate genes that I characterized earlier. Several base changes were detected, both in patients and in healthy control individuals, and none could be linked with the disease. Two other candidate genes are still in progress, and some other genes are being worked out by our collaborators.

We hope to accelerate our efforts to a quicker identification and characterization of the culprit gene of HNA. With this I would like to thank the CMTA for giving me the opportunity to perform this exciting research project.

INTERIM REPORT, NOVEMBER 2001

Moore Postdoctoral Fellowship

Fellow: **ANTHONY REDMOND, Institute for Neuromuscular Research, Children's Hospital at Westmead**
***Academic preceptors*: PROF. ROBERT OUVRIER and ASSOC. PROF. GARTH NICHOLSON**

SUMMARY OF ACTIVITIES

Review of the literature. As part of the familiarization process the Fellow has developed a major review of the literature relating to CMT and its effects in the lower limb. This review, covering 180 papers, chapters, and monographs, is one of the most comprehensive studies of the literature in the area of the physical manifestations of CMT. The material in this review will also form part of a book chapter: Chance P., Escolar D., Redmond A.C., Ourvrier RA. *Charcot-Marie-Tooth Disease in Neuromuscular Disorders of Infancy and Childhood.* Jones R.H., Darras, B. (Eds) Butterworth Heinemann 2002 (in press)

Splinting trial. Ethics clearances were obtained in June 2001. Seventeen patients have been recruited to date, although some difficulties have been experienced with recruitment because of incomplete medical records and address changes. Also the Concord trial, which was originally running as a pilot to the Moore fellowship trial, had not wound up as expected, contributing to delays.

The anticipated final recruitment is now 24 patients at the children's hospital site, by the end of the fellowship term, compared with the 30 anticipated originally. Preliminary plans are, however, in place to extend the study beyond the term of the fellowship to achieve the targeted numbers. In a useful development, to make best use of data from the two centers, the protocols have been amended slightly from the original application to allow some comparison and pooling of data from the Concord Hospital study. This will now allow the combination of some results from both trials and further analysis of the wash-out effects following cessation of splinting as well as increasing the sample size and statistical power.

Australian Charcot-Marie-Tooth Health Survey 2001. Discussions with the CMTAA early in the Fellowship led to the development of a major survey of the daily living and physical effects of CMT in the association's membership. The Institute and the Moore fellow developed, in conjunction with the CMTAA, a postal survey to establish CMT-specific effects, and foot-linked and general health-related effects of life with CMT. This large, three-part survey involved a lengthy section covering CMT-specific issues.

GIFTS WERE MADE TO THE CMTA

IN HONOR OF:

Susan Adams
Elizabeth Adams

Vincent Bertolino
Paul R. Flynn

Robert Bowers
Mr. & Mrs. Vincent Loughran

Barbara Castle
Thomas & Rosaline Bird

Stephanie DiCara
Mr. & Mrs. Sam DiCara
The Crowther Family

Benji, Carol & Stuart Feen
Vivian & Michael Feen

Robert Friedmann
Agnes Aronsohn

Renee Gelman
Leon Gelman

June Gunn
Ruth Gill

Mia Gussert
Michael & Marianne Poja

Emily Louer
Mr. & Mrs. Arthur Mayers

John & Barbara Phillips
Pauline Phillips

Phyllis Sanders
Errol Blank

Lois Smith
Juan & Verjean Zeller

Linda Sowl
Fred & Amy Sowl

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William & Joan Caro
Matthew & Ellyn Hoffman
Barbara & Danny Howell
Trent Pendley
Ruth Rozen
Gary Weinstein

Jack Walfish
Linda & Jerry Walfish

Arla Van Almen
Richard Van Almen II

IN MEMORY OF:

Elia Atalla
Yacoub E. Atalla

Brooxie Dezern Bean
Nell Dezern Barnette
Charles Dezern
Jack Dezern
Mrs. Jesse Dezern
Larry Dezern
Peggy Dezern Jumper
Lorene Dezern Lineberry
Marlene Dezern Taylor

Estelle Bechhoefer
Herbie & Kathy Bersteen

Elaine Blum
Thomas & Nancy Dinwiddie

Mary Dearing
Katherine Touchstone

Priscilla Eldredge
Mr. & Mrs. Douglas Moody

Carl Erffmeyer
Dave & Marilyn Brightman
Dave & Christine Dial
Paul Schmidt
Lowell & Faith Wendland

Importantly, the survey also employed two previously validated questionnaires, the SF-36 and the Foot Health Status Questionnaire which will allow the comparison of the effects of CMT with other chronic disorders.

A fund raising effort to support the survey raised approximately $5,000 which has supported printing, postage and telephone costs etc. The momentum within the CMT community resulting from this high profile initiative has proved to be a highly beneficial spin-off from the venture. A brief interim summary of the data entered to date is provided on page 10 for your information.

At the time of writing we have received more than 250 completed forms (~60% return), and follow-up is expected to yield a return approaching 350 (80%+). The closing date for submission of the completed forms is December 31st 2001. A brief interim summary of the data entered to-date is provided for your information. A full report will be tendered at the end of this study. Again the Institute would be pleased to collaborate with the CMTA in the US if there was felt to be any merit in extending the survey to the US population.

PUBLICATIONS

The Moore Fellow was a keynote speaker at the Biennial Australian National Podiatry Conference in Canberra in 2001. In all, four papers were presented at this conference that involved work conducted as part of the CMT studies. The profile associated with the speaker's invited status was valuable in disseminating the scientific information but also in raising the awareness of CMT in this professional group.

The validity and reliability of a simple new method for rating foot posture. *Proceedings of the 19th Australasian Podiatry Conference.* May 16th-19th 2001 Canberra ACT. Australasian Podiatry Council, Victoria. 2001.

A paper derived from this conference has been submitted to the journal *Gait and Posture.*

Redmond A., Burns J., Crosbie J., Peat J., Ouvrier R. A novel rating system for quantifying foot posture : the Foot Posture Index. *Gait and Posture* (submitted)

A number of other papers are in draft. These will report the remaining stages in the validation of the rating instrument, and the results of the splinting trial and the national CMT survey. Copies of these will be provided as appropriate.

In summary, despite slower than anticipated recruitment onto the splinting trial, general progress has been excellent and the appointment of the Moore Fellow has led to some significant developments in CMT research in Australia. The Institute and the clinical service have benefited greatly from the focus on the physical aspects of the disease, and this benefit has already impacted on patient care. The CMTA in Australia have also been able to generate significant momentum as a result of the involvement of the Moore Fellow, and the broader impact of the Fellowship has been far in excess of the anticipated effects on clinical activities.

We would welcome the opportunity to discuss any of these developments further and wish to thank again, the CMTA for their continued support.

Robert Freeman
Mr. & Mrs. Frank Gunnison

Paul Friedman
David & Debra Stepansky

Marah Griffith
Mitchell & Rebecca Azar
Suzanne Black
Conemaugh Twp. Area Primary School
Arthur & Maxine Cook
Christine Crichton
Grant & Jackie Croyle
Mr. & Mrs. Clayton Dovey, Jr.
First Summit Bank
Peggy Fuller
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Michale & Sharon Lovette
Dr. & Mrs. Don Lowry
Sally McIlwain
Neighbors & Friends from Somerset Pike Area
Calvin & Donna Overdorft
Mark Pasquerilla
Linda Policicchio
Patrick Regan
Louise Spigel
Duane Swager
George & Natalie Wolfe
Sandra Zamian

Henry Haskell
Belinda & Barry Gimre
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John Hill
Ronald & Betty Lou Munro

William Lamnick
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Charlotte Kettlewood

Roslyn Levenstein
Kathleen Smith

O. D. Moreland
Mary Helton

Claude Parrish
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David Reilly, Sr.
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Rosemary Mull
Marlene Davidson

Thurman Smith
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Jerry Wolter
Mary Wolter

Gladys Young
Mother/Baby Unit, Valley Hospital
Betty Re

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at
www.charcot-marie-tooth.org

PRELIMINARY RESULTS

Australian CMT Health Survey

At the time of writing, responses have been received from 280 people with CMT. 180+ have been entered onto the Foot Health Status Questionnaire (FHSQ) system, and 169 into the master database. Data entry is continuing, and follow-up calls have commenced. At the anticipated closing date of December 31st 2001, we anticipate having received in excess of 300 responses.

BACKGROUND

We present responses from 169 cases from whom we have complete data. There are data for more females (100) than males (69). For these 169 people, 113 are in long-term relationships, with 20 separated/divorced/widowed and only 31 of the adult respondents permanently single. (The remainder were children.) Overall, this suggests that there is a good degree of social support for most of the respondents with CMT. We also do not know how many of the single people live with parents or other family, but it is likely to be several.

The age range so far is wide, ranging from seven to eighty-seven years. The average age of our respondents is 51 years. The average age at the onset of symptoms was 23, although in some cases it is much younger than this. On average 11 years passed between the onset of symptoms and the time when a diagnosis of CMT was given (at an average of 34 years of age).

Diagnosis was an issue, as expected, with 56 (33%) reporting that their original diagnosis was incorrect. Typical wrong diagnoses included polio (6), muscular dystrophy (4), and cerebral palsy (3).

A surprising eighty-one respondents (48%) were not sure of the type of CMT type they have. Of those who were certain, 55 (62%) have CMT1A (the hypertrophic type), 15 (17%) have CMTX (the sex-linked type), 8 (9%) have CMT2 (the axonal type), 3 (4%) have Dejerine-Sottas type, and 7 (8%) reported having other types. One hundred and eighteen people had undergone one of the several available genetic tests and 92 reported that the type of CMT they have had been confirmed by the genetic testing.

PREGNANCY

For women of childbearing age, 25 women had been diagnosed with CMT before their first pregnancy and 15 had received genetic counselling. Interestingly, of the 18 who responded to the question regarding whether they would have *liked to have had* some genetic counselling, 6 said no, 5 said yes, and 7 were not sure.

Overall, respondents to the survey reported their experiences for 162 pregnancies. In only 32 (20%) was there was no change to the CMT. Eighty-three (51%) reported that the CMT worsened a little and 27 (17%) reported that the CMT was definitely worse. In 8 (5%) their CMT became much worse, and for 11 (7%), it became very much worse.

The types of problems reported by the expectant mothers were typically cramps and further weakening of the arms and legs. Approximately two thirds of the people reporting the symptoms associated with pregnancy described "severe" cramps, and just under half reported further weakening.

OTHER FEATURES ASSOCIATED WITH CMT

Fifty four (32%) of our respondents mention scoliosis as a feature of the CMT, although for 22 it was mild only; for the rest it was evenly spread over the degrees of severity. Weakness in the hands is obviously common, and only 22 (13%) had no weakness in the hands. Ninety-two (54%) reported a "little" or "moderate" amount, and for 49 (29%) of our respondents the weakness is severe. All but one person reported some tremor in the hands, and although only 12 people reported the tremor as "severe", the proportion of CMT-affected people with tremors is much higher than is usually supposed. All but one person also reported increased sensitivity to cold—this was "a lot" or "severe" in 55 (33%), and a similar picture is found in the legs and feet and it is usually more troublesome here.

One hundred and forty-seven people (87%) have weakness in their legs/feet and this is perceived as being moderate to severe in 138 (82%). As a result of the muscle imbalances associated with the weakness 21 (12.5%) have significantly flat feet, and 114 (67%) have significantly high arched feet.

To assist with mobility, ten people use a wheel chair, although for some of these it is only an occasional aid. Forty three (25%) use a walk-

er or a cane, 48 (28%) use in-shoe orthoses and 37 (22%) AFO type orthoses. Around the home, 45 used aids to help in the kitchen, and 21 used aids to help with tasks such as dressing. The relationship between these aids and age and time since diagnosis will be explored in the full analysis.

Balance is often reported as a problem associated with CMT. Interestingly, the proportion of people whose balance was unaffected by both walking and standing still was similar at 37 (22%), and for these people balance simply did not appear to be an issue. However in those whose balance was affected, standing still was associated with more severe problems than walking.

More than half reported having to bend slightly at the knees to preserve balance, and a significant 114 (two thirds) reported falling completely to the ground as a result of CMT-related balance problems.

TREATMENTS

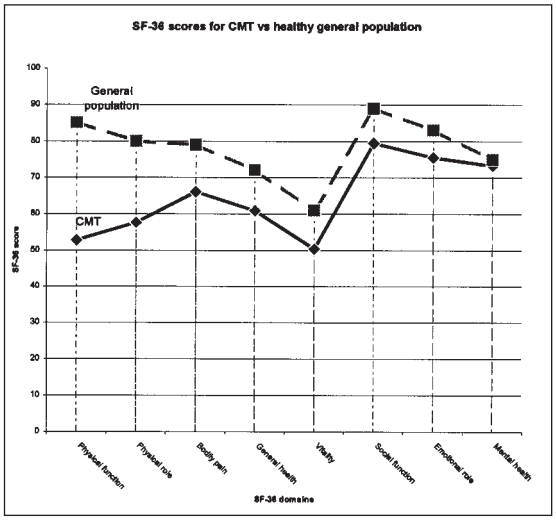
People have tried such a variety of treatments that we are unable to present all of the information here. In particular, the number of surgical and alternative treatments has caused us some problems and these will take some sorting out. For the standard conservative treatments we now know that 67% of people with CMT have tried stretching exercises. They were generally considered easy to do and 26 (23%) people reported that they were "very helpful" or "100% effective". On the other hand, 11 others (10%) reported that stretching was useless.

Forty-two (25%) had tried daytime AFOs, and again they were considered easy to use. This time three quarters of the users found them very helpful. Using similar splints but at at night was not seen as being quite so favorable. Seventeen (10%) had tried night splints and they were not reported as being particularly difficult to use. However, 12 (70%) of these people reported that they were ineffective or only minimally effective.

Seventy people had tried in-shoe orthoses, and these were easy to use and effective in approximately two thirds of cases. Of the more aggressive non-surgical treatments available, only 12 people had tried plaster casts to stretch out the feet/legs. Generally, plaster casts were considered more difficult to comply with, although half thought the treatment was helpful.

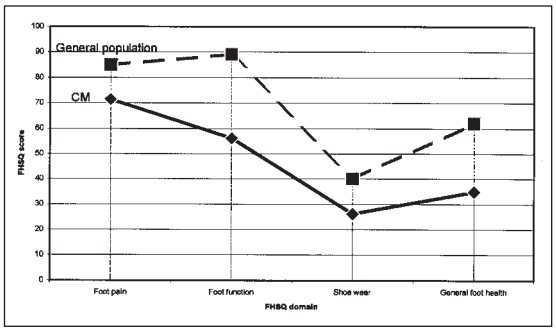
Finally we had included the two less specific questionnaires (the FHSQ and SF-36) to allow some comparison with other groups. While this will be covered in much more detail in the future, even the initial findings are very significant.

The general health data (SF-36)



All the physical scores are lower than for the general population, but the mental health scores are fairly comparable. This suggests that the typical person with CMT cannot help but be limited to some extent in the physical aspects of his or her life, but that despite this is very well adjusted psychologically. This is a testament to the strength of character we have encountered within the CMT community. These results will be compared with a range of other chronic problems in the future, but are already providing some illumination about the effects of CMT on the general health.

Foot Health Status Questionnaire (FHSQ) data



For the FHSQ the results are again quite illuminating. The results are interpreted in the same way as the SF-36 results in that the higher the score the better the health of the group. It is quite expected, given the effect of CMT on the feet, that the results for this survey in the CMT group are slightly lower than for the general population. Foot pain is an issue, but the level of pain does not appear to be hugely disabling across the board, although the impact of the foot changes in CMT will affect the reports of foot function. Shoe wear is clearly important, and some efforts to improve access to well-fitting, comfortable footwear will be a priority. Once the rest of the data are compiled, these results will be added to the information above and we will be comparing the CMT results with results from previous studies that have used the same questionnaires. This will provide information vital for our attempts to get recognition of the impact of CMT on the affected person.

The continuation of the article about the various phenotypes of HNPP will appear in the next issue of the newsletter. Space constraints precluded its being in this issue.

Searching for causes of CMT

By HIROSHI TAKASHIMA MD, PhD,
Baylor College of Medicine,
Department of Molecular and Human Genetics

PRX mutations cause recessive Dejerine-Sottas neuropathy as well as CMT and Congenital Hypomyelinating Neuropathy.

The overall goal of our project is to identify new genetic causes of CMT and thereby understand the pathophysiology of these disorders. The information gained from these studies could be used to improve or design therapies for human inherited peripheral neuropathies.

To identify the new cause of CMT, we recruited patients without mutations in known CMT-associated genes. We screened for mutations of known genes (PMP22, MPZ, GJB1, EGR2, MTMR2, NEFL) in over 250 families, and reported the distribution of CMT mutations and clinical findings. (*Annals of Neurology* 2002,51, in press; *Neurogenetics* 2001, 3; 153-157) Based on our results, 32.7% of CMT families did not have any mutations of known genes. This result indicates that we should find more new causes of CMT.

We hypothesized that the following 5 genes would be good candidates as a cause of CMT: PMP2 (peripheral myelin protein 2), MAG (myelin-associated glycoprotein), PRX (periaxin), CASPR1, and CASPR2. We screened for mutations in PMP2 and MAG by direct sequencing analysis, we identified several polymorphisms but no disease-associated mutations in these genes. These studies were performed by direct sequencing method, the gold standard for mutation detection. However, because the labor and reagent costs of DNA sequencing are considerable, we tried to change the initial screen method for mutation detection from DNA sequence to DHPLC (denaturing high-performance liquid chromatography), which is an economical and highly sensitive method based on

PRELIMINARY REPORT

"Surgical Gene Therapy for Fetal Peripheral Nerves"

By ROGER LEBO, PhD, FACMG

The one-year postdoctoral fellowship, "Surgical Gene Therapy for Fetal Peripheral Nerves" began at Boston University School of Medicine. This project is testing whether genes carried by viral expression vectors can be delivered and expressed in fetal nerve cells that grow into peripheral nerves. These would form the basis of long-term therapy for the slowly progressive CMT diseases.

The fellow, Dr. Willmar Patino, and I moved to George Washington University and four months after the move, the animal experimentation committee approved resuming our work with new mouse fetuses. To date, we have delivered and expressed the reporter gene in fetal brain and meninges. Currently, we are using the remaining three months of funding to study the precise locations of transfected cells to determine whether any of the peripheral nerves are expressing this gene during the three days following gene injection.

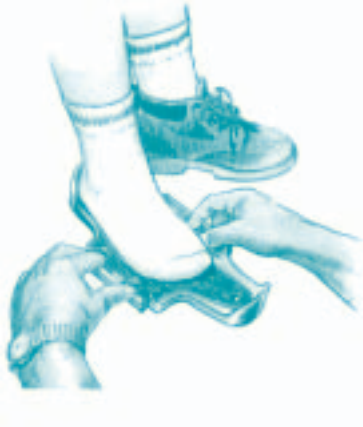
The possibility of doing gene therapy in unborn fetuses is a promising approach to ameliorate the symptoms of the slowly progressive later-onset Charcot-Marie-Tooth diseases. In this protocol, we tested the efficiency of in utero gene delivery of a reporter gene that was injected into the cerebrospinal fluid that bathes

recent reports. We tested DHPLC sensitivity and established optimal DHPLC conditions for mutation detection using patient samples known to have PMP22, MPZ, GJB1, or EGR2 mutations. We found that DHPLC was as sensitive as DNA sequencing (*Genetics in Medicine* 2001, 3; 335-342). Subsequently we screened for mutations of three candidate genes (PRX, CASPR1, and CASPR2) by DHPLC, and identified that PRX mutations cause recessive Dejerine-Sottas neuropathy (Am. J. Hum. Genet. 2001, 68; 325-333). We did not identify disease-causing mutations in CASPR1 and CASPR2. Recently our study revealed PRX mutations also cause Charcot-Marie-Tooth neuropathy and congenital hypomyelinating neuropathy (submitted). This finding is important for the diagnosis of recessive and sporadic cases of CMT. As periaxin interacts with cytoskeltal and membrane proteins, these interacting proteins have an important role in myelin and may cause CMT or related neuropathies.

I would like to thank the CMTA for giving this fellowship, and express my appreciation to my mentor Dr. Lupski for providing me with this research.

the brain and spinal cord. Preliminary results in these studies found that different nerve cells in the brain as well as cells in the meninges, which are the membranes that cover the brain and spinal cord, were targeted successfully. The remainder of this project will characterize the efficiency and specificity of these methods that can be applied in the future to deliver therapeutic genes into the central nervous system of fetuses prenatally diagnosed with a neurological disorder. We shall also look to see whether any nerve roots that lead to the peripheral nerves affected in CMT patients were targeted.

10 TIPS TO A GREAT SHOE FIT



1 Shoe sizes are not standard.
Sizes vary between shoe brands and styles. A size 8M from one manufacturer might fit like a size 8N from another. Don't select shoes by the size marked on the shoe, start with a size range and go from there.

2 Have both feet measured every time you purchase a pair of shoes.
Over the course of your lifetime, your feet will change in both size and shape. For many people, one foot is slightly longer and/or wider than the other, so fit the largest foot first.
Bonus tip: Go to a shoe store that measures both feet and wear the type of socks you will use for the specific activity.

3 Select shoes that match the shape of your foot.
If your foot shape matches your shoe shape, you're on the right track to good shoe fit.

4 When you shop for shoes, try on various types and styles.
Judge shoes by how they fit your feet. Don't select any style that feels too tight, too loose, or irritates parts of your foot. If shoes feel too snug or too loose at the try-on stage, your feet may hurt later on.

5 Shoes should be as wide as your feet, and longer.
When shoes press the ground during walking or running, feet elongate.
Bonus tip: Allow adequate space (3/8" to 1/2") at the end of the shoe for your longest toe.

6 Make sure the widest part of your foot (the "ball") fits comfortably into the widest part of the shoe.
This match permits shoes to bend where your feet flex, giving you a more functional and more comfortable wearing experience.

7 Heels should fit comfortably in the shoes.
Don't buy shoes too small just to avoid heel slippage. If your foot has excessive slippage in the heel of your shoe, try a different shoe, or ask your shoe fitter to make some minor adjustments.

8 Inserts or orthotics affect the way a shoe fits.
Shoe inserts or foot orthotics will take up shoe space intended for your feet. If you require inserts or orthotics, you'll need a roomier shoe; otherwise, the inserts can't function properly and your shoes won't fit right.

9 Choose shoes appropriate for the activity AND the time you perform that activity.
Feet change shape and size during the day AND under different conditions: after exercise, in warm weather, with weight gain, or from sitting to standing. When shoe shopping, remember that your feet are generally larger after an activity than preceding it, so buy accordingly.

10 Walk in the shoe to make sure it feels comfortable.
No need to do a marathon run while trying on shoes, but at least take a walk around the store. Shoes express your fashion sense and affect your health and activities. So choose wisely.
Bonus tip: Shop stores that offer full service, including a good size and width selection and staff trained in proper shoe fitting and measuring.

(This information was provided by the Pedorthic Footwear Association, From the National Shoe Retailers Association.)

Results of a Study on Reorganization of the Axon Membrane

By DR. EGUARDO JOSE ARROYO

Myelinated nerve fibers result from a series of interactions between axons and two kinds of glial cells. In the peripheral nerves, myelin sheaths are formed by Schwann cells; in the brain and spinal cord, they are formed by oligodendrocytes. Myelinated fibers are specialized for the rapid transmission of electrical impulses. Electrical impulses travel quickly because electrical current is concentrated at thin gaps between adjacent myelin sheaths called nodes of Ranvier. At nodes, sodium ions pass through sodium channels, which are highly enriched in the nodal membrane. Thus, the current "jumps" from node to node to node along the nerve fibers, traveling about ten times faster because the nerve fibers are myelinated.

Historically, myelin sheath was considered to function merely as electrical insulation around the axon, but this concept has been drastically modified by a series of discoveries. It has become increasingly clear that the paranodal region of the myelin sheath plays an essential role in promoting axonal conduction. As the name implies, the paranodal region is the region of the myelinated axon on either side of the node. At the paranode, unique structures called septate-like junctions join the edge of the myelin sheath to the axonal membrane. A pair of axonal proteins, contactin and Caspr, interact with a protein called neurofascin 155 on the glial membrane, forming the septate-like junctions. Thus, paranodes are sites where axons and myelinating glial cells are physically connected, and could serve as communication links between the two cells types. In addition, paranodes appear to serve as a fence between the node and the rest of the axon (called the internode). The part of the internode that is immediately adjacent to the paranode is called the juxtaparanode. The axonal membrane of the juxtaparanodal region contains high concentrations of potassium channels (Kv1.1 and Kv1.2). The paranodes keep these potassium channels away from the node, so that they do not participate in axonal conduction in normal myelinated fibers.

Although their function in normal myelinated fibers is uncertain, these potassium channels appear to play a prominent role in demyelinated axons. In several genetically altered mice, including mice that lack Caspr or contactin, septate-like junctions do not form, and Kv1.1 and Kv1.2 potassium channels are no longer separated from the nodal membrane. Unlike normal mice, in these mutant mice, potassium channel blockers dramatically affect electrical conduction. Thus, one important function of the paranode is to sequester Kv1.1 and Kv1.2 channels beneath the myelin sheath, so that they do not interfere with electrical conduction.

In my project in Dr. Scherer's laboratory, I asked how the localization of these nodal, paranodal, and juxtaparanodal proteins was affected by inherited causes of demyelination. I selected the myelin-deficient rat, an animal model that has a mutation in the proteolipoprotein (PLP) gene. Mutations in this gene can cause a profound absence of myelin in the brain and spinal cord (but not in the nerves). The myelin-

MORE FUNDING FOR RARE DISEASE OFFICE

After a contentious legislative year, at the end of December 2001 the House and Senate Appropriations Committees approved an increase of funding for the National Institutes of Health (NIH) amounting to almost 15%. For the first time, Congress has increased funding for the NIH Office for Rare Diseases (ORD) to $10,341,000. Funding for the Office had stagnated at approximately $2 million per year, so this five-fold increase is a reflection of the letters, phone calls, and visits of concerned patients and family members to their federal elected officials asking for more funding for the ORD.

NORD (National Organization for Rare Diseases) has asked Congress to appropriate $24 million for the ORD, which will enable the office to open several clinical research centers for rare disorders. A bill is currently pending before Congress (The Rare Diseases Act, S.1379), which would make the NIH Office for Rare Diseases permanent by writing it into law, and to appropriate $24 million to the office next year. This interim step provides over $10 million to the ORD during 2002.

Unfortunately, an extra $2 million slated for the FDA's Office of Orphan Products Development was reduced by the House and Senate Conference Committee to approximately $700,000 more than last year's funding for orphan disease research grants ($12.5 million to $13.2 million). New treatment discoveries from the NIH (e.g., orphan drugs, devices, and medical foods) must be approved for marketing by the FDA. The lack of adequate FDA funding can seriously delay or prevent availability of new treatments for rare disorders that are not of great interest to the commercial sector.

deficient rat is a genetically authentic animal model of the most severe and clinically devastating diseases that affect myelinated fibers in humans. These rats die around 21 days after birth.

I found that node-like clusters of sodium channels form normally in myelin-deficient rats, and always adjacent to (albeit incompletely formed) myelin sheaths. Even after oligodendrocytes die (large numbers die in myelin-deficient rats), node-like clusters of sodium channels persist for days. The known molecular components of paranodes (contactin, Caspr, and neurofascin 155), however, do not ever appear to cluster in myelin-deficient rats, and septate-like junctions are not found. Further, Kv1.1 and Kv1.2 potassium channels appose node-like clusters of sodium channels. Based on these results, I predicate that potassium channel blockers would have a pronounced effect on axonal conduction in myelin-deficient rats.

Previous studies have shown that the loss of a myelin sheath results in the reorganization of the axonal architecture. Nodal clusters of sodium channels are lost after demyelination, but reappear after remyelination. Similarly, the paranodal proteins (Caspr, contactin, and neurofascin 155), and juxtaparanodal proteins (Kv1.1 and Kv1.2) dissipate after demyelination, but recluster during remyelination. My results emphasize that the clustering of nodal, paranodal, and juxtaparanodal proteins depends on normal axon-glial interactions.

This work will be published soon in one of the leading journals in neuroscience:

Arroyo, E.J., T. Xu, S. Lambert, S.R. Levinson, P.J. Brophy, E. Peles, and S.S. Scherer (2002) Genetic dysmyelination alters the molecular architecture of the nodal region. J. Neurosci. (in press)

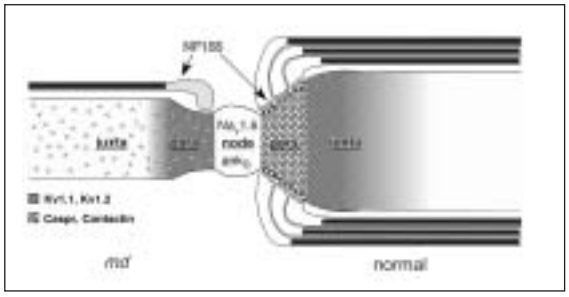


Figure 1. The organization of the axonal membrane in myelin-deficient (md) and normal rats. In this schematic image, the axon is depicted as intact, whereas the glial cells are depicted as being hemisected, in order to reveal the axoglial junctions. The localization of nodal (sodium channels and ankyrinG), paranodal (contactin, Caspr, and NF155), and juxtaparanodal proteins (Kv1.1 and Kv1.2) in normal rats is shown on the right. The left side of the figure depicts P21 md rats, in which nodal proteins can be localized with or without oligodendrocyte ensheathment, whereas contactin and Caspr are diffusely localized, and Kv1.1 and Kv1.2 abut the nodal membrane.

CMT in the News

A syndicated columnist from Wickliffe, Ohio, Dr. Peter Gott, featured a question on CMT in combination with other problems in a recent column.

Dear Dr. Gott,

I have been diagnosed with Charcot-Marie-Tooth disease, complicated by osteoarthritis, rheumatoid arthritis and pseudogout. I'm an active woman of 70. How can I strengthen my muscles to maintain independence?

Dear Reader,

You are unlucky enough to have four unrelated diseases, the combination of which could lead to significant disability.

CMT (peroneal muscular atrophy) is an inherited disorder marked by slowly progressing weakness and muscle wasting in the lower legs; sometimes the hands are affected as well. This is due to nerve degeneration. In its mildest form, it causes foot deformities, such as high arches and club foot.

In more advanced cases, the affliction leads to diminished perception of pain and temperature, marked weakness and a "storkleg" deformity, because of muscle atrophy. There is no cure.

However, physical therapy and orthopaedic appliances, such as braces, may help maintain function; surgery to stabilize the feet can be of value.

Osteoarthritis, on the other hand, is confined only to the joints and will affect all of us sooner or later, because it is the age-related wearing-down of joint surfaces. The disorder causes stiffness, pain and lack of mobility. Along with physical therapy and exercise, there are many medications to relieve symptoms of osteoarthritis, including the two flavors of the month: Celebrex and Vioxx.

Rheumatoid arthritis, a chronic autoimmune disorder, also affects only the joints, which become swollen, painful and—late in the disease—deformed. Treatment includes physical therapy, anti-inflammatory drugs, cortisone, gold salts, methotrexate and others. Severe cases may require joint replacement.

The cause of pseudogout is unknown, but the disease is characterized by intermittent attacks of acute arthritis, leading to eventual calcium deposits in joint cartilage and, in advanced form, destruction of the joint. Colchicine and Indocin often lessen pain and swelling.

In your case, I believe that combination therapy is in order. You should be using anti-inflammatory medicine and physical therapy, plus exercise and heat treatments; such a combination should reduce your level of pain to the point where your independence is not severely compromised. Finally, you should be examined by an orthopaedic surgeon for braces and possibly, surgery to correct any deformities the diseases may have caused.

Support Group News

California - Berkeley Area

Group Leader, Ruth Levitan, had knee replacement surgery on Monday, January 14, 2002. Her knee was replaced with one of chrome and plastic and ligaments were tightened or loosened as necessary. She returned home on Friday, January 18 and will use crutches and/or a walker for about two weeks. Physical therapy will take place a few times a week and she will do exercises every day, which she reports are expected to hurt...like ****.

We wish her a speedy recovery!

California - Northern Coast Counties

Group Leader Fred Brown has announced the schedule of meetings for 2002. They will be held on March 2, July 6, and November 2. Meetings are held at Freda's home at 1:00 PM on the announced dates.

Colorado - Denver Area

Marilyn Munn Strand sent some good advice for the new year: *Throw out non-essential numbers, including age, weight and height. Let the doctor worry about them. That is why you pay him/her. Keep only cheerful friends. The grouches pull you down. Cherish your health. If it is good, preserve it. If it is unstable, improve it. If it is beyond what you can improve, get help. Tell the people you love that you love them, at every opportunity. Remember: Life is not measured by the number of breaths we take, but by the moments that take our breath away!*

New York - Horseheads

Angela Piersimoni, the group leader, and her support group were featured in a lengthy article in the Health section of their local paper, The Star Gazette, last fall. The article discussed the characteristics of CMT, the problems it produces, and the ways that different people deal with it, from denial to searching for all the information that's available. Angela was quoted as saying, "For whose who want to understand CMT, the CMT Support Group is there. Support says it all," according to Angela. "Sometimes the conversation just goes on and on. On nights like that, it's very gratifying."

Supreme Court Narrows Disability Law

On January 8, 2002 the U.S. Supreme Court ruled that a person who is "disabled" under the Americans With Disabilities Act (ADA) must have substantial limitations of his or her daily functional abilities—not only limitations that affect job performance.

The ADA is the 1990 federal law that protects the civil rights of people with disabilities. Employers are required to make "reasonable accommodations" for disabled workers so they will be able to do their jobs. The law defines disability as "a physical or mental impairment that substantially limits one or more of the major life activities," "a record of such impairment," or "being regarded as having such an impairment." The law was designed to prevent discrimination against people with disabilities, especially in the workplace.

The Supreme Court unanimously ruled that the definition of substantial limitations to major life activities needs to be "interpreted strictly," and therefore a person is not disabled if his or her condition does not prevent performing daily tasks such as dressing, walking, toileting, etc.

The case, which is one of three ADA cases on the Supreme Court's 2002 calendar, involved a woman with a repetitive motion injury who asked her employer (Toyota) to assign her to a job involving minimal use of her arms. The decision means that in the future courts will have to consider whether a person's disability affects his or her functioning in daily living activities along with the ability to do his or her job. Thus people who do not have serious impairments that interfere with daily functional activities may not qualify for the protections of the law.

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@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

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
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) 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

Ask the Doctor

Dear Doctor,

I'm wondering what values of creatine phosphokinase (CPK,CK) are to be expected in individuals with CMT syndrome. I imagine the values will vary with the degree of muscle wasting, but I'd like to have a reference regarding the possibility of CK abnormality. Without this information, elevations of CK in CMT patients may be attributed to other possible diagnoses, confusing the situation.

A member of the CMTA's Medical Advisory Board replies:

Chronic peripheral neuropathies (including CMT) should cause a minimal, if any, elevation of the CK levels.

(Editor's note: The following question was sent to Dr. Andrew Yeager, University of Pittsburgh Cancer Institute, by a CMT patient.)

Dear Doctor,

Having read that you were able to cure a young man of a genetic disorder by the use of cord blood from stem cells, I am interested in the possibility of a similar therapy working for someone like myself who suffers from an inherited peripheral neuropathy.

The Doctor replied:

I assume you have Charcot-Marie-Tooth disease, or a similar disorder, caused by overexpression of the PMP-22 (peripheral myelin protein) gene.

Unfortunately, the transplantation of cord blood stem cells does not grow normal nerves, muscles, or other tissues of this type, and would not have an application in your condition.

Dear Doctor,

A study published in the November 2001 issue of the journal Neurology *reported a significant reduction in the severity of neuropathic pain among patients taking an antidepressant called bupropion, which is marketed by GlaxoSmithKline under the name Wellbutrin. In the study, patients with neuropathic pain, but not depression, were given either bupropion or a placebo, and 71% of those given bupropion reported a decrease in pain, as compared with 10% of the patients taking the placebo. Some of the patients described mild side effects, but bupropion unlike trycyclic antidepressants normally prescribed for neuropathic pain, appeared not to pose the risk of causing irregular heartbeats in cardiac patients.*

Would bupropion be of any benefit in reducing nerve pain associated with CMT?

A member of the CMTA's MAB answers:

That is correct. Bupropion probably works for some patients with neuropathic pain, but it remains to be seen whether it works better than traditional tricyclics, or Neurontin.

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:_____

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Amount Enclosed: _____

☐ Check Enclosed ☐ VISA ☐ MasterCard

Card #_____

Exp. Date _____

Signature _____

Gift Given By:

Name:_____

Address:_____

_____

Letters to the Editor:

Dear CMTA,

For the CMT patient being fitted for orthotics, one word of advice: STAND.

Stand while the cast is hardening on your ankle. Stand with all your weight on the foot being cast. The arch of your foot—even a high, cramped CMT foot—is ordinarily compressed (flattened to some extent) when you step on it. If a cast is taken of a relaxed foot, the arch of the resulting brace will be too high. When you step on it, your weight will be thrown to the outer edge of your foot. The loss of balance may make walking difficult—tiring, dangerous, and perhaps painful.

If you think you may be troubled by a high-arch brace, you can easily check it—and perhaps improve your balance. Just pad the inside of the brace, at the bottom, without covering the arch. Your insert should look like a bare footprint in sand. In my case, such padding ended years of pain which had severely limited my walking. I hope others may have the same good result.

—N. H., Pittsburgh, PA

■

Dear CMTA,

I am a member of your association, male, married and 43 years old. In Hong Kong, CMT is not a common disease. I would like to share my past experiences with your country's patients. Since I am Chinese, my English is not good, so I hope you can understand my explanation.

From the age of 1-12 I had trouble running, jumping or riding a bicycle because my balance was so bad. I walked like a Dolphin and it was easy to sprain my ankle. My hands shook and I could not move my toes. I had trouble making friends. From 12-19, I added dropped foot to the list of problems and my legs resembled the reverse champagne bottle. The disease was more obvious and serious.

At 19, I went to work and, since my outward appearance was fairly normal, my employer treated me normally. However, I could not do fine hand functions, like handling cash. It was easy for me to sprain my muscles. I started on medication for pain and began to feel more stress.

Now, my appearance is not normal and I avoid social situations. I am afraid people will look at me and ask me why I look different. I also suffer from mild hypertension and depression. I have inflammation of my knee, due to my increased weight, some sexual dysfunction, and athletes foot. I am on many medications and I receive psychological counseling. According to my experience, the anti-hypertension medications make the body lose potassium and weaken the muscles.

—A. W., Hong Kong

■

Dear CMTA,

This is Sameer Bansal, a citizen of India, who suffers from CMT. I was diagnosed in 1994 and then subscribed to your newsletter. I found it to be of immense help to me and my sister (another CMT patient). In simpler words, we are fans of your magazine. It has helped us gain so much confidence and has told us so much more about the condition. In fact, it has changed our attitude towards life! Thanks for being there.

My father is a practicing ophthalmologist in India. My maternal uncle has been settled in New York for the last 20 years or so. It is through him that we came to know about your existence.

I am currently in the final year of a Bachelors in Computer Applications. It is only because of your information that I may be applying for a job or further studies in the US after completing my graduation.

—S. B., India

■

Dear CMTA,

I have just reread the December 2001 issue of the newsletter. I found page 5, Pedorthic Management of CMT, very informative, as well as the article on page 14 on Foot Care for the Numb Foot. I always enjoy the Ask the Doctor section. I would like to know how to contact Comfort Shoes to see if they are available in Massachusetts.

If possible, I would like to know if anyone has information on what I call frozen fingers, which make me very clumsy in cold weather.

I'm going to pass this issue on to my neurologist after I have made copies of the pages I want to keep.

—J.P., Hyde Park, MA

(Editor's note: Comfort Shoes may be contacted through their home page at www.comfortshoe.com or by calling them in St. Louis, MO at 1-314-822-3300.)

WRITE TO US!

Pat Dreibelbis, Editor
The CMTA Report
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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, 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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