THIS ISSUE WAS ENTIRELY FUNDED BY A GRANT FROM NEW ENGLAND BIOLABS FOUNDATION

National Foundation for Peroneal Muscular Atrophy

# THE NFPMA REPORT

Spring, 1989 Issue Vol. 3 No. 2

Providing information on Charcot-Marie-Tooth disease (or Peroneal Muscular Atrophy), the most common inherited neurological disease. 

## SEPTEMBER CMT CONFERENCE

### Wilmington, Delaware

**by Karol B. Hitt**

The A.I. duPont Institute of Wilmington, DE and the NFPMA are sponsoring a three day educational conference for CMT patients/families and medical professionals September 8-10, 1989. The meetings will be held at the Institute which is a multispecialty children's hospital. The scope of the meeting for professionals will cover CMT and other peripheral neuropathies, however, the patient program will cover only CMT disorders.

**PROGRAM SCHEDULE**

Friday, September 8 is devoted to the medical professional and is expressly for physicians, podiatrists and physical and occupational therapists. The program is entitled, "Peripheral Neuropathies in Children". Following introductory remarks by Dr. Michael Shy of Thomas Jefferson Medical School and Dr. Howard Shapiro of the NFPMA, the morning topics are:

-CMT Clinical Manifestations, Dr. Harold Marks, A.I. duPont;

-Genetics, Review and Update, Dr. James Lupski, Baylor University College of Medicine

-EMG Studies, Dr. Robert Lovelace, Columbia University College of Physicians and Surgeons;

-Physical Therapy, Dr. Carol Oatis, Philadelphia Institute for Physical Therapy;

-Podiatric Management, Dr. Gilbert Hice, Pennsylvania College of Podiatric Medicine;

-Orthopedic Management, Dr. Richard Bowen, A.I. duPont Institute;

-Dejerine-Sottas/Congenital Hypomyelination Syndrome, Dr. John Griffin, Johns Hopkins School of Medicine.

The afternoon topics are:

-Guillain-Barre Syndrome, Dr. Charles Bean, Neurology Associates, Wilmington, DE;

-Chronic Inflammatory Neuropathy, Dr. John Sladky, Children's Hospital of Philadelphia;

-Bell's Palsy in Children, Dr. James Riviello, St. Christopher's Children's Hospital of Philadelphia;

-Hereditary Sensory Neuropathies, Dr. Felicia B. Axelrod, New York University Medical Center;

-Refsum's Disease, Dr. Hugo Moser, J.F. Kennedy Institute of Baltimore;

-Brachial Plexus Injuries, Dr. Michael Painter, University of Pittsburgh.

Saturday, September 9 is devoted to the CMT patient/family and is open to medical professionals also. The day begins at 9 AM with a physical therapy workshop conducted by Dr. Oatis. At 10 AM registration begins for the day's program. Dr. Marks, who is Chief of the Division of Neurology at the Institute, will open the day with a presentation of the clinical findings of CMT. Dr. Lupski will follow with a discussion of CMT genetics. Both speakers will answer questions from the audience.

Allison Harter, (above) who had foot surgery at A.I. duPont in June and July, 1988, is now training to run i. 5K race in May, 1989. Allison, a 14-year old CMT patient, has accomplished this through regular supervised physical therapy and exercise following her successful surgery.

Following lunch, the afternoon session will begin with Dr. Oatis speaking on physical therapy for the CMT patient, and following her will be Dr. Bowen and orthopedic management of the CMT patient. Included also will be an occupational therapist discussing the CMT hand. Ann Lee Beyer, Columbia University doctoral candidate, will conclude the formal presentations with the Psycho/ Social Impact of CMT on the Child/

*Continued on page 2*

INSIDE
The NFPMA Report

September CMT Conference From
t
Research Update 3
Heterogeneity 8
Ask the Doctor 10
Support Group News 11

Adult. Again, these speakers will answer questions from the audience. Concurrent with Mrs. Beyer's presentation, Steve Gullick (see Winter NFPMA Report) will conduct a children's workshop. Steve, a CMT patient and professional mime, works with children through music and mime reaching them in a very unique way.

This concludes the formal program, but we now go into the informal part which we call P to P. This can be patient to patient or parent to parent; whatever you call it the result is the same---people talking and learning from one another. This will be done very informally and the topics will be what you request. Currently, we have been asked to have groups for CMT and Pregnancy and physical therapy following foot surgery. If you have a topic, please, contact us; we will arrange for a small group discussion on your topic. These groups will be announced at the conference.

On Sunday, September 10, support group leaders and NFPMA board members will meet to share concerns and ideas. This will be our first gathering on a national basis, and we are looking forward to meeting those involved from other parts of the country. Here again, if you the CMT patient/family have a concern or suggestion, please tell us so we may bring it to the group. Write to us in advance or tell us at the conference; we wish to know how you feel.

**THE COST**

The cost for the Saturday conference is $10.00/adult and $5.00/child with a maximum charge of $25.00/family. This charge includes the day's meetings and lunch. This nominal fee results from A.I. duPont's profound commitment to children. We are very indebted to them for their professional and financial involvement in this conference. At 6 PM you are invited to stay for dinner at the Institute and a further chance to socialize. The charge for this meal is $10.00 per person.

**THE ACCOMMODATIONS**

A block of rooms has been reserved at the Brandywine Sheraton Hotel, 4727 Concord Pike (route 202), Wilmington, DE 19803. A special conference rate of $63.00/night has been arranged. This rate is for a single or double with children in the room being $5.00 additional. If you are making reservations specify you are going to the A.I. duPont - NFPMA Conference, and that will assure you of the special rate. The Sheraton's number is 302/478-6000; you must call this number as the Sheraton 800 number cannot take this reservation due to the special rate. To receive the special rate you must make your reservations by August 9, 1989.

The hotel is three and one-half miles from the Institute, and they run a free shuttle service if you do not wish to drive. If you are considering flying they do not go to the Philadelphia airport, however there are other limo services that go between the airport and Wilmington.

Wilmington is a lovely city with many very interesting places to see in the city and surrounding area. A few of them are Longwood Gardens, one of the world's most magnificent gardens; the Brandywine Museum, featuring three generations of Wyeth artists; Winterthur, a duPont mansion which houses the world's greatest collection of American decorative arts made between 1650-1850; the Hagley Museum, site of the first duPont black powder works; and the Nemours Mansion and Gardens. The A.I. duPont Institute is located on the grounds of the mansion, although the Institute is entirely separate. The formal French gardens of the mansion occupy 300 acres, and the mansion is set among the gardens.

**FOR MORE INFORMATION**

See our sidebar on Page Two for detailed directions. For more information about the area call the Delaware State Travel Service at 800/441-8846 and ask for the free pamphlet "Discover the Brandywine Valley". The pamphlet includes a small but good map of the area. Another free pamphlet, "Visitor's Guide to Greater Wilmington's Delaware", can be had by calling the Wilmington Convention and Visitor's Bureau at 800/422-1181.

*Continued on page 3*

## WE'VE MADE GETTING THERE EASY!

Traveling by car to the Institute is as easy as following these directions.

From South

*Via I-95:* North to US 202 (Concord Pike); north on US 202 to Rt. 141; left on Rt. 141; left onto Rockland Road to the Institute.

*Via US 13:* North to Rt. 41/141; north on Rt. 41/141 to I-95; north on I-95 to US 202 (Concord Pike); north on US 202 to Rt. 141; left onto 141; left onto Rockland Road to the Institute.

From Southern New Jersey

From Delaware Memorial Bridge take I-95 North to US 202 (Concord Pike); north on US 202 to Rt. 141; left onto Rt. 141; left onto Rockland Road to the Institute.

From Northern New Jersey

South on I-295 or New Jersey Turnpike to US 322 West to Commodore Barry Bridge. After bridge, take I-95 South to US 202 (Concord Pike); north on US 202 to Rt. 141; left onto Rt. 141; left onto Rockland Road to the Institute.

From Philadelphia and Southeastern Pennsylvania.

*Via I-95:* South to US 202 (Concord Pike); north on US 202 to Rt. 141; left onto Rt. 141; left onto Rockland Road to the Institute.

*Via US 1:* To US 202 (Concord Pike); south on US 202 to Rt. 141; right on Rt. 141; left onto Rockland Road to the Institute.

*Via Rt. 52:* South to Rt. 141; left onto Rt. 141; right onto Rockland Road to the Institute.

*Via Rt. 41:* South to Rt. 48, Rt. 48 to Rt. 141; left onto Rt. 141; right onto Rockland Road to the Institute.

Directions to the Sheraton

Follow the directions to get to Rt. 202 (Concord Pike), adjusting for whether you are coming from the north or south, and just proceed to the hotel. The hotel is located next to a major shopping mall and is north of Rt. 141. They also have a pamphlet with a map which is free upon request.

*Continued from Page 2*

This also includes an area map.

In conclusion, we are pleased to be doing these meetings. It is the first time that a professional and patient conference has been combined. Our participants are all authorities in his/her field, and the meetings should be interesting and informative. We hope you can join us; we feel we will all benefit.

**TO REGISTER**

To register for the conference please complete the combined GET IN TOUCH -- CONFERENCE REGISTRATION form in this issue. Please send in your registration by September 1, 1989. All are welcome to attend, and if not registered prior to the conference, please plan on arriving by 10 AM. Advance registration will help us to plan for lunch, which is included in the conference fee

❁

***Conference Will Earn Continuing Education Credit for Qualified Medical Professionals***

Continuing Education Credit will be given. Interested medical professionals should contact the Medical Education Department, A.I. duPont Institute, 1600 Rockland Rd., Wilmington, DE 19899 or call 302/651-6750.

# RESEARCH UPDATE •••••••• AN INTERVIEW WITH DR. JAMES R. LUPSKI

by David B. Hitt

Dr. James R. Lupski is an Assistant Professor at the Baylor College of Medicine' s Institute for Molecular Genetics and the Department of Pediatrics in Houston, Texas. Dr. Lupski, who, in addition to his medical degree holds a Ph.D. in Molecular Biology from New York University, studies CMT at the molecular level. Recently, much of his research has focused around studying "clusters" of extended families with large numbers of CMT patients in them. Dr. Lupski, a CMT patient will speak at the Wilmington conference.

*Hitt: Dr. Lupski, where were you working prior to coming to Baylor and what was the future of your research?*

LUPSKI: Before coming to Baylor, I was a research faculty member at the NYU Medical Center, doing Biochemistry research. Two focuses of my research involved looking at the genes responsible for D. replication in a particular bacteria (E. coli) and investigating genetic processes in other very simple life forms.

*Hitt: Is there any reason why your research at NYU was limited to simple organisms?*

LUPSKI: Simple organisms such as prokaryotes (organisms without a real nucleus) are often studied by molecular biologists because their genetic mechanisms are much better understood than those of eukaryotes (organisms with a genuine nucleus). Also, precisely because of their simple structure, it is possible to carry on highly refined studies of prokaryotic organisms. Later on, the results of these studies can be applied to more complex systems such as human genetics research.

*Hitt: Where did you get your training in Molecular Biology?*

LUPSKI: In addition to the formal training I received at NYU in the medical scientists training program, I also had the opportunity to work at Cold Spring Harbor labs in Long Island. There I was fortunate to participate in some of the earlier experiments which used genetic engineering techniques. Cold Spring Harbor, as some NFPMA members might know, is directed by Dr. James Watson who was recently appointed director of an ambitious project to sequence the human genome.

*Hitt: Did you do CMT research before coming to Baylor?*

LUPSKI: No, in fact I had had no experience in human genetics research. However, my desire to conduct research in this area was one of the reasons I came to Baylor and, specifically, the Institute for Molecular Genetics.

*Hitt: What is the Institute for Molecular Genetics?*

LUPSKI: The institute was founded three years ago by Dr. C. Thomas Caskey. Essentially, the idea behind its creation was to bring together scientists with "hard core" research backgrounds in genetic engineering or molecular biology and team them up with clinicians in the study of human disease. It is important to realize that molecular biology and genetic engineering are relatively "young" sciences, and the mechanics of applying the results of research to the challenges of clinical medicine is still a process that is evolving.

*Hitt: What sort of CMT research are you currently doing?*

LUPSKI: Currently, I am involved in research which is being sponsored by the Muscular Dystrophy Association. CMT is one of forty muscular dystrophy related diseases for which the MDA funds research. Because the disease is inherited, much of our efforts go toward finding families with CMT patients in them and including as many of them in our study as possible. In this project, I have been working closely with Dr. Carlos Garcia, a neurologist and a neuropathologist, who runs the MDA clinics in New Orleans, LaFayette, and Baton Route, LA. Generally, we track down members of CMT afflicted families and make arrangements for them to be examined by Dr. Garcia or another neurologist depending on where the patient lives. The neurologist then evaluates each family member to determine whether he/she fits the clinical criteria for a diagnosis of CMT. Because CMT presents such a broad spectrum of symptoms and because the disease can manifest itself quite subtly, The clinical neurologist's role in this research is vital. Without this work, it would be impossible to accurately assess phenotypic expression in these family groups. After each family member has been examined, the next phase of the research involves collecting blood specimens from each family member. Usually, I arrange to do these at family barbecues, so a number of blood samples can be collected at once. Finally, much of the actual analysis of DNA from blood samples is done by Dr. Pragna Patel, an assistant professor at Baylor, myself, and our associates.

*Hitt: How many family groups are you studying?*

LUPSKI: Approximately 30 families have been located for study, 3 or 4 of which we have been able to collect blood samples from. The families tend to be very large; one family we studied has more than 250 identified members, 35 of which have CMT.

*Hitt: What are you hoping to learn from your research?*

LUPSKI: Two ultimate goals come to mind. First, we hope that a thorough study of these families will expand our clinical understanding of the disease. CMT is rare and, because most doctors have little useful knowledge about it, underdiagnosed. Textbook descriptions of the disease tend to be inaccurate, further muddling the limited awareness clini-

*Continued on page 4*

*Continued from Page 3*

cians have of the disease. One thing we are doing in our research, then, is collecting a database of symptoms so we can get a general feeling of what CMT patients are like. Also, patterns of inheritance and some sense of the timetable for the progression of the disease is being gained from the physical examinations.

Ultimately, of course, we would like to determine what gene or genes are responsible for CMT. There are over 100,000 genes determining human characteristics. One thing we are hoping to do in our research is to find the location of the CMT genes on the genome. If we can find out where these genes are located, we can then assess what role they play in normal nerve cell functioning and see what goes wrong in CMT.

*Hitt: Do you see future benefit for CMT research coming from Dr. James Watson's genome program?*

LUPSKI: There is a lot of excitement about the genome project among genetic scientists. As you know, Dr. Watson is attempting to determine the location of genes controlling every aspect of functioning and behavior. Critics of the project say that it won't yield useful information. "Knowing the structure of the genome alone doesn't tell us much," seems to be their feeling. If the genome project gets underway and is supported, though, I think it will have a watershed effect. It should make our jobs easier because all the mapping information will be available to us before we begin research. I see nothing but benefit coming from the project.

*Hitt: Where do you think CMT research will be in ten years?*

LUPSKI: That is a very tough question. I don't have a crystal ball, but I can state with conviction that the next two years will bring a lot of change. Linkage for the major forms of the disease will be clearly established and a basic sense of where the genes are on the genome should also be gained. Finding the actual gene responsible for the disease will then be an arduous task that could take months or years.

*Hitt: What benefits from current research do you see for the CMT patient community?*

LUPSKI: That is another difficult question. If we consider Duchenne muscular dystrophy, research has made prenatal diagnosis of the disease possible. In the case of a non-fatal disease like CMT, such a test might have limited value, but it would obviously be useful for parents to know their child will develop CMT. For instance, we know that CMT often goes undiagnosed and thus there are thousands of people who suffer with some level of disability, without realizing they have CMT. Knowing in advance that the disease is present will help in the early treatment of patients. Also, it is possible to imagine some therapeutic treatments coming from current genetic research. In the case of diabetes, for instance, genetic engineering techniques have allowed us to clone the gene for human insulin and produce this substance for patient use. Previously, diabetes sufferers were treated with pig or bovine insulin.

*Hitt: You mention Duchenne muscular dystrophy. Do the recent breakthroughs in the study of this disease have any direct bearing on future CMT studies?*

LUPSKI: They certainly do. The methodology used to find the gene responsible for Duchenne muscular dystrophy is one we're hoping will be useful in the study of CMT. In the case of Duchenne, researchers concentrated their study on individuals that were symptomatic not only for Duchenne, but also for other X-linked inherited diseases. They found one patient, for example, who was not only symptomatic for Duchenne, but for four other diseases as well. Applying what they knew about the locations of the genes on the X-chromosomes, they speculated that all were located in the same region. Knowing this made searching for the specific locations of the genes much easier. Rather than looking for a needle in a haystack, researchers were now only looking for the needle in a grass basket. Ultimately, of course, it was discovered that one genetic mechanism, a deletion of a portion of the X-chromosome, was responsible for all the diseases observed.

The most significant result of the Duchenne work was the speed and relative ease with which the gene responsible for the disease was mapped. If a similar methodology could be applied to the study of CMT, researchers might find the gene responsible for CMT much faster than by ordinary research methods. In the questionnaire that I have asked CMT patients to fill out, several questions look for evidence of multiple inherited disorders within the same individual. By disseminating questionnaires like this and making the patient community aware of the significant role they play in CMT research, societies like NFPMA do an incredible service to the research community. Also, regardless of whether they fill out a questionnaire, I would like to strongly urge any CMT patients who have other inherited disorders to contact either me or NFPMA. The contribution they make to CMT research could be invaluable.

## ATTENTION CMT PATIENTS

Dr. James Lupski, who was interviewed for this issue of the NFPMA Report, requests that CMT patients who have a second inherited condition contact him. Please, when you write give the name of the second condition. Also, CMT patients who have a known chromosomal anomaly are asked to contact Dr. Lupski. You may write Dr. Lupski at the NFPMA, University City Science Center, 3624 Market St., Philadelphia, PA 19104

***Editor's Note:***
We encourage anyone who falls in either of these categories to contact Dr. Lupski. His research is concerned with the locations of the CMT genes, and would be greatly facilitated by having a pool of those CMT patients who have another inherited condition. The NFPMA **will not** release your name to anyone else.

**LETTERS**
We want to hear from you, so write us:
National Foundation for Peroneal Muscular Atrophy
University City Science Center
3624 Market Street
Philadelphia, PA 19104

**FOR THE NFPMA**
This material is presented for educational purposes only and is not meant to either diagnose or prescribe. While there is no substitute for professional medical care for Charcot-Marie-Tooth Disease, these briefs offer current medical opinion that the reader may use to aid and supplement a doctor's treatment.❄

**ATTENTION**
If you are moving please send your change of address to the NFPMA, University City Science Center, 3624 Market Street, Philadelphia, PA 19104. It will help us if you enclose your former mailing label from a previous NFPMA Report.❄

## LUPSKI/NFPMA QUESTIONNAIRE

Name_____ Address_____

Telephone Number (___)_____

This questionnaire is strictly for research purposes and is being distributed to all CMT patients in the NFPMA database. You are one of the largest known groups of CMT individuals and as such could do a great deal to educate physicians about CMT. This form will be time consuming and difficult. You should be able to answer questions 1-21 and 38-44 without a physician's help. However, questions 22-37 require data from your physician (neurologist). If it is not possible for your doctor to answer questions 22-37, then please submit the form with just the patient answered questions completed Please, answer all questions on both sides to the best of your knowledge and return the completed form within six weeks to Karol Hitt, NFPMA, University City Science Center, 3624 Market St., Philadelphia, PA 19104.

Please circle the correct answer (Y=yes, N=no)

1)Sex: M ___ F ___ 2) Date of Birth: ___/ ___/ ___ 3) Age: _____

DIAGNOSIS

4)AGE AT ONSET OF SYMPTOMS:_____ 5) AGE AT DIAGNOSIS: ____

6)ORIGINAL DIAGNOSIS GIVEN: _____

7)FIRST SYMPTOM (circle only one answer): 1) general medical exam 2)sensory loss 3) muscle weakness 4) foot deformity 5) scoliosis 6) gait disturbance 7) decreased exercise tolerance 8) muscle cramps 9) loss of balance (falling often) 10) decreased use of hands 11) numbness (feet and hands) 12) difficulty finding shoes 13) hammer toe 14) constantly walking on toes

15) other _____

8) SYMPTOMS SINCE DIAGNOSIS (circle as many as apply):

1) sensory loss in feet 2) sensory loss in hands 3) muscle weakness 4) foot deformity 5) scoliosis 6) gait disturbance 7) tremor 8) decreased exercise tolerance 9) muscle cramps 10) loss of balance 11) decreased use of hands 12) numbness 13) cold feet or hands 14) hearing loss 15) breathing problems 16) chronic nerve pain 17) trouble swallowing 18) excessive choking 19) regular difficulty digesting food 20) difficulty defecating 21) other _____

9) 1) OCCUPATION: _____

2) Forced to retire early due to CMT: Y/N/.

**GENETICS**

10) a)FAMILY HISTORY OF CMT: Y/N/. b) ORIGIN OR RACE _____

11) IF FAMILY HISTORY PLEASE GIVE AVERAGE AGE AT ONSET IN FAMILY MEMBERS: 1) <5 years old 2) 5-10 years old 3) 10-20 years old 4) 20-30 years old 5) 30-40 years old 6) 40-50 years old 7) 50-60 years old 8) >60 years old

12) AFFECTED FAMILY MEMBERS AND AGE AT ONSET (___): give number

Mother: Y/N/. ____ Father: Y/N/. ____

Maternal Grandmother: Y/N/.____ Paternal Grandmother: Y/N/. ____

Brother(s): Y/N/. _____ Sister (s): Y/N/. ____

How Many Brothers Out of Total: ___ How Many Sisters Out of Total: ___

13) INHERITANCE PATTERN: 1) autosomal dominant 2) autosomal recessive 3) x-linked 4) no pattern

14) (a) IF CMT IS ON YOUR MOTHER'S SIDE OF THE FAMILY, HAS IT EVER SEEMED TO SKIP A GENERATION? Y/N/.

(b) IF CMT IS ON YOUR FATHER'S SIDE OF THE FAMILY, HAS IT EVER SEEMED TO SKIP A GENERATION?Y/N/

15) GENETIC COUNSELING OBTAINED: Y/N/.

16) IS THERE A FAMILY HISTORY OF OTHER NEUROLOGICAL DISEASES? Y/N/.

17) PLEASE NAME OTHER NEUROLOGICAL DISEASE _____

18) FAMILY HISTORY OF OTHER GENETIC (INHERITED) DISEASES: Y/N/.

19) PLEASE NAME OTHER GENETIC DISEASE: _____

20) FAMILY HISTORY OF MENTAL RETARDATION: Y/N/.

21) FAMILY HISTORY OF RECURRENT SPONTANEOUS ABORTIONS : Y/N/.

**CLINICAL SIGNS**

22) FOOT DEFORMITIES: Y/N/.; pes cavus Y/N/.; varus Y/N/.

equinocavovarus Y/N/.; claw (hammer) toes Y/N/.; flat feet Y/N/.; other Y/N/. (Age at onset ____)

23) ENLARGED PERIPHERAL NERVES: Y/N/. (Age at onset _____)

24) DECREASED DEEP TENDON REFLEXES: Y/N/. (Age at onset ____)

Distal: Left 0 1 2 3 4 Right 0 1 2 3 4
Proximal: Left 0 1 2 3 4 Right 0 1 2 3 4
25) TREMOR: Y/N/. (Age at onset ____)
26) SENSORY LOSS: Y/N/.; pin: Y/N/.; vibration: Y/N/.
position sense: Y/N/. temperature: Y/N/.
27) SPIDER ANGIOMAS: Y/N/. (Age detected: ____)
28) SCOLIOSIS: Y/N/.; date detected ____/____/____ degree curve ____
(age detected ____)
29) HIP DEFORMITY: Y/N/.; 1) dislocation 2) acetabular dysplasia 3) subluxation 4) normal 5) other (age detected ____)
30) HIP X-RAY: Y/N/.; date ____/____/____
31) WEAKNESS: Y/N/. (strength on scale 0 to 5; 5 strongest, 0 no movement)
right upper extremity: proximal 0,1,2,3,4,5, distal 0,1,2,3,4,5
left upper extremity: proximal 0,1,2,3,4,5 distal 0,1,2,3,4,5
right lower extremity: proximal 0,1,2,3,4,5 distal 0,1,2,3,4,5
left lower extremity: proximal 0,1,2,3,4,5 distal 0,1,2,3,4,5
right peroneal: 0,1,2,3,4,5 left peroneal: 0,1,2,3,4,5
right ant. tib.: 0,1,2,3,4,5 left ant. tib.: 0,1,2,3,4,5
right ext. h.1: 0,1,2,3,4,5 left ext h.1: 0,1,2,3,4,5
32) PLANTAR REFLEX: 1) right toe upgoing 2) right toe downgoing
3) left toe upgoing 4) left toe downgoing 5) no reflexes
LABORATORY TESTS
33) NERVE CONDUCTION:

| | Peroneal | Median | Ulnar |
|---|---|---|---|
| Motor | _____ | m/s _____ | m/s _____m/s |
| Sensory | _____ | m/s _____ | m/s _____m/s |
| Distal Latency | _____ | m/s _____ | m/s _____m/s |

34) EMG: Y/N/.
Action potential (Polyphasic): _____
Recruitment: _____
Positive Wave: _____
Fibrilation: _____
35) WAS DIAGNOSIS PROVEN BY SURAL NERVE BIOPSY: Y/N/.
36) CSF PROTEIN: normal _____ increased _____ decreased, amount - _____
37) SERUM AMINO ACIDS: cysteine ____ (normal range - )
lysine _____ (normal range - )
38) DATE OF LAST NEUROLOGICAL EXAM: ____/____/____
39) DATE OF LAST EXAM BY A PHYSICIAN: ____/____/____
40) TREATMENT: 1) special shoes 2) braces 3) surgery 4) cane or other walking device 5) manual wheelchair 6) electric wheelchair 7) electric scooter 8) physical therapy 9)orthotics 10)arch supports 11) other _____
41) SPECIFIC MEDICINE FOR CRAMPING OR SPASM: Y/N/.
If yes, what _____and was it effective: Y/N/.
42) DID YOU HAVE SURGERY: Y/N/.
43) TYPE OF SURGERY: 1) triple arthrodesis 2) tendon transfers
3) hammer toe correction 4) hand 5) achilles lengthening 6) other _____
44) FINAL DIAGNOSIS: 1) CMT 2) CMT II 3) Probable CMT
3) Other _____
45) Have you been pregnant? Y/N/
46) If so, during pregnancy, did your CMT symptoms worsen? Y/N/.

# MEDICAL ALERT

Certain Drugs Toxic to the Peripheral Nervous System. This is a list of neurotoxic drugs which could be harmful to the CMT patient. Before taking any medication discuss it fully with your doctor for possible side affects.

Adriamycin
Amiodarone
Chloramphenicol
Cis-platinum
Dapsone
Diphenylhydantoin (Dilantin)-
Disulfiram (Antabuse)
Glutethimide (Doriden)
Gold
Hydralazine (Apresoline)
Isoniazid (INH)
Mega Dose of Vitamin A
Mega Dose of Vitamin D
Nitrofurantoin (Furadantin, Macrodantin)
Nitrous Oxide (chronic repeated inhalation)
Penicillin (Large IV doses only)
Pyridoxine (Vitamin $B^6$)
Vincristine

# NFPMA CONTRIBUTIONS

| In Memory Of | Contributor |
|---|---|
| Clarence Kluenner | Mrs. Ed. L. Kluenner |
| Troy Myrick Dr. | Karen Edelson |
| Glenn D. Veatch | Sharon Batten |
| Samuel Wilkinson | Elizabeth W. Esch |
| Edward M. Willis | M/M Sylvan Shapiro |
| Ronald Trethewey | Nancy Trethewey |
| Jack Goldman | Lois & Morry Friedlander |
| McKenzie King | Connie King |
| Esther Rieken | Jeanell Haynie |
| Jerome Rothman | Dr. & Mrs. Howard Pallay |
| Jack Goldman | M/M Alan Greenwald |
| Mandel Kramer | Shirlie & Harry Green |
| Irving Finkelman | Fred & Diane Frankel |
| Nat Kunken | Sylvan & Lorene Shapiro |
| Martin Moskowitz | Lorene & Sylvan Shapiro |
| Virginia Bradwick Lee | Sophia L. Bradwick |
| Jerome Rothman | Sarah D. Rothman |
| Icel Pierce | Libbie Pitegoff |
| Icel M. Pierce | Darwin Arms |
| Icel M. Pierce | Brenda Hubble |
| Icel M. Pierce | Joy Godwin |
| Icel M. Pierce | Janice Garboden |
| Icel M. Pierce | Mary Lankford |

| In Honor Of | Contributor |
|---|---|
| Hart & Minna Wurzburg | M/M Michael Wurzburg |
| M/M Henry Eldredge | M/M Douglas H. Moody |
| Hart & Minna Wurzburg | Shirley Solomon |
| Hart Wurzburg | M/M Joseph Lellever |
| Daran A. Paone | Mrs. Max A. Meyers |
| Minna Wurzburg | M/M Edwin Rose |
| Eugene Feen | Shirlie & Harry Green |

***GET IN TOUCH !***

*REGISTER FOR THE SEPTEMBER CMT CONFERENCE*
**September 8-10, 1989**
NUMBER ATTENDING_____
○ $10.00/adult ○ $5.00/child
○ $25.00/family max.
Number Attending 6 p.m. Dinner _____@ $10.00
AMOUNT ENCLOSED $_____
❑ I will not be attending the conference, but please add me to your mailing list.

*The NFPMA Report*
University City Science Center
3624 Market Street

## *I want to be in touch!*

Name: _____

Address: _____

_____

Phone Number (_____) _____

Tell us about yourself:
❑ CMT Patient ❑ Interested Supporter
❑ Medical Professional ❑ CMT Family Member
❑ Other

**FILL THIS FORM OUT AND RETURN TODAY**

## VCR Tape Rental

The NFPMA will rent four lectures which were taped at patient conferences sponsored by the Foundation. The tapes are for play on a VHS VCR. Beta tapes are not available. The speakers are authorities in their fields and lecture topics include: Neurology, Physical Therapy, CMT Genetics, and Orthopedic Surgery. Single lecture tapes (1 hr., 15 min.) rent for $10, and the double lecture tapes (2 hrs., 30 min.) rent for $15. The rental fee includes prepaid return postage. To order a tape, fill out our *I want to be in touch!* form and send it to us with a check or money order payable to the NFPMA. Please check the appropriate boxes:

❑ Put me on the mailing list!
❑ CMT Genetics — $10
❑ CMT Neurology — $10
❑ Orthopedic Surgery — $10
❑ Physical Therapy — $10
❑ Physical Therapy/Orthopedic Surgery — $15 on (one tape)
❑ Neurology/Genetics — $15 (on one tape)

## HETEROGENEITY AND COMPLEXITIES OF THE CMT SYNDROME

**Dr. Lowell Williams**

*A conversation between medical and biochemical CMT Researchers who have CMT themselves*

HS: Lowell, what do you think is the best direction for research in CMT?

LLW: Howard, let's begin at the beginning. One of the biggest problems in directing CMT research is making an initial diagnosis of who should be included in a specific study. As you know, the condition can be called peroneal muscular atrophy or Charcot-Marie-Tooth Syndrome or hereditary hypertrophic motor sensory neuropathy. The multiple names give an idea of the problem of deciding what group of symptoms and signs should form the diagnostic criteria for study design.

HS: Haven't the neurologists classified types of CMT?

LLW: Yes, but the types are often not clear-cut. Dr. Peter Dyck of Mayo Institute first addressed this problem effectively in 1968 when he suggested the various presentations of CMT be given different numbers. For example, the patients in group CMT I demonstrate dominant inheritance, enlarged peripheral nerves, and lower than normal nerve conduction velocities. A second form, Type II CMT, called the neuronal variety, also has dominant inheritance, but usually is without nerve enlargements, and nerve conduction velocities are within normal limits. It seemed that the characteristic CMT microscopic finding of segmental demyelination of nerves in the feet and hands was only present in Type I, but now it has been found in both forms. CMT III originally was described a progressive spinal muscular atrophy without sensory loss. Other CMT categories added later include hypertrophic neuropathy of Dejerine-Sotas with recessive inheritance, ataxia, increased spinal fluid protein and decreased nerve conduction velocities. In addition CMT can be combined with other neurologic defects such as retinitis pigmentosa, neurosensory hearing loss, other cranial nerve deficits, epilepsy, and many other symptoms. Some consider these as separate categories of CMT.

HS: It sounds as if CMT is a difficult diagnosis to make.

LLW: Now you are understanding the problem for neurologists, but it is even more complicated. There are related syndromes such as Friedreich Ataxia and hereditary spastic paraplegia with peroneal muscular atrophy which also make diagnosis difficult. Commonly the distinctions between these categories are blurred by overlapping symptoms in the patient, or family members with the same gene but different symptoms. Over the years several competent neurologists, such as Drs. Buchthal, Brady, Thomas, Hardy and others, have suggested different classifications to clarify certain issues.

HS: But, can investigators go ahead with the research study after selecting a certain CMT category with defined diagnostic criteria?

LLW: Yes, but with some reservations. Here are more confounding facts. Dr. Skre, a Norwegian neurologist, was able to analyze patients' records from a large section of Norway since CMT is a reportable and government-subsidized condition there. Using strict neurologic criteria, he found that the incidence of definite diagnosed CMT was approximately 1/3000. But he also observed that about a third of the relatives of the CMT patients had mild neuropathic symptoms which

**ABOUT THE AUTHOR**
The author, Dr. Lowell Williams is a medical doctor and research scientist at Columbus Children's Hospital, Columbus, Ohio. Dr. Howard Shapiro is a biochemist and NFPMA's Director of Scientific Program.

## NFPMA REMEMBRANCES

Your gift to the NFPMA can honor a living person or the memory of a friend or loved one. Acknowledgement cards sent *in honor of* or *in memory of* will be mailed by the NFPMA on your behalf. These do.tions 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 NFPMA by completing the form below and mailing it with your check to *NFPMA, University City Science Center, 3624 Market Street, Philadelphia, PA 19104.*

### HONORARY GIFT

In honor of: (person(s) you wish to honor)

_____

Send acknowledge to:

.me: _____

Address: _____

_____

Phone Number (____) _____

Occasion:

❑ Birthday ❑ Holiday _____

❑ Wedding ❑ Thank You

❑ Anniversary ❑ Other _____

### MEMORIAL GIFT

In memory of: (.me of deceased)

_____

Send acknowledge to:

.me: _____

Address: _____

_____

**Amount Enclosed: $** _____

❑ Check if you would like the amount of your gift revealed.

**GIFT GIVEN BY**

.me: _____

Address: _____

_____

did not meet strict criteria to make a diagnosis of CMT, but were definitely not normal. In fact, this finding was so consistent that he suggested a separate category for them, called Un (unspecific neuropathy). Later, when Dr. Dyck was attempting to diagnose patients whose neuromuscular disease had been difficult to categorize, he discovered that his patients often had a relative with obvious CMT. Therefore, Dyck's patients could fall in Skre's category of Un relatives with the poorly defined deficits.

HS: Why is this important?

LLW: Any real attempt to understand the basis for disease symptoms must account for the symptoms whenever or wherever they occur. These rules are called Koch's Postulates, and were used to prove that certain bacteria caused certain disease symptoms. Briefly, the postulates require that an organism had to occur when the symptoms were present and had to be recoverable; that the organism must not be found when the symptoms were absent; and that the symptoms must occur when the organism is introduced.

HS: But CMT is a "genetic" or inherited disease.

LLW: True. When these requirements are applied to an inheritable disease, they would refer to a "gene" rather than an organism. The presence of the gene in the DNA of the person indicates that he/she has the disease. The gene's absence means that it will not ever develop. However, since it is obvious that some CMT patients are more affected, having more muscle and nerve loss than others, a concept called "penetrance" was developed to explain these differences. Unfortunately, we don't understand the circumstances or biochemistry of penetrance at all. Variability in genetic diseases may have another explanation. Possibly it may relate to the recently recognized complex control of interactions between genetic elements leading to expression of a gene.

HS: But what about these mildly affected relatives? Might they develop symptoms later? Are they carriers of the "CMT gene?"

LLW: Those are good questions, but we don't know the answers. I would give them a qualified maybe until we have more information. But so far, a single CMT gene associated with all CMT families has not yet been located on a particular chromosome. However, several good studies show that a location on Chromosome 1 near the Duffy blood type and apolipoprotein B loci is a definite possibility for a proportion of Type I CMT. Also, the X chromosome is a likely place for the sex-linked variety of CMT using the same reasoning as in Duchenne muscular dystrophy. This is an area of active research in several centers.

HS: What else is being done in CMT research?

LLW: Electrodiagnostic tools are being used to define and understand the character of the peripheral nerve responses in CMT. Dr. Lovelace's work at Columbia University and Dr. Gillette's study at NIH with the F-wave are important. In Columbus, we are examining the possible relationship of autonomic nervous system defects in contributing to CMT symptoms of cold weather intolerance, skin changes, and sensory loss in feet and hands. We have found significantly lower oxygen in CMT hands after cold. Our pilot data agrees with Charcot's original suggestion that these abnormalities may be important to skin discoloration and discomforts of CMT patients. Recently, Dr. Dyck has emphasized possible oxygen starvation in the glove and stocking distribution of peripheral neuropathy in diabetes. There might be a similar "anoxic" process in the similar distribution of CMT sensory loss. We are fortunate that many centers all over the world have contributed electrodiagnostic information about CMT.

HS: Are there studies to characterize the CMT gene directly so that someone can begin to treat CMT?

LLW: Unfortunately, we are still a long way from finding out what the "faulty protein product" of the CMT gene might be, but there are studies to address this directly. Since the myelin or nerve sheath covering is defective and poorly formed around CMT nerves, our group of the Wexner Institute for Pediatric Research is measuring fat metabolism in CMT patients. Previously, we tried to replace a serum fatty acid, called linoleic acid, by diet in CMT patients but serum levels remained lower than normal. We are now testing the ability of CMT skin fibroblasts to metabolise fats. Possibly some of the fatty acids have been used to make immune substances, since we have also found altered immunoregulation in CMT patients. There may be a faulty enzyme in CMT fat metabolism. Your organic acid study looks at possible metabolic defects, too.

HS: Yes, we measured approximately 150 metabolites found in urine to get a broad overview of physiological status in a group of patients.

LLW: That is a valuable contribution to an understanding of the basic biochemical problems in CMT families. I hope you will have opportunities to continue your work. The multiple forms of CMT suggest that there may be several biochemical defects.

HS: So, I'll ask again. What do you think is the best direction for CMT research?

LLW: The heterogeneity of CMT bothers me. There is such variability in end-result in families and between patients. Could there be an underlying process not yet considered? Some have even suggested a latent or persistent virus. Until we know exactly what is wrong in CMT nerves and their Schwann cell sheaths, we had better pursue all of these directions. The metabolic studies are certainly an important arm of this process. Even if one CMT gene location is found, we must still identify the faulty protein coded by that gene. From the difficulties making a diagnosis or even a classification of CMT, it is my guess that there must be several, possibly many interacting genes to produce these variations in CMT syndrome. I hope that new techniques in molecular biology, being carried out by Drs. Bird, Chance, Ionasescu, LeBow, Lupski and others all over the world, will enable us to resolve the problem of heterogeneity in CMT at the genetic level. Then we may be able to define the biochemical nature of the defects.

Howard, you and I, and others with CMT are fortunate to have so many who care about finding these answers.

HS: I agree.

❁

# ASK THE DOCTOR

*Dear NFPMA:*

*I was diagnosed with CMT about five years ago, after the birth of my first child. I am now 28 years old. I have been to an orthopedist, two neurologists, a clinic at UCLA, and a clinic at USC. After a great deal of expense, I am sadly resolved to the fact that there is nothing to be done. I was, and still do, but with great limitations, exercise including swimming, bike riding and water skiing. Even with all this the doctors still recommend not exercising saying, "You may hurt yourself."*

*In reading the Spring/Summer newsletter, it was great to hear others who have the same feelings and problems. I struggle with myself everyday because I find it so hard to accept my limitations. My husband sympathizes with me, but I don't think he can fully understand.*

*Now for the reason I am writing to you. We want to have more children and having two already we honestly believe that Pregnancy has had a great deal to do with the initial development of my CMT. I went from a dormant stage to further complications. I saw it mentioned in the newsletter that there may be some link between Pregnancy and the progression of symptoms. Doctors I have spoken with just about refuse to even enter this possibility into thought. I don't want to end up a cripple so I do feel I have to try and find any information that is available about CMT and Pregnancy to use as a basis for this decision to have more children.*

*For a brief background, I was diagnosed in 1982 with CMT after the birth of my first child. I experienced loss of muscle strength and muscle size in my calves and difficulty in things like climbing stairs. With continued exercise I regained some of the strength I lost, but again with the second child I experienced the same thing. It is like taking one step forward and two steps back, never regaining total strength or muscle mass. After EMG's, muscle studies, blood tests, and nerve conduction studies I would describe myself as operating at 50% of my capacity. My greatest problems now are ankle weakness, foot drop, and emotional conflicts.*

D.P., CA

Dear D.P.:

The NFPMA has had a number of inquiries concerning the increase of CMT symptoms, particularly weakness, as the result of Pregnancy. Normally, with correct rehabilitation and physiatry care, appropriate obstetric management, and orthopedic and neurologic advice most CMT patients do not suffer abnormal deterioration. However, we also have experience with a few patients (three over ten years) who have deteriorated.

Principally, the problems have become most evident in the last three months of Pregnancy; in one case necessitating use of a wheelchair for a previously independently ambulatory patient. In the affected cases, in spite of minor improvement after delivery, no patient has ever regained strength to an equivalent pre-Pregnancy level.

There is very little literature on this and, together with my colleagues at the Columbia University Neurological Institute and Ann Lee Beyer, a doctoral candidate and NFPMA support group leader, we are studying this problem. We welcome letters from patients and their physicians, especially with reference to endocrine and immunological factors, and with objective demonstrations of such phenome. A thoughtful article was written on this problem in the journal Neurology by Prof. Martin Pollock and his colleagues (1) from the University of Otago at Dunneden, New Zealand. [ (1) Pollock, M., Nukada, H., & Kritchevsky, N. Exacerbation of Charcot-Marie-Tooth disease in Pregnancy, Neurology (Nv), 1982;32;1311-4]

Robert E. Lovelace, M.D. Medical Director, NFPMA Professor of Neurology and Director of Division of Neuromuscular Diseases, Columbia University

**EDITOR'S NOTE**

Send letters about *CMT and pregnancy* and other CMT problems directly to the NFPMA. We will refer them to the appropriate physician. ❋

*The NFPMA Report* is published by the National Foundation for Peroneal Muscular Atrophy, a tax exempt not-for-profit corporation incorporated in the Commonwealth of Pennsylvania (established 1983).

*The NFPMA Report* is produced by The Journey Enhancement Group, Inc., a diverse Apple Macintosh® computer sales and publishing company, 250 Tanglewood Lane, King of Prussia, PA 19406. 1 (800) 992-9494.

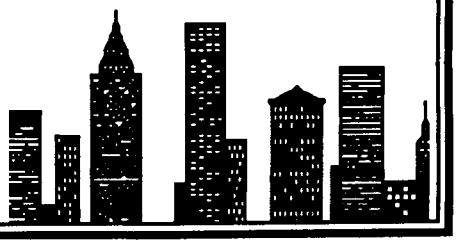
Letters and inquiries may be addressed to:

Editorial Staff, NFPMA Report
National Foundation Foundation for Peroneal Muscular Atrophy, University City Science Center
3624 Market Street
Philadelphia, PA 19104

**Call (215) 664-6010 for more information.**

## MIDWEST NFPMA ACTIVITIES

We wish to thank Robert Wright, M.D., and Valerie Maragos, M.D., for their respective neurology and rehabilitation presentations, at out April CMT Patient/Family Conference which was held at the Rush Presbyterian-St. Luke's Medical Center in Chicago. Howard Shapiro, Ph.D., of the NFPMA, also spoke at this meeting presenting an overview of the current research strategies for investigating CMT. On the same trip, Dr. Shapiro, also presented a lecture at the American Medical Association's symposium entitled, "Self-Help Groups and Health Care Providers in Partnership." Our thanks to Drs. Maragos and Wright, for donating their time and expertise, and to Sunny Sonnenschein and Stuart Feen for assisting with the local CMT meeting plans.



# Support Group Notes

A primary goal of the NFPMA is to become a truly successful advocate for those with CMT. Its message must reach the patients, their families, and the medical and research communities. Patient family support groups, a growing and vital part of the NFPMA program, inform and support anyone who must deal with this often overlooked disease.

There are already several NFPMA support groups. These chapters are spirited and growing stronger, but more groups are needed in other parts of the United States.The NFPMA will gladly help you to set up a chapter in your area. For information contact the NFPMA by mail or call (215) 664-6010.

Perhaps there is a chapter meeting near you. You are cordially invited to join these groups in their upcoming events.

**San Diego, California**
Contact: Gary Oleze (619) 792-1427

**San Francisco, California**
Contact: David Berger (415) 491-4801
After 6:00 p.m.

**Greater Dallas, Texas Area**
Contact: Dr. Karen Edelson, D.P.M. (214) 542-0048

**Parsons, Kansas**
Meeting: Spring, 1989
Where: Labette Community College, Parsons, KS
Contact: Tammy Taylor (316) 421-5286

**Indianapolis, Indiana**
Contact: Elaine Donhoffner (317)841-0241
Robert Birdwell (317)352-0235

**Detroit, Michigan**
Contact: Marrianne Tarpinian (313)883-1123

**Chicago, Illinois**
Contact: Carol Wilcox (312)445-2263

**Cleveland, Ohio**
Contact: Norma Markowitz (216) 247-8785

**Boston, Massachusetts**
Contact: Eunice Cohen (617)894-9510

**Rochester, New York**
Contact: Neale Bachmann (716)554-6644
Bernice Roll,(716)584-3585

**New York, New York**
Meeting: June 3, 1989
Where: Rusk Institute of Rehabilitation Medicine
Room RR 610 (6th Fl. Research Wing)
400 East 34th Street (at First Avenue)
New York, NY 10016
Time: 1:00-4:00 p.m.
Contact: Linda Phillips Goldfarb (212) 481-3419

**Northern New Jersey**
Where: Englewood Hospital, Clinic Conference Room, 350 Engle Street, Englewood, NJ 07631
Contact: Ann Lee Beyer (201) 391-4624

**Central New Jersey**
Meetings: June 17, 1989
Where: Princeton Medical Center, Lambert House, Classrooms #1&2
Time: 10:00 a.m.
Contact: Janet Selah (201) 281-6289

**Delaware Valley, Pennsylvania**
Meeting: Holy Redeemer Hospital in Meadowbrook, PA
Contact: Rex Morgan, Jr. (215) 672-4169

**Tidewater, Virginia Area**
Contact: Mary Jane King (804) 591-0516
Ellen Morton (804) 851-7046
Where: Riverside Hospital, School of Professional Nursing, J. Clyde Morris Blvd. Newport News, VA

**Greater Atlanta, Georgia**
Contact: Molly Howard (404) 253-5632
Sue Saye (404) 565-5950

**Orlando, Central Florida Area**
Contact: Mary Beeler (407) 295-6215
Meeting: Third Saturday of Every Month

**Fort Pierce Area, Florida (Atlantic Coast)**
Contact: Dorothy Stefanovich (407) 461-1016

*Call your nearest group today for more information!*

**OF INTEREST TO OUR READERS!**

*THE NFPMA REPORT* welcomes your ideas and article suggestions. For example, you may submit a human interest story telling of your experience of living with CMT. Or, medical professionals can forward articles of a clinical or medical nature that would be of general interest to our readership.

The following back issues of *THE NFPMA REPORT* are available at $2.50 a copy:

Winter '88
Spring/Summer 1988
Winter '88
Spring '87
Summer/Fall'87
Winter '87

Write or call the NFPMA (215)664-6010

## Peroneal Muscular Atrophy (CMT)...

.....is the most common inherited neurological disease, affecting approximately 125,000 Americans.

.....is also known by its historical name, Charcot-Marie-Tooth disease, for the three doctors who first reported on it in 1886.

.....is slowly progressive, causing deterioration of peripheral nerves which control sensory information and muscle function of lower legs and forearm voluntary muscles.

.....causes degeneration of peroneal muscles (located on the front of the leg below the knee) and subsequent atrophy of additional lower leg and forearm muscle groups.

.....causes foot-drop walking gait, foot bone abnormalities, high arches and hammer toes, problems with hand function, occasional lower leg and forearm muscle cramping, loss of some normal reflexes, occasional partial sight and/or hearing loss problems and scoliosis (curvature of the spine) may be present.

.....does not affect normal life expectancy.

.....has no effective treatment, although physical therapy and moderate physical activity are beneficial.

.....is usually inherited in an autosomal dominant pattern, affecting half the children in a family with one PMA parent.


# *THE NFPMA REPORT*

*information on Charcot-Marie-Tooth disease from the*
**National Foundation for Peroneal Muscular Atrophy**
University City Science Center
3624 Market Street
Philadelphia, PA 19104

**BULK RATE**
**U.S. Postage Paid**
**Ronkonkoma, NY**
**Permit # 1390**


**TO:**