Synapse

Serving the Primary Lateral Sclerosis Community since 1997 Autumn, 2001

PLS Gene Discovered

The discovery of the first gene linked to PLS was announced on October 3rd.

Two independent teams of scientists reported in the journal Nature Genetics that they discovered a gene that can cause either a rare form of juvenile onset PLS or a rare form of juvenile onset ALS. The leader of one of the teams was Teepu Siddique, M.D. of Northwestern University Medical School's Department of Cell and Molecular Biology.

The gene is an autosomal recessive gene, and has been named "ALS2". Whether a mutation in the ALS2 gene causes ALS or PLS depends on the mutation. A mutation found in one specific place on the ALS2 gene causes juvenile onset ALS. Either one of two mutations in other locations on the ALS2 gene cause juvenile onset PLS.

"We are currently looking at other families with juvenile onset PLS who don't have a mutation in the ALS2 gene, to discover more PLS genes", said Dr. Siddique. "And we plan on also looking at cases of adult onset PLS."

The ALS2 gene encodes a protein called "alsin". Dr. Siddique theorizes that the mutated form of ALS2 that causes juvenile onset PLS may create a form of the alsin protein that still retains partial function, and causes PLS. More significant loss of function of the alsin protein caused by another mutation to the ALS2 gene results in ALS.

Dr. Siddique added that the alsin protein may have the same functional pathway as the recently discovered "atlastin" protein that causes juvenile onset HSP (hereditary spastic paraplegia). (See next article.)

(*Continued on page 2, column 1.)*

New HSP Gene Discovered

By John Fink, M.D.

This has been a very important year in HSP (hereditary spastic paraplegia) research.

We have identified a new gene that causes dominantly inherited HSP. Thus far, we have found mutations in this gene in six families. Three of these families have the same exact mutation but do not appear to be related.

So far, the common feature of families that have HSP due to mutations in this new gene is the age at which symptoms first appear. Each affected subject developed symptoms before age 10 (usually in early childhood). For most individuals, the disorder either did not worsen appreciably, or worsened only very slowly. It is not clear to me whether "mild apparent worsening of symptoms over ten years" is due to subtle progression of the underlying spinal cord disorder; or is due to lack of muscle stretching and strenghtening and physical therapy.

We have insights (*Continued on page 3, column 1.)*

What is HSP and why am I writing about it?

By Mark Weber

In this issue you'll notice that I combined news about PLS and HSP (hereditary spastic paraplegia). You may wonder why.

PLS and HSP share a number of similarities.

Some PLSers have symptoms only from the waist down. (Ok--they may have minor arm/hand involvement, *(Continued on page 3, column 2)*

(Continued from page 1, "PLS gene discovered)

Sources:

1. Yang et al., "The gene encoding alsin, a protein with three guanine-nucleotide exchange factor domains, is mutated in a form of recessive amyotrophic lateral sclerosis", Nature Genetics, Vol. 29, October, 2001, pp. 160-165.
2. Hadano et al., "A gene encoding a putative GTPase regulator is mutated in familial amyotrophic lateral sclerosis 2", Nature Genetics, Vol. 29, October, 2001, pp. 166-173.
3. Shaw, "Genetic inroads in familial ALS", Nature Genetics, Vol. 29, October, 2001, pp. 103-104. ♦

Comment on ALS2 Gene Discovery

By Jennifer Thomson, mdmfoo@yahoo.com

This is REALLY BIG NEWS! Looking for the PLS gene was like looking for a needle in a haystack, now it is like looking for a needle in a pin cushion (well, maybe a very full pin cushion). It also makes the genetic link between ALS and PLS. This is so important and significant to future PLS research. Now they know more about where to look and what to look for. They are very interested in collecting PLS blood and trying to find more PLS genes.

I hope every single person on this list will contact Nailah Siddique about participating in the blood collection study. They need our blood to continue looking for other PLS markers. We need to give them so much blood they will be amazed at the people with PLS and want to work all that much harder for us. Please, give them a call. Do it today!

♦

From: Nailah Siddique
Subject: PLS Study info

We are continuing a study involving sporadic motor neuron diseases (ALS, PLS) that we thought your support group might be interested in knowing about. The cause of sporadic diseases of the motor neuron are unknown.

We are interested in determining whether genetic factors may "predispose" an individual to developing these. In the past, research has looked at cause and effect in sporadic motor neuron disorders one variable at a time. We suspect that these disorders may be the result of not one, but several genetic factors coming together. Recent advances in the field of statistical genetics make it possible to answer such questions if there are sufficient study participants available.

Blood samples from patients with ALS or PLS and their parents are needed for this study. If the parents are not available then samples from the patient's brothers and sisters may be used. We need 400 samples from patients with each disorder and appropriate family members in which each person donates 2 tablespoons of blood. We will supply the needed tubes and instructions for returning the samples via Federal Express without charge to the participants. Most physicians and labs will draw the samples without charge, but we will pay for drawing the samples if applicable.

There is no immediate benefit to the patients, but an understanding of the causes of motor neuron disorders may eventually help patients.

Anyone willing to participate in such a study or wishing to discuss may contact us at the numbers below.

We appreciate your work in disseminating information to the ALS/PLS community and look forward to working together on this endeavor.

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Neuromuscular Disorders Program
Northwestern University
(312) 503-2712
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Teepu Siddique MD
Director, Neuromuscular Disorders Program
Professor of Neurology
Professor of Cell and Molecular Biology
Northwestern University
Chicago, IL 60611

♦

(From page 1--HSP Gene Discovered)

into the function of this gene and are designing experiments to study these functions. We will study how gene mutations disrupt this function. This will help us understand the biochemical abnormalities that cause HSP.

Our findings were presented at the American Society of Human Genetics meeting in San Diego, and were published in the November issue of Nature Genetics.

This is a major step forward in our understanding of the causes of HSP. The information we have learned already permits us to perform diagnostic testing. Our preliminary studies indicate that approximately 25% of families with dominantly inherited HSP that begins in childhood are due to mutations in this gene. The important thing to note is that the likelihood of having mutations in this gene is greatest when everyone affected with HSP has symptom onset in childhood. Families in which some individuals have childhood onset and other individuals have onset in adulthood are less likely to be due to mutations in this gene.

Nonetheless, by testing for mutations in this gene and for mutations in the previously identified dominantly inherited HSP gene (spastin), we can diagnose at least 55% of subjects with dominantly inherited HSP. This information can be applied to prenatal testing.

I understand that spastin gene analysis has become available at Athena Diagnostics. Mutations in this gene cause 40 to 45% of dominantly inherited HSP. This is a major step forward in providing diagnosis for HSP.

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University of Michigan
Ann Arbor, MI 48109-0940
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FAX (734) 615-6340

The article is:
Zhao et al., "Mutations in a newly identified GTPase gene cause autosomal hereditary spastic paraplegia", <u>Nature Genetics</u>, Vol. 29, November, 2001, pp. 326-331. ♦

(From page 1--What is HSP…?)

but nothing significant.) If they had a family history of similar symptoms they would be diagnosed with HSP. But without a family history, some neurologists would diagnose them with PLS. Others would still call it HSP or "apparently sporadic HSP".

Some PLSers experience those symptoms and also have speech problems, or symptoms in all four limbs, or both. If they have no family history of similar symptoms, they have PLS. But if they have a family history, they have HSP.

So far, no one knows whether any version of HSP shares the same cause as a corresponding form of PLS. But if you attend a meeting with HSPers, they appear indistinguishable from PLSers. We share the same gait problems. Some HSPers also have the same speech problems as some PLSers. The difference appears when you ask an HSPer about his/her family. That's when you'll hear about the symptoms experienced by their children, parents and grandparents.

Serious scientific progress has been made on HSP. At least five separate genes have been discovered that are responsible for various forms of HSP. (See the previous article about the "atlastin" gene discovered recently by John Fink, M.D., of the University of Michigan.) And at least ten HSP gene loci have also been discovered.

Further, the ALS2 gene discovered by Dr. Teepu Siddique (Northwestern University) that causes juvenile-onset PLS is theorized to encode for the same class of protein as the protein encoded by the "atlastin" HSP gene discovered by Dr. Fink.

Why does this matter?

A group of PLSers and HSPers are currently creating a foundation to fund medical research and education on PLS and HSP. Dr. Fink is very active in helping to create the foundation, and is committed to including PLSers along with HSPers in the group.

Also, some meetings known only to PLSers or HSPers will now be known and open to both groups. *(Continued on page 4, column 1.)*

(From p. 3, column 2--What is HSP…?)

You'll see some of those meetings mentioned here.

I have great hopes for this new collaboration between HSPers and PLSers. Anyone interested in volunteering to work for the new foundation is urged to contact Mark Weber at (978) 258-0712, markw732@yahoo.com or Kathi Geisler at (978) 256-2673 kathipro@aol.com.

Together, we will find the cure. ♦

New England PLS/HSP Meeting

There will be a New England PLS/HSP luncheon, meeting, and social outing on Saturday, December 1st, beginning at 11:00 am. The event begins at Skip's restaurant in Chelmsford, MA. (978-256-2631) The cost is $16.50 and must be paid in advance. You can choose a chicken or fish luncheon. Skips is accessible.

Skips is located at 116 Chelmsford St. (Rte. 110). Take Rt. 495 to exit 34. From 495N, go left off the exit; from 495S, then go right off the exit.

After social time, sharing, and dining, we will have a meeting to hear about PLS/HSP news and discuss what we would like to do as a local group.

At approximately 1:30, there will be a social outing for those interested to visit Lowell's American Textile Museum, a short drive from Skip's.

This relatively new museum details the history of the textile industry in America, long the major economic force in New England. See examples of machinery and products from different periods in history, as well as an operating weaving room and wool mill. There is currently a special exhibit on 200 years of stylish hats. The admission price is $6. The museum closes at 5:00 p.m. and is accessible. There is a gift shop.

Skip's is holding a dining room for us, and I need to give a count and pay in advance. Please RSVP to Kathi Geisler at: KathiPro@aol.com. ♦

Connecticut PLS/Spastic Paraparesis Support Group Formed

By Dolores Carron

I am please to inform you that as of Monday, September 10, 2001, I officially registered our support group as the very first PLS support group in the world. The name of our group is the Connecticut Connection. It is open to persons who have, or are interested in, PLS or spastic paraplegia (hereditary or sporadic). Our meetings will be held in various locations in CT. Membership is by no means limited to CT residents.

The mission of our group is to provide mutual support, information, and socialization through experiential sharing by peers who face similar challenges and through appropriate speakers. Needless to say, meetings will be held in handicapped accessible locations. For those who are unable to attend meetings, it is my hope that we will provide home/hospital visitation, as well as e-mail and telephone contact. I want to clearly convey the message that "you are not alone". Ultimately, I hope to distribute a newsletter. There are no dues.

Anyone interested should call me, Dolores Carron, 139 Forest Drive, Newington, CT 06111, phone 860-666-9862, e-mail d.carron@worldnet.att.net. ♦

Starting your Own Support Group

By Dolores Carron

Several of you have expressed interest in organizing support groups in your state. I have sent to those who have requested it, copies of the letters I used to publicize my intentions. I will do likewise, for anyone who e-mails their request to me, along with their postal address. My e-mail is d.carron@worldnet.att.net .

I first obtained mailing lists from telephone books and Internet yellow pages for all the Connecticut neurologists and CT newspapers, daily and weekly. Unfortunately, about 5% of those addresses were no longer current, so I had those returned to me. I was able to get corrected addresses for some, not for others. It was, *(Continued on page 5, column 1.)*

(From previous page--Forming own support group)

admittedly, no small task--very costly and labor intensive--but if I could do it, so can you. In a small state as CT, I sent about 300 neurologist mailings and about 75 newspaper mailings. Those mailings included a postable notice, a cover letter, and copies of my previous newspaper coverage as a validation of previous support.

I have developed a membership application and will be sending that, along with a flyer about out first meeting and reservation form. I have been fortunate to find local sponsors who will help with financial support of our activities. ♦

Fourth Annual HSP Conference

The date for the Fourth Annual Philadelphia HSP Conference is set for Sunday November 11, 2001 and will be held, as usual, at The Adam's Mark Hotel. John Fink, M.D. will be speaking. The meeting will begin with a luncheon at noon and will end at 5:00 pm. PLSers are encouraged to attend.

Please let me know if you plan to attend and if anyone else will be attending with you. Please send first and last names, as well as the city and state of your residence, so it can be added to name badges.

The cost will be $35 per person. Please contact me directly. I look forward to hearing from you and seeing you again as well as meeting some new people!!!!

Lisa R. Chadwick
LRRC@juno.com or lchadwic@umich.edu
215-612-5814 (home) ♦

Georgia HSP/PLS Meeting

Kathi Geisler is planning an HSP/PLS gathering and luncheon at 11:00 am on Sunday, December 9, 2001, in Atlanta, Georgia, to be held at a restaurant at or near the airport, at 11:00 a.m.

We are hoping that Dr. John Fink will have time available to attend.

Contact Kathi Geisler at KathiPro@aol.com (978) 256-2673, for details as they become available. ♦

Update -- NORD's PLS Research Grant

Two scientists have applied for NORD's $100,000 PLS Research Grant. NORD's scientific advisory board will review their proposals and make their recommendations to NORD late this winter.

NORD could fund both, neither, or just one of the proposals. They are expected to make their decision by March, 2002. ♦

Update -- NORD's PLS Education Fund

By Linda Gentner, Lkgentner@aol.com

We reached, and exceeded, our PLS Research Fund Goal. Now we need to concentrate on our PLS Education Fund.

Given that most of us had a difficult time receiving a PLS diagnosis, I think we all agree that we can take an active part in educating our doctors about PLS. We decided (at NORD's suggestion) to have a brochure written and mailed to the medical community about PLS. NORD recently wrote a brochure on a rare neurological children's disorder, and from writing to mailing, the cost was a staggering $35,000. Their mailing went to 84,000 neurologists, and that was the reason for the high cost.

Now we can say that our cup is two-thirds full. If you don't need those gifts at Christmas, in lieu of a gift, consider asking your friends and relatives to make a donation in yourir honor to the PLS Education Fund.

Send donations to:
NORD, Attn: Jean Campbell
P.O. Box 8923
New Fairfield, CT 06812-8923

Please indicate that the money is for the PLS Education Fund, and who it is being given in honor of (if that is the case).

If we all work together, we'll be at our second goal in no time. ♦

Autumn in Carolina is Big Success

By Jane McCord, EJMcCord@aol.com

Hi Everyone,

I just thought I would let you all know that I just arrived back home from the fantastic weekend at Don and Bettie Jo Wilson's great Autumn in NC. Don and Bettie Jo did a great job of arranging everything, Don cooked all the food for the fantastic lunch they had for us, Bettie Jo contributed a lot to the booklet Angela Dixon made for all of us (which was a marvelous task she lovingly did), the two speakers were great (they were Bettie Jo's gal that gives her massages and a gal that is a speech therapist), and I could go on and on. Most of us stayed at the Holiday Inn Select, where the rooms were great (except for Ronnie's room which was outlandish - LOL) and nicely situated for all the functions. Friday night we ate at a barbecue restaurant and Saturday night we had great meals at a seafood restaurant.

I'm sure others will be writing to tell you how much they enjoyed the weekend, too. We all feel that we can't say enough for the magnificent effort that Don Wilson put into preparing all the food, making copies of directions and maps, greeting everyone as they arrived, etc. It was outstanding!

My niece, who went with me, thought the whole group was very up beat. She loved meeting and joking with everyone, and was thrilled that I had asked her to accompany me. She certainly hopes to see them all again sometime in the future.

It was hard saying good byes, as usual, but I hope everyone there had a nice trip home (and for some a nice sightseeing vacation following our meeting).

I love each and every one of you, and look forward to seeing you all again. ♦

Spring Fling In Berkley Springs, West Virginia

By Ronnie Grove, frogrove@intrepid.net

Well folks, the Spring Fling has been flung and a mighty good flang it was. We had nine PLSers, seven caretakers, my parents and two of my very good friends.

We talked, we laughed, we shared, we ate, we asked, we told, we got tired and rested and then ate some more. I thank each and every one of you for making the trip and for being there and making the meeting a success. Frank Levy, thanks for supplying the addresses. Joe Alberstadt, thanks for getting these meetings started. Carol Alberstadt, Carol Ames, Keith Strasser, Jim Dixon, Don Wilson, Olson Crouse and Elaina Glassman, thanks for being such wonderful caretakers. And last, but not least, Joe, Ed, Marie, Angela, Bettie Jo, Vivian, Jeffrey, and Joan, thanks for sharing this crappy disease with me. But thanks mostly for being there to make it seem not so bad for a day or two.

For all the rest of you PLS-Friends: if you have never met another PLS person you owe it to yourself to do so as soon as possible. Call a meeting if it is only two people. And if anyone wants to try a larger meeting and feels they need help, just give me a holler. It does not need to be fancy or require a lot of work. I enjoyed every minute I spent preparing for this meeting. There is nothing quite like sharing with someone who has "been there, done that". Hope you all have a chance to do that soon. And for those who missed this one, don't worry, there will be another one--early next April. ♦

Ohio PLS Connection a Success

By Bonnie & Don Lucas, blucas@winesburg.com

What a wonderful time we had together this weekend (July 14 - 15, 2001). Jane McCord came in from Florida. Julia Walker and her daughter from Cincinnati, David and Lois from the Amish country also arrived. We spent the day together on Friday. Julia made it quite late and we all met her for supper. We all gabbed until they just about threw us out of the restaurant. Then we went next door to the hotel and continued our visit.

We exchanged funny stories about PLS situations we have found our PLSers in. We should all collect these stories and share them with everyone. We took over another restaurant for a portion of Saturday afternoon. *(Continued on next page.)*

(From previous page--Ohio Connection)
I am very impressed with the wonderful people that I met. We made some fast and lasting friendships. So go ahead and meet with other PLSers--even if it is only two or three of you. ♦

(Editors note: Don's Lucas's diagnosis was recently changed to ALS. My heart was heavy when I got the news. I know that Don and Bonnie are in everyone's prayers, as they are in mine.)

Wonderful PLS Meeting in Washington State

By Carolyn Myrick, cmyrick@hotmail.com

I had an opportunity to meet Claudia last weekend. My husband and I drove down to Oregon. It was only a 2 hour drive. Claudia has a wonderful family. She invited us to her home, which is beautiful. We also had chocolate cake--Yum Yum. I agree with all of the others who have said you that everyone should have an opportunity to meet someone else with PLS. ♦

Home Modifications

By Don Wilson, dcwilso@attglobal.net

Here are a few web sites that may be helpful in considering home modifications.

UNIVERSAL DESIGN AT BUFFALO
IDEA web site: http://www.ap.buffalo.edu/~idea
RERC web site: http://www.ap.buffalo.edu/~rercud

RESOURCES FOR HOME MODIFICATIONS
http://www.aarp.org/universalhome
Good site for browsing

UDA
http://www.uniteddesign.com
Choose "Free Home Planning Guide", fill out form and download this twenty-two page guide to remodeling/planning

ABOUT.COM
http://disabilities.miningco.com
From the NetLinks area choose "Accessible Homes". Choose Universal Design & Home Accessibility. Scroll down to the end of the page to "Remodeling Examples" and choose either "Bertha's Home" or Leona"s Home". Good Examples of modification projects with graphics and costs. (Iowa State University)

TOWARD A BARRIER-FREE HOME
http://www.independentliving.org Type "housing adaptation" into search box.

THE PRINCIPLES OF UNIVERSAL DESIGN
http://www.design.ncsu.edu/cud/pubs/udprinciples.html

FUNDING

FANNIE MAE
http://www.fanniemae.com/index.html

HUD PROGRAMS
http://www.hud.gov/search.html
Under the "Own a Home" heading, choose "Home Improvements" and then choose About HUD's rehabilitation and repair home loan

Under the "Own a Home" heading, choose "Home Improvements" then choose "Rural Home Improvement and Repair Loans/Grants". At the disclaimer choose: http://www.rurdev.usda.gov/agency/rhs/rhsprog.html

Under the "Citizens" heading, choose "People with Disabilities" then under "HUD Initiatives" choose "Housing". Once in this area, choose the area of interest. "Modification funds" will direct you to HUD programs for home modification money.
The HUD site is very large and contains a wealth of information. Browse for information to support your housing needs.

Under the "Business" heading, choose "funding". Scroll through this site for funding options. Check out the "Private Funding Sources".

(Continued from previous page--Home Modifications)

ASSISTIVE TECHNOLOGY FUNDING RESOURCES
http://www.infinitec.org/kitchenfundres.html
Good listing of funding sources with telephone numbers

I hope that you are able to find the assistance that you need. ♦

Itzhak Perlman Makes Music

Itzhak Perlman, the violinist, came on stage to give a concert at Avery Fisher Hall at Lincoln Center in New York City.

If you have ever been to a Perlman concert, you know that getting on stage is no small achievement for him. He was stricken with polio as a child, and so he has braces on both legs and walks with the aid of two crutches. To see him walk across the stage one step at a time, painfully and slowly, is a sight. He walks painfully, yet majestically, until he reaches his chair. Then he sits down, slowly, puts his crutches on the floor, undoes the clasps on his legs, tucks one foot back and extends the other foot forward. Then he bends down and picks up the violin, puts it under his chin, nods to the conductor and proceeds to play.

By now, the audience is used to this ritual. They sit quietly while he makes his way across the stage to his chair. They remain reverently silent while he undoes the clasps on his legs. They wait until he is ready to play. But this time, something went wrong.

Just as he finished the first few bars, one of the strings on his violin broke. You could hear it snap--it went off like gunfire across the room. There was no mistaking what that sound meant. There was no mistaking what he had to do.

People who were there that night thought to themselves: "We figured that he would have to get up, put on the clasps again, pick up the crutches and limp his way off stage - to either find another violin or else find another string for this one." But he didn't. Instead, he waited a moment, closed his eyes and then signaled the conductor to begin again. The orchestra began, and he played from where he had left off. And he played with such passion and such power and such purity as they had never heard before.

Of course, everyone knows that it is impossible to play a symphonic work with just three strings. I know that, and you know that, but that night Itzhak Perlman refused to know that.

You could see him modulating, changing, recomposing the piece in his head. At one point, it sounded like he was de-tuning the strings to get new sounds from them that they had never made before. When he finished, there was an awesome silence in the room.

And then people rose and cheered. There was an extraordinary outburst of applause from every corner of the auditorium. We were all on our feet, screaming and cheering, doing everything we could to show how much we appreciated what he had done.

He smiled, wiped the sweat from his brow, raised his bow to quiet us, and then he said, not boastfully, but in a quiet, pensive, reverent tone, "You know, sometimes it is the artist's task to find out how much music you can still make with what you have left."

What a powerful line that is. It has stayed in my mind ever since I heard it. And who knows? Perhaps that is the way of life - not just for artists but for all of us.

Here is a man who has prepared all his life to make music on a violin of four strings, who, all of a sudden, in the middle of a concert, finds himself with only three strings. So he makes music with three strings, and the music he made that night with just three strings was more beautiful, more sacred, more memorable, than any that he had ever made before, when he had four strings.

So, perhaps *(Continued on next page.)*

(Continued from previous page--Perlman makes music)

our task in this shaky, fast-changing, bewildering world in which we live is to make music, at first with all that we have, and then, when that is no longer possible, to make music with what we have left. ♦

PLS/HSP Resources

1. PLS/HSP Web Sites:

The PLS Web site:
http://www.geocities.com/freyerse/index.html

The PLS Awareness Site:
http://www.geocities.com/mdmfoo/PLS.html

The HSP web site:
http://hspinfo.org

2. On-line PLS/HSP Discussion Sites:

For PLS support:
http://groups.yahoo.com/group/PLS-FRIENDS

For PLS News:
http://groups.yahoo.com/group/PLSers-NEWS

For HSP support:
Click on the link for the HSP Online Support Group (HSP-L List) at http://hspinfo.org

Calendar of Events

November 11, 2001
Fourth Annual HSP Conference
(PLSers invited)
Philadelphia, PA
Contact: Lisa Chadwick
(215) 612-5814
LRRC@juno.com
Lchadwick@umich.edu

December 1, 2001
New England HSP/PLS Gathering
Chelmsford, MA
Contact: Kathi Geisler
(978) 256-2631
Kathipro@aol.com

December 9, 2001
Georgia HSP/PLS Gathering
Atlanta, GA
Contact: Kathi Geisler
(978) 256-2631
Kathipro@aol.com

Connecticut PLS/Spastic Paraparesis Support Group
For dates and locations contact:
Dolores Carron
(860) 666-9862
d.carron@worldnet.att.net

Subscriptions, Comments or Suggestions

For a free subscription to <u>Synapse</u>, or to make comments or suggestions, please contact the editor:

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