

# THE COPPER CONNECTION

December 2001

## Wilson's Disease Semi-annual Meeting Informational Abstracts

Due to the September 11th tragedy at the World Trade Centers in New York and the Pentagon, the Wilson's Disease Semi-annual Support Meeting was cancelled. The following are abstracts by the doctors who graciously accepted our invitation to speak at the September meeting at the NIH. While the meeting was unfortunately cancelled, there is information of importance for you in their abstracts.

### **Genetic Testing For Diagnosis Of Wilson Disease.**

Ferenci Peter, Prof. of Medicine, Dept. of Internal Med. IV  
University of Vienna, Austria

More than 150 mutations of the Wilson Disease (WD) gene have been described so far. Due to this large number, mutation analysis is of limited value for diagnosis of WD and is still based on the presence of typical symptoms or laboratory abnormalities. If the disease is diagnosed by phenotypic criteria, mutation analysis does not add any additional information. This may change if gene therapy will become a therapeutic option in future. Genetic testing may be useful in patients with unclear phenotypical diagnosis, for population screening and for testing of first degree relatives of a patient. Basically there are two different approaches for gene analysis:

**Direct mutation analysis** should detect specific mutations of a particular gene. This can be achieved by specific PCR-based mutation assays or by direct sequencing of the whole gene. If a mutation has a high frequency in a certain population, detection of a particular mutation may be helpful to support the diagnosis of WD. This is the case for the H1069Q mutation in patients of Central or Eastern European origin (detectable in 50 to 85% of patients), the R778L mutation in patients from Far-Eastern countries (about 1/3 of patients) or mutations in the 2'-UTR in patients from Sardinia. The genetic diagnosis of WD can only be made, if mutations on both chromosomes can be detected. The absence of a detectable mutation never excludes WD. An abnormal, yet undescribed sequence, detected by direct sequencing, does not allow the diagnosis of WD unless it is proven that it is a disease causing mutation and not just a DNA-polymorphism. Due to the low carrier rate and the large number of

(continued page 2, GENETICS)

## CHICAGO HERE WE COME....

The 2002 Wilson's Disease annual meeting will be held in Chicago, Illinois. The location is the Hyatt Rosemont (near O'Hare International Airport). Reservations can be made by calling (847) 518-1234 or 800-233-1234 and requesting the "Wilson's Disease Association rate". The room rate is \$99.00 single/double; \$124.00 triple or \$149.00 quad.

The following is a tentative schedule:

Friday, May 3: Hospitality reception

Saturday, May 4: Meeting all day  
(includes breakfast and lunch)

Sunday, May 5: Meeting 8:30am-Noon  
(includes breakfast)

Look to the next newsletter for prices for the conference, as well as registration information. For any other questions, please contact Stefanie Kaplan (stefaniekaplan@yahoo.com).

### **Living Related Donor Surgery And Wilson's Disease**

Michael L. Schilsky, M.D., Division of Liver Diseases  
Recanati/Miller Transplant Institute, New York, NY

Living related donor liver transplantation in which part of the donor liver is removed and placed into a recipient was adopted due to a lack of available cadaveric donor organs for needy recipients for liver transplant. The first living donor surgeries in the United States were performed on pediatric recipients utilizing the left lobe of the liver from the donor. In the United States, living donor surgery is currently utilized for acute and chronic liver disease in pediatric patients, but only for chronic liver disease in adults. In adult living donor transplant, the use of a larger portion of the right lobe is now favored over the

(continued page 2, DONOR)

**(GENETICS, continued)**

mutations, screening for WD in the general population by genetic analysis is not feasible.

**Indirect genetic testing** using haplotype analysis does not require the demonstration of a mutation but only can be performed in asymptomatic siblings of an index patients, if both parents can also be tested. The haplotype marker pattern identifies the abnormal genes and their inheritance within the family. If both mutations of the index patients are known, direct mutation analysis is the method of choice for testing asymptomatic siblings. Today genetic testing is the gold standard for family analysis.



### **Surgical Treatment Of Movement Disorder Associated With Wilson's Disease**

Peter Hedera, MD, Department of Neurology  
University of Michigan, Ann Arbor

Wilson disease (WD) is caused by abnormal accumulation of copper that may damage the liver and parts of the brain playing an important role in the control of movements, called basal ganglia. Patients suffering from WD may experience tremor, slow movements, poor coordination, slurred speech and abnormal posturing (dystonia). Potentially devastating neurologic consequences may be prevented by early recognition and treatment. However, WD is often recognized late and only after patients developed severe movement disorder. Moreover, some patients treated with penicillamine may experience further progression of their symptoms that may be not reversible after the change of therapy.

Treatment of WD can be divided into therapy targeting the copper overload (chelation and maintenance therapy) and symptomatic treatment of neurologic complications. Surgical therapy is rarely used in patients with WD and should be considered only in patients 1) who did not respond to medical treatment and 2) who have disabling symptoms. Moreover, surgery should be considered only after there is no expected improvement after chelation therapy and the neurologic deficit is considered irreversible.

Tremor (essential or due to Parkinson's disease) can be treated surgically by targeting the part of the brain called thalamus, either by thalamotomy or by deep brain stimulation.

Dystonia is another common disabling symptom in patients with severe WD. Medical treatment of idiopathic dystonia (due to unknown cause) or secondary dystonia (caused by other disorders, including WD) is often unsatisfactory. Surgical treatment targeting the part of basal ganglia called globus pallidus (pallidotomy) has been effective in some patients with severe dystonia.

**(DONOR, continued)**

left lobe. Selection of donors requires a match of blood group, the lack of other medical problems in the donor, a reasonable size match, appropriate anatomy and proper social screening. Only about one third of adult patients on transplant lists have available donors. While rare donor deaths have been reported worldwide, the mortality has been estimated as 1-2 per 500 donor surgeries. Donor morbidity occurs, but most donors recover and are capable of returning to work within 2-3 months of their surgery. Survival of live donor grafts is excellent and comparable to cadaveric organs. Recipient and donor graft size nears normal liver size approximately one week to ~ 1 month after the surgery. Special considerations for living donor transplant for patients with Wilson's Disease include exclusion of the disorder in first degree relations that are potential donors. In pediatric patients transplanted for Wilsonian fulminant hepatitis, the use of donor grafts from asymptomatic heterozygotes has been reported to be successful. Living donor transplant surgery allows predictable timing of the liver transplant, permitting both medical and quality of life issues to be taken into account in the decision to proceed for transplant. Recent discussions regarding the ethics of living donor transplant suggest caution in proceeding with this modality of therapy, and suggest that its performance should be limited to centers of excellence with appropriate expertise. Further systematic studies and follow-up of recipients and donors are needed to better be able to judge the risk for donor and benefit to recipient, however the continued increase in the number of potential recipients and shortage of donor livers suggests that living donor surgery will remain an important component of transplant programs worldwide.



### **Wilson's Disease With d-Penicillamine And Zinc Sulphate**

Anna Czlonkowska, 2<sup>nd</sup> Department of Neurology,  
Institute of Psychiatry and Neurology, Warsaw Poland  
Department of Experimental and Clinical Pharmacology,  
Warsaw Medical University, Warsaw, Poland

The registration of Wilson's Disease (WD) patients was started in Poland in the 1950s. Since that time the Institute of Psychiatry and Neurology has been the only place in Poland where complex diagnostic methods have been available (ceruloplasmin and copper in serum, copper excretion in urine, radioactive copper functional test and recently mutation analysis) and where patients suspected of WD can be consulted. Here the first patients in Poland were treated with BAL, d-penicillamine (d-P) and zinc sulphate (Zn). The patients diagnosed usually remain under the supervision of the Institute.

**(continued page 3, d-PENICILLAMINE)**

**(d-PENICILLAMINE, continued)**

Up to now we have diagnosed and treated 362 WD cases. 243 (67,5%) cases had neurological, 52(14,2%) hepatic, 5 (1,1%) psychiatric, 3(0,8%) hepatic and neurological manifestations at onset and 59 cases (16,2%) were in pre-clinical stage at time of diagnosis.

*Treatment failure.* From 244 diagnosed cases 67 (27.5%) died in the period between 1958 to 1992. 126 patients took d-Penicillamine or Zn (only a few patients for short time) regularly and in that group 11 (8.7%) died, 4 deaths were unrelated to the disease. 102 patients were not treated regularly and among them 56 (54.9%) persons died. Additionally in this period of time we diagnosed 70 cases only according to the family history. No one from them was treated and 60 died (85.7%).

Our data indicates that main causes of failure of treatment of WD is poor compliance which leads to progression of the disease or late diagnosis when disease signs are very advanced and initiated treatment is ineffective. To be able to answer the question as to whether Zn or d-Penicillamine is more effective in treatment of WD and which patients benefit most from one of those drugs, more extensive observation is required, necessitating the performance of multi-center, prospective trial. However, this would not be easy, since clinical signs in WD are very variable, and there is no standard classification of the disease severity. In addition, a prolonged period of observation would be necessary.

**1. Fulminant Liver Failure**

Some patients with WD, present for the first time with acute liver failure and encephalopathy (acute liver failure with encephalopathy is defined as fulminant liver failure). These patients do not usually respond to chelation therapy hence the consensus among Hepatologists is to list these patients for urgent liver transplantation. Another group of patients with WD who present with fulminant liver failure are those who do not comply with chelation therapy, these patients are also considered for urgent liver transplantation.

**2. Decompensated cirrhosis**

Most of the patients show regression of symptoms and signs of liver disease after few months of copper chelation therapy. Failure of chelation therapy or decompensation of liver disease in terms of difficult to treat portal hypertension, ascites or onset of other rare complications of cirrhosis that are not amenable to medical treatment qualify for liver transplantation.

**3. Neurological disease with stable liver function**

Liver transplantation for this group of patients is controversial but has been performed successfully with alleviation of neurological signs and symptoms. Although liver transplantation has been successful with about 10% mortality in the first year, long term complications of immunosuppression and cost implications has to be kept in mind.

Long-term patient and graft survival following liver transplantation for WD is excellent, with patients reporting a normal quality of life.

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## Liver Transplantation for Wilson's Disease

Anil Dhawan MD, FRCPCH, Consultant Pediatric Hepatologist, King's College Hospital London, United Kingdom

Liver transplantation has become an accepted mode of treatment for patients with end stage liver disease either because of the sudden failure of the liver function (acute liver failure) or in patients with chronic liver disease. The current one and 5 year survival rates in our centre are more than 90% and 80% respectively with good quality of life. Most of the patients with Wilson's Disease respond well to the currently available copper agents, but about 15% of the patients require liver transplantation. The indications for liver transplantation could be discussed under three headings:

1. Fulminant liver failure
2. Decompensated cirrhosis
3. Neurological disease with stable liver function

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## Wilson's Disease In India

Dr. Ashish Bavdekar, Associate Consultant Pediatric Gastroenterologist, Liver Unit, Dept. of Pediatrics, K.E.M. Hospital, Pune, India

Wilson's Disease (WD) is being increasingly reported from many centers in India. They have a range of presentations: (a) Neurological - seen in children as young as 7-8 years and usually the diagnosis is made months/years after the onset of illness (b) Liver disease - This includes children presenting with acute or chronic liver disease. (c) Other presentations like bony deformities, anemia, etc., are also common. Inadequate awareness of the disease among medical professionals is an important cause of delay in diagnosis and onset of treatment. While tests like ceruloplasmin are available in most hospitals, a reliable urinary copper estimation is not readily available. Hepatic copper estimation is possible at only 2-3 centers all over India. D- penicillamine (DP) is the commonest chelater used because of its availability. However it is expensive and have caused serious side-effects in some of our children. Trientine is no longer available and is very

**(continued page 4, INDIA)**

## **Medical News**

Brought to you by the WDA Medical  
Advisory Group

### **Treatment of Wilson's Disease with Zinc**

**Fred Askari, M.D.**

Zinc acetate has been used for over two decades to treat Wilson's Disease, and it is now an FDA approved treatment that is receiving widespread acceptance. Zinc works by inducing enzymes in the gut to block copper absorption and by inducing enzymes in the liver to soak up free copper and block liver toxicity. It is now the treatment of choice for many patients on maintenance therapy and for special situations such as during pregnancy and childhood. Zinc needs to be taken an hour away from food and other medicines, usually three times daily. The main side effect is dyspepsia that occurs only in some people taking zinc, and it can be averted in many cases by adjusting dosing schedules. The main concern with long term treatment with zinc (as well as a concern with all other forms of treatment of Wilson's Disease) would be the potential for over treatment which may lead to copper deficiency. Fortunately, this is relatively unusual. This should be monitored by having annual tests for 24 hour urine copper and zinc levels. If copper levels get too low, zinc doses can be reduced before the symptoms of copper deficiency, primarily manifested as anemia, occur.

So keep taking your zinc carefully and have your urine copper and zinc checked at least once a year.

### **Copper Levels**

**Michael L. Schilsky, M.D.**

**Question:** What are the copper levels of a Wilson's Disease patient?

**Answer:** A Wilson's Disease patient usually has blood copper levels that are typically low because the ceruloplasmin (which contains 90% of the copper in the blood) is low. Only in severe liver failure does the copper in the blood become high in a Wilson's Disease patient.

## **Treatment Options For Wilson's Disease**

Wilson's Disease belongs to the group of neurodegenerative diseases. If left untreated, it will cause death of neuron cells and development of neurological problems. Therefore, the mainstay of the treatment of Wilson's Disease is copper chelation therapy and medications that prevent absorption of copper. Neurological problems should be treated only if they are causing a functional impairment.

Treatment options include speech and physical therapy and treatment with medications. The most appropriate form of treatment should be determined after detailed examination by a neurologist. Some of the medications that can be used include medications used for Parkinson's disease (for slow movements and muscle stiffness) such as levodopa, pramipexole or ropinirole, medications used for tremor (shaking) such as propranolol or primidone, medications used for dystonia (involuntary posturing of neck, trunk or limbs associated with muscle stiffness) such as botulinum toxin injections, and medications used for involuntary movements such as quetiapine or reserpine.

The Wilson's Disease Association gratefully acknowledges partial support of this newsletter by Gate Pharmaceuticals, manufacturer and developer of Galzin®.

### **(INDIA, continued)**

expensive (5 times the cost of DP). An over the counter, zinc sulphate preparation is available in India. Though very cheap (1/20<sup>th</sup> the cost of DP), we have found an unpredictable response to this preparation. All the WD children diagnosed at our center are started and maintained on DP lifelong. Zinc sulphate is only used for children who develop side-effects to DP or those from economically deprived families who cannot continue DP therapy. Liver transplantation is not available in India and children presenting with acute liver failure have a uniformly poor outcome. An effort is being made at our center to look for mutations causing WD in our country. The common mutation in Europe His1069Gln was not found in 47 children studied so far. Some mutations seen in our children are R778R and C271X. A parent support group (ROWIKEM, RO=Rotary, WI= Wilson's disease, KEM=KEM Hospital ) has been started at our hospital since 1990 to help the children with WD.

## **Why do I give time and money to Wilson's Disease? Because I am the beneficiary of what others gave before me.**

If we, those few with an interest in Wilson's Disease patients, do not give money and time, who will? Many patients already diagnosed and many others still to be diagnosed need our generosity. While we are giving them hope and help, WE GIVE OURSELVES THE SATISFACTION OF HELPING OTHERS BY DONATING.

A dollar a week is only \$52 a year and a dollar a day is only \$365 a year. How many of us can honestly say that we can not afford a dollar a week. And if we can, why don't we help others as others have helped us?

Contributions pay for education, research, support, newsletters, meetings, and expenses of daily operation such as Internet services, phone and stationary. There are no paid employees.

Contributions are entirely tax deductible. PLEASE GIVE GENEROUSLY NOW and regularly. Ask friends and relatives to give. There is no shame in asking for help for other people.

We are also able to accept legacy gifts, arrange a variety of trust opportunities, accept matching corporate gifts and bequests as we have in the past.

Please send all contributions to

The Wilson's Disease Association  
4 Navaho Drive  
Brookfield, CT 06804

Please direct any questions to H. Ascher Sellner, M.D. President 1 (800) 399-0266 Or (203) 775-4664.

### DONATIONS

We gratefully acknowledge the following people for contributing to the Wilson's Disease Association:

|                              |           |
|------------------------------|-----------|
| Sandra K. Neff Memorial Fund | \$883.64  |
| Jack L. Levin                | \$1000.00 |

### HOW TO OBTAIN CUPRIMINE OR SYPRINE

(If not available through their  
normal sources)

- 1) Call the Merck Sharp Dohme site in your country.
- 2) If they do not have a site in your country, call the Merck National Service Center at: 1-800-672-6372, and they will forward your request to the appropriate contact.
- 3) The National Center will request the following information:
  - Requester's name, agency, phone, fax, e-mail
  - Product shipping address/contact/phone/fax
  - Product name/strength/pack size/NDIC (catalog #)/total quantity of product expected
  - Medical emergency? Level of urgency?
  - Copy of prescription, including diagnosis
  - Regulatory/shipping/importation requirements

If you need any further assistance, please contact:  
Mary Graper at (414) 961-1290 or by e-mail,  
mltgraper@aol.com.

### **Availability of Syprine**

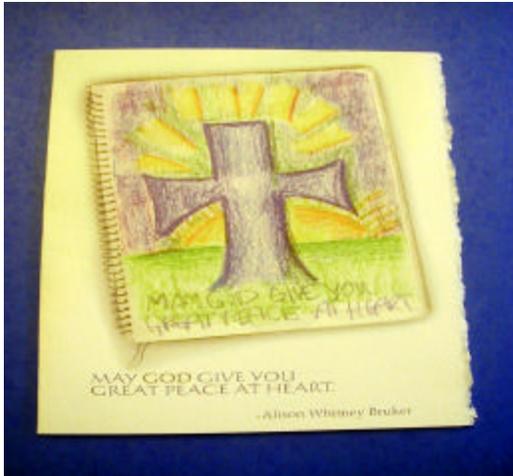
Have you had a problem obtaining Syprine? If so, we want to hear about it.



The WDA Board of Directors met, by teleconference, on October 10. During the meeting, the Board decided to continue efforts to ensure that patients being treated with Syprine will not have difficulty in filling their prescriptions.

If you have been told there is a shortage of Syprine or you have experienced a delay or any other inconvenience in purchasing Syprine, please send us the details. Include information about where you tried to purchase it and at what type of pharmacy—local, chain, or mail order—what the problem was, and how the problem was resolved. Was there a break in your treatment? If so, did you experience any adverse effects because of it? Did the problem necessitate a medication change? Are you using Syprine because it was the drug used for your initial treatment or did you switch to it due to problems with another medication?

We need your help so that we can help you! Please send information to Mary Graper, 5572 N. Diversey Blvd., Whitefish Bay, WI. 53217 or mltgraper@aol.com.  
Thank you for your help.



Cards are: 4" x 6", side-fold, ecru, deckle edge.  
Package of 10, envelopes included

FRONT: As shown, "MAY GOD GIVE YOU  
GREAT PEACE AT HEART"

BACK: Message reads:

"ART WORK BY ALISON WHITNEY BRUKER WHO  
DIED APRIL 10, 2001 AT THE AGE OF SEVENTEEN OF  
WILSON'S DISEASE A GENETIC DISEASE CAUSING  
COPPER ACCUMULATION. ALL PROCEEDS WILL AID  
IN PUBLIC AWARENESS AND EDUCATION"

Price: \$10.00/pack

## WILSON'S DISEASE ASSOCIATION FUNDRAISER

Beautiful note cards, generously donated by the family of Alison Bruker, a deceased Wilson's Disease patient.

Alison was a 17 year old high school honor student, who excelled in fine Arts. She created "many wonderful pieces of art, poetry, songs, letters, and one-act plays." Two months before Alison was to graduate from high school, and go on to attend the University of Georgia, she became mysteriously ill. By the time local and out of state physicians finally diagnosed Alison with Wilson's Disease, her liver had failed. She died on April 10, 2001, four days after her diagnosis.

Following her death, Alison's family discovered this crayon drawing in one of her sketch books. Despite their intense grief they took it as a sign that Alison's death would not be in vain. Therefore, these cards have been created in hopes that no one will suffer from Wilson's Disease.

All proceeds will go to the WILSON'S DISEASE ASSOCIATION INTERNATIONAL.

### ORDERING INFORMATION

To order please send check (payable to the WILSON'S DISEASE ASSOCIATION)  
OR VISA/MASTERCARD INFORMATION TO:

Karen Bruker, 1138 Monte Sano Avenue, Augusta, GA 30904 E-mail: kbrucker@home.com or  
Mary Graper, 5572 N. Diversey Blvd., Whitefish Bay, WI 53217 E-mail: mltgraper@aol.com FAX 414-961-0533

### Send Us Your Letters

We would like to hear from WDA members. Send us your letters, news to share, or other information that you would like to share with other WDA patients and families. Please mail to:

Delia Ruiz, Copper Connection Editor,  
P.O. Box 1225,  
Pismo Beach, CA 93448

or e-mail to DRNDVR@aol.com.

### CHANGE OF ADDRESS?

Have you moved recently? Do you have a new address? Please take a moment today to send us your correct address so that you will not miss out on future Copper Connection issues. This also helps us keep our mailing list updated and the Post Office happy. Please use the Membership Form to make any changes.





**Wilson's Disease Association**  
Ascher Sellner, M.D. President  
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E-mail: hasellner@worldnet.att.net  
WDA Website: www.wilsonsdisease.org

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Len Pytlak - Vice President  
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**WILSON'S DISEASE ASSOCIATION, INTERNATIONAL**

The Copper Connection, Editor  
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(FORWARDING SERVICE REQUESTED)

**TO:**