

# THE COPPER CONNECTION

June 2002

## 2002 Annual Wilson's Disease Association Meeting Highlights

### Initial Therapy For Wilson's Disease

Michael L. Schilsky, M.D.

Initial treatment for Wilson's disease consists of medical therapy and liver transplantation. Medical therapy includes chelating agents—penicillamine, trientine and the experimental agent tetrathiomolybdate, and treatment with zinc salts. Patients with symptomatic disease require initial treatment with chelating agents, and there is a growing experience for combination treatment using a chelating agent and zinc. Zinc may be used as initial therapy for patients with presymptomatic disease.

The transition from initial treatment to maintenance therapy is typically made following 2-12 months of treatment, the time varying for varying degrees of illness and rates of response to treatment. Medical therapy must be maintained for life. Liver transplantation is needed for patients that have acute liver failure due to Wilson's disease, or those that develop liver failure following discontinuation of their medical therapy.

Along with medical therapy, there is an increasing recognition of the need for a team approach to the  
(continued page 2, THERAPY)

### Semi-Annual WDA Meeting (re-scheduled)

Saturday, November 16, 2002  
Miami, Florida

This meeting will be held in conjunction with the Movement Disorder Society meeting. There will be a lecture program planned for the morning and a support activity in the afternoon. All WD patients and families are welcomed to attend the scientific section of the Society meeting.

Those interested in attending can e-mail Dr. Sellner (hasellner@worldnet.att.net)

Additional information will be available in the next newsletter.

### Advances in the Treatment of Wilson's Disease

George J. Brewer, M.D.

It is becoming clear that the best initial treatment of patients who present with brain damage from Wilson's disease is tetrathiomolybdate (TM). The best initial treatment of patients who present with liver disease is either trientine plus zinc or TM plus zinc. Which is better remains to be determined, and a study is planned.

For maintenance therapy and treatment of presymptomatic patients, zinc acetate is favored because of its very low toxicity. Pediatric doses are becoming better established at 25 mg twice daily until age 6, 25 mg three times daily until age 16 or 125 pounds whichever is  
(continued page 2, ADVANCES)

### Liver Transplant For Wilson's Disease Longevity and Consequences

Michael L. Schilsky, M.D.

Liver transplantation has evolved in less than two decades from an experimental therapy to the standard of treatment for patients with liver failure. For Wilson's disease, liver transplantation offers a chance for a metabolic cure and has saved the lives of hundreds of patients worldwide. This cure however, does not come without its costs in human life and morbidity, as well as economic costs for medication and medical follow-up. One year survival for liver transplant for Wilson's disease for  
(continued page 5, LIVER)

**(THERAPY, continued)**

initial care of many patients with symptomatic Wilson disease. This team may consist of liver specialists, neurologists, psychiatrists, speech therapists, physical and occupational therapists and social workers, along with the patients primary caregivers. The use of the team approach at our Center of Excellence at the Mount Sinai Medical Center in New York was discussed.

**(ADVANCES, continued)**

sooner. The adult dose is 50 mg three times daily. All zinc doses should be separated from food and beverages other than water by at least one hour.

Zinc therapy should be monitored by following 24 hour urine zinc and copper. Urine zinc levels should be over 2 milligrams if the patient is taking zinc properly. Lower levels suggest poor compliance, that is, not taking the zinc adequately. Urine copper levels will begin relatively high in untreated patients, but will gradually decrease so that after a year of zinc therapy they should be less than 125 micrograms (normal is 20-50). If the copper levels begin increasing progressively, it means things are going in the wrong direction, usually because of poor compliance. A 20% fluctuation from one time to another can be expected, and should not be cause for alarm.

If the copper levels get into the normal range, particularly below 40, over treatment copper deficiency needs to be worried about. The first medical problem from copper deficiency is anemia. If the urine copper gets below 40, and

especially if the patient becomes anemic, the dose should be lowered and perhaps temporarily stopped. The frequency of monitoring depends upon the situation. Everyone should be monitored at least once yearly. New patients, and patients with compliance problems, should be monitored more frequently.

It is important that pregnant Wilson's disease patients take anti-copper therapy during pregnancy to protect their own health. Our data collected on pregnant Wilson's disease patients on zinc therapy indicate excellent protection of the mother's health. However, occasional birth defects occur, and our data suggest that these tend to occur in women with the tightest copper control. Since copper deficiency is known to be teratogenic (cause birth defects), our data suggest that if the copper levels are on the low side, there is increased risk of birth defects. This suggests keeping copper levels in a little higher range (urine copper of 100-150) during pregnancy, rather than under tight control. The same remarks, of not keeping tight control, would be applicable to trientine and penicillamine. In addition penicillamine has a specific teratogenic effect, which is a good reason for choosing a different anti-copper drug during pregnancy.

In conclusion, the anticopper therapy of Wilson's disease has made good strides over the years, with zinc increasingly acknowledged as the optimal therapy for maintenance. Zinc formulation deserves work to improve the therapy, specifically, to prevent gastric irritation and to make once/day dosing feasible, both of which would improve compliance. Poor compli-

ance with therapy is a continuing problem, with patients dying needlessly every year just because they didn't take their medicine.

**Hepatitis B Vaccines**

All Wilson's disease patients who have not had hepatitis are recommended to have the hepatitis B vaccination to help prevent future liver damage.

**Wilson's Disease  
Resource Books**

Dr. George J. Brewer has recently published two Wilson's disease books which are now available.

Wilson's Disease: A Clinician's Guide to Recognition, Diagnosis, and Management

This book can be ordered from Kluwer Academic Publishers (via the internet [www.wkap.nl/](http://www.wkap.nl/)) ISBN # 0-7923-7354-5

Wilson's Disease for the Patient and Family: A Patient's Guide to Wilson's Disease and Frequently Asked Questions About Copper

This book can be ordered from Xlibris.com (Paperback \$17.84, Hardback \$28.79, eBook \$8.00).



## **A Message For Fellow WD Patients**

By Laura Lokken

I would like to warn all Wilson's disease patients to get involved in their treatment! Get a second opinion. Don't assume your doctor knows everything about Wilson's disease, or that they only have correct information. I made that mistake and it has proven to be a very serious (potentially life-threatening) one.

I was diagnosed 21 years ago at the age of 19 after a liver biopsy. My oldest sister had died from Wilson's disease 8 months earlier. Although until my diagnosis and a posthumous liver biopsy on a frozen cross-section of my sister's liver, we had been told that she had died from a combination of types of hepatitis. After several years on Cuprimine, I was placed on zinc sulfate so that my husband and I could safely have children. I stayed on zinc sulfate for the next 12 years or so. Everything seemed fine until August of 2001. My tests showed that my liver was not functioning properly. The second liver biopsy in September showed major scarring had occurred. I was told that on a scale of 1-4 (4 being the worst), that the scarring I had rated a three. At the time I was diagnosed, I had minimal damage to my liver. The reason for my liver damage turned out to be that I had been taking the zinc sulfate with food all those years.

### ***ZINC SULFATE (ANY ZINC) DOESN'T WORK WHEN TAKEN WITH FOOD!!***

My doctor didn't know this. Neither did the pharmacists. Now, I am getting treated with Galzin (zinc acetate—on an empty stomach) and Cuprimine. However, even with a trip to a center of excellence 1000 miles away (round trip) and different treatment, I don't know what will happen. I am the only person Dr. Askari at the University of Michigan knows of that is being treated with these two medications. He is concerned about my developing adverse reactions (toxicity) to the maximum dose of Cuprimine that I am on. I also have to be concerned about the possibility of internal bleeding and liver failure now. I may need a transplant some day.

### **Ceruloplasmin: Does It Rise After Therapy?**

Fred Askari, M.D.

The topic of what happens with ceruloplasmin levels in people with Wilson's disease is less straight forward than we would like. In short, what happens to ceruloplasmin levels can be different for different people. The ceruloplasmin is actually normal in between one out of five and one out of ten people with hepatic Wilson's disease at the time of diagnosis. In general, the ceruloplasmin level falls a bit on treatment, but sometimes it is so low at the time of diagnosis that the clinical lab tests do not accurately show this drop.

Other times it does not drop at all on treatment even as the urine copper and serum free copper drops. The ceruloplasmin level may fluctuate over time. It is influenced by other things in addition to copper levels like the use of steroids, hormones,

birth control pills and liver inflammation; all of which can make it rise as well.

Many labs do not run an oxidized ceruloplasmin, which is a measure of functional ceruloplasmin. Instead, some use a more automated assay which measures total ceruloplasmin levels, which may make it difficult to compare ceruloplasmin levels from one lab to another. The same lab may change its techniques over time as well. In short, monitoring ceruloplasmin levels alone is not a particularly useful clinical marker of response to therapy. Urine copper levels, as well as serum free copper levels (calculated from the ceruloplasmin level and total serum copper level) are more useful clinically.

One in 5 of carriers, but not patients with  
Wilson's Disease, have a low  
ceruloplasmin.

Dear Friend ,

All of us share some interest in Wilson's disease because of which we have reason to better appreciate the blessings of life. Our Association is trying to do all it can to find patients early in their disease, to get them well treated and to help them with all of their medically-related problems. We have many people generous with their efforts and their money. But the efforts must persist since the disease will go on and on. Some are disabled for life and need help for life.

The maintenance of existing services, although unfortunately limited, can only be improved with your commitment of time and especially money. Please give now even if you have given recently. No one is as interested in the welfare of Wilson's patients than those of us affected directly or indirectly. Please give Wilson's disease as much as you give all other charities. Or, perhaps you may consider giving the majority of your charity to the cause of Wilson's disease.

Even small contributions make a difference because many of them add up to a large amount. If you can afford a large contribution you will assist the Association in taking giant steps forward in the pursuit of its goals. We can also help you with planned giving of stock and property now or from your estate.

Please give to the best of your ability. You will be supporting the primary organization for Wilson's Disease throughout the world.

Sincerely,  
The Wilson's Disease Association

### **Medical News**

Brought to you by the WDA Medical  
Advisory Group

**Question:** Can Galzin dissolve and remove the ALREADY ACCUMULATED COPPER in the brain? Or will it only control further accumulation of copper?

**Answer:** There is a negative copper balance with zinc treatment; more copper goes out than in. In time, all extra stores of copper (even in the brain) are removed. Proof of this is the loss of Kayser-Fleischer rings in treated patients with time on zinc.

**Question:** Do urine copper levels remain high with penicillamine treatment?

**Answer:** Penicillamine chelates copper and then allows it to be excreted in the urine. With regard to urine copper values on penicillamine therapy, they are generally higher than with zinc acetate therapy or trientine therapy. They can be as high as several grams per 24 hours when therapy is initiated, and the urine copper concentration should slowly decrease over time on effective therapy.

Congratulations to  
**Darla Lawrence**  
and her family on  
the arrival of their  
little baby boy.



**Trace William** was  
born on April 7, 2002 and weighed  
9 lbs 4 oz.

### **DONATIONS**

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

Yolande Desjardins and Family	\$100
Ms. Andreina Pastorino	\$40/month
GATE Pharmaceuticals	\$500

## Replacing The Wilson's Disease Gene ATP7B

Michael L. Schilsky

Wilson's disease is due to mutations on chromosome 13 of a gene known as ATP7B. The protein encoded by this gene is a copper transporter that is mainly expressed in the liver and is responsible for the excretion of excess copper into bile. In patients with Wilson disease, this protein is either absent or is non-functional, and copper accumulates. When a patient undergoes liver transplant, the new liver will contain normal functioning ATP7B protein and excrete copper normally and produce ceruloplasmin with copper as well—so the patient no longer has the disease.

There is expression of the gene in other tissues, and there was some initial concern that in organs like the brain there could still be problems with copper retention. However clinical experience has shown that the overall body burden of copper returns to normal with time following liver transplantation.

Inherent in liver transplantation are the surgical and medical comorbidities associated with the procedure and medications needed to prevent organ rejection. Overall survival for Wilson's disease patients has improved greatly with liver transplant, as shown in our publication that details our experience in 21 patients transplanted at The Mount Sinai Medical Center that was published last year (Emre S, Atillasoy EO, Ozdemir S, Schilsky ML, Rathna Varma CVR, Thung SN, Sternliebl, Huy SR, Sheiner PA, Schwartz ME, Miller CM. Orthotopic liver transplantation for Wilson's disease: A single center experience. *Transplantation* 72: 1232-1236, 2001)

### Pregnancy and Wilson's Disease

Irmin Sternlieb, M.D.

It is not uncommon for symptomatic women with Wilson's disease to suffer irregular periods and multiple miscarriages. These are the consequences of malfunction of the liver causing hormonal changes which are reversible with successful treatment of the underlying disorder. But is the treatment hazardous for the fetus?

Review of the literature and personal experience indicate that women successfully treated with either penicillamine, trientine or zinc uninterruptedly, have excellent chances for carrying through uncomplicated pregnancies and for delivering normal babies. However, precautions are indicated in women with dilated veins in the stomach or esophagus which may rupture and bleed because of the increased abdominal pressure caused by the enlarging uterus.

There is no report of an untoward reaction to a baby nursed while the mother continued on an anticopper regimen.

### (LIVER, continued)

acute liver failure is about 90%, and with rare exceptions, those that survive one year continue to survive long-term. Infectious and neoplastic disease due to immunosuppression remains a concern, especially in the pediatric population and during the early post-transplant period. Long term effects of immunosuppression include possible impairment of kidney function, high blood pressure, hypercholesterolemia and other effects.

Living donor transplant has improved the availability of livers for pediatric patients in need of transplants. Adult to adult liver transplants also offers new opportunities to expand the liver donor pool, but is not without potential for consequences to the donor and recipient.



### 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 WD 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](mailto:DRNDVR@aol.com).

### **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.



### **Testing For Wilson's Disease**

Fred Askari MD

A liver biopsy is generally not performed as the first test to evaluate Wilson's disease. It can be dangerous, with about 1% of people having one or more complications due to the procedure.

The recommended tests to run are:

- 1) two 24 hour urine collections
- 2) ceruloplasmin
- 3) serum free copper
- 4) Ophthalmologists exam for Kayser Fleischer rings
- 5) liver function studies
- 6) if the diagnosis still remains in doubt, then a liver biopsy can be performed.

### **FYI: Galzin**

Athena Pharmacy no longer provides Galzin. GATE Pharmaceuticals should be contacted directly. They can ship directly to a person or a pharmacist. Many wholesalers do not carry Galzin. The pharmacy has to do a little extra work to locate the right source. Insist that they do it.

GATE Pharmaceuticals  
151 Domorah Dr.  
P.O. Box 1008  
Montgomeryville, PA 18936  
USA  
1(800) 292-4283

### **Over-the-Counter Zinc vs Galzin**

George J. Brewer

Zinc therapy is the optimal treatment of Wilson's disease during lifetime maintenance, including the pediatric years, treatment of presymptomatic but affected patients, and pregnant women who have Wilson's disease. If it is available, and can be afforded, I strongly favor Galzin (zinc acetate) for Wilson's therapy, because it is a pharmaceutical preparation, which insures accurate dosing and absence of contaminants. However, if Galzin isn't available or can't be afforded, such as in undeveloped countries, the use of over-the-counter zinc preparations such as zinc gluconate is the next best option. This form of treatment will generally be superior to other forms of treatment available to such patients.





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

**Wilson's Disease Association**  
Ascher Sellner, M.D. President  
4 Navaho Drive, Brookfield, CT 06804  
(800) 399-0266  
E-mail: hasellner@worldnet.att.net  
WDA Website: www.wilsons-disease.org

**WDA Board Members**

Ascher Sellner, M.D. - President  
Len Pytlak - Vice President  
Carol Terry - Treasurer  
Carol Sellner - Secretary

**Board Members**

Luke Chung	Kevin Peters
Nancy Hoffman	Sparky Terry
Stefanie Kaplan	Jack Levin
Carl Nacht, M.D.	Jacqui Taylor
Henry Kaplan, M.D.	Mary Graper

**Honorary Board Member**

Janene Bowen

**CHANGE OF ADDRESS?**

Please notify the Wilson's Disease Association of any address changes so that we may keep our database updated. Please use the Membership Form to make any changes.

*Inside This Issue:*

- ♦ *2002 WDA Annual Meeting Highlights*
- ♦ *Wilson's Disease Resource Books—Order info*
- ♦ *Testing For Wilson's Disease*

**WILSON'S DISEASE ASSOCIATION**

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

(FORWARDING SERVICE REQUESTED)

**TO:**