

THE COPPER CONNECTION

May, 2004

WDA's First Annual Student Writing Competition Competition Topic: Promoting The Early Diagnosis of Wilson's Disease

Introduction by: Henry Kaplan M.D., J.D. - WDA Board Member and
Professional Education and Medical Relations Committee Chair

Early diagnosis of Wilson's disease makes a difference because it leads to appropriate treatment which preserves neurologic function, prevents liver disease and alleviates distressing psychiatric symptoms. Early diagnosis and appropriate treatment saves lives, preserves health and dramatically reduces the impact of Wilson's disease on patients and their families.

To raise medical students' awareness of Wilson's disease, the WDA created a medical student writing competition focusing on early diagnosis. More than three hundred notices were sent to academic medical center department chairs of pediatrics, internal medicine and gastroenterology. Significant cash prizes were offered to the winning students and modest recognition was offered to their faculty sponsors.

The entries were evaluated by members of the Medical Advisory Committee and others. In March, 2004, the winning paper was selected: "Promoting the Early Diagnosis of Wilson's Disease" by Jessica Korman, a third year medical student at Mount Sinai School of Medicine. The WDA is pleased to present that paper in *The Copper Connection*.

WINNER OF WDA STUDENT WRITING COMPETITION

Promoting the Early Diagnosis of Wilson's Disease

Jessica Korman MSIII
Mount Sinai School of Medicine

Wilson's disease (WD) is an autosomal recessive disorder that affects approximately 1 in 30,000 individuals¹ around the world with about 1 in 90 persons being heterozygote carriers^{2,3}. It results from mutations of the adenosine triphosphate 7B (ATP7B) gene, on chromosome 13. This gene encodes a copper ATPase transporter located in hepatocytes and is responsible for excreting excess copper into bile and for the secretion of copper into plasma bound to ceruloplasmin⁴. The genetic defect results in copper accumulation causing hepatocellular injury. Eventually, hepatocytes release stores of copper into the circulation that deposits in extra-hepatic sites, particularly in the brain and cornea.

Treatment in the asymptomatic or early stages is straightforward, inexpensive, and has few side effects. However, undiagnosed and untreated WD progresses to liver failure and death. Unfortunately, diagnosis of early WD has remained a challenge since Kinnear Wilson first described it in 1912 because the clinical manifestations are so highly variable and often subtle. Patients are either recognized by symptomatic presentation, when a sibling is diagnosed, or most tragically at autopsy. Clinicians must be keenly aware and maintain a high index of suspicion for the range of presentations. This critical early diagnosis prevents progressive liver damage and disabling neuropsychiatric disease. The current mainstays of medical therapy for WD are penicillamine, trientine and zinc. Tetrathiomolybdate, a chelating agent, is still under investigation. If diagnosed early enough, zinc therapy can be initiated in childhood. It is safe, inexpensive, widely available, and highly effective in preventing the progression of WD^{5,6}.

It is well established that the diagnosis of WD can be made definitively by the presence of Kayser-Fleisher (KF) rings on ophthalmologic slit-lamp examination, and a reduced serum ceruloplasmin (normal value: 20-50 mg/dL; WD < 20 mg/dL)².

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WILSON'S DISEASE ASSOCIATION

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The Wilson's Disease Association is a nonprofit 501(c)(3) organization.

Our Mission Statement: The Wilson's Disease Association funds research and facilitates and promotes the identification, education, treatment and support of patients and other individuals affected by Wilson's disease.

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President's Message

Greetings to those of you I had the privilege to see at the 2004 Annual Conference, and to those of you who were not able to attend. Those who attended can surely vouch for what a great conference it was. The 42 member audience at "Past, Present, Future" had the opportunity to learn from the best about the latest developments in Wilson's disease treatment.

Thanks to the generosity of our speakers, who attended at their own expense, the WDA was able to provide the most current information about Wilson's disease. As Dr. Irmin Sternlieb was unable to attend, Ann Hunter graciously filled in at the last minute talking about WD from a patient's perspective. Thank you Ann! Special thanks are also in order to Henry Kaplan M.D. J.D. for speaking in Dr. Sternlieb's absence at the conference banquet, along with Dr. Michael Schilsky, on "Promoting the Early Diagnosis of Wilson's Disease". Substituting for Dr. T. U. Hoogenraad, who was also unable to travel to Phoenix, was our own WDA Board Member Jeff Eckland J.D.. Dr. Hoogenraad kindly provided his presentation materials to Jeff who did an excellent job of delivering his topic. Thank you Jeff!

As usual Drs. Askari, Brewer, and Schilsky were on hand to offer their expertise and personal insights to the group. We owe them much gratitude for their years of involvement and continued support of WDA programs and patient care. A new resource for the WDA, but not new to the study of Wilson's disease, is Dr. Sihoun Hahn. Dr. Hahn provided information on new research and programs he is instituting at Mayo, Rochester. We gratefully acknowledge his participation and willingness to share his wisdom with our group.

It was also my great pleasure to present a cash award to Ms. Jessica Korman, a medical student at the Mount Sinai School of Medicine, for her winning submission to the Medical Student Writing Competition: "Promoting the Early Diagnosis of Wilson's Disease." It is encouraging to know that young, soon-to-be physicians are taking the time to learn and write about Wilson's disease.

Lastly, I want to thank each and every one of you for your input and support efforts. Much of our program content is derived from requests and suggestions from our membership. Your letters, phone calls and e-mails help us to help you by offering topics that are of concern and interest to you. Your support and encouragement of others in our Wilson's "family" is

truly inspiring. I have yet to attend a WDA gathering where there wasn't someone who was attending for the first time, never having met another patient, and really unsure about being there. This year was no exception. But, in all cases by the time the weekend is over they leave the meeting feeling that they are a part of something special. That something special is the warm supportive environment that all of you provide. I also hope you all join me in thanking our entire Board of Directors, our Executive Director, and those who volunteer their time and/or financial resources to make the continued mission of this Association possible.

I am counting on seeing even more of you next year at the 2005 Annual Conference in Coral Gables, Florida April 29 – May 1!

Regards,
Mary L. Graper
President

Executive Director's Message

Dear Friends:

Once again, I come away from the WDA's Annual Conference with a continued admiration for our membership and its volunteers. It was great seeing so many familiar faces as well as make new friends. All of you continue to amaze me with your resilience and determination. An addition to this year's Conference was the Association's first WDA Annual Conference Banquet. At the Banquet, the winner of our first Medical Student Writing Competition, Jessica Korman, was presented her award by Mary Graper. I hope all who plan on attending the conference in Florida next year will register for the Banquet. I think I can speak for everyone by stating a great time was had by all. Next year's conference will be held in Coral Gables, so look for the Registration Application in the December newsletter.

I would like to take this opportunity to thank our Corporate and Individual Sponsors for WDA's Annual Conference:

- M & I Private Bank
- Regina Services Corporation
- The Evictor, Inc

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- The Party Store
- Rock of Ages
- Dr. Sihoun Hahn
- Many anonymous donors.

It is our hope that next year this list will increase so that the Association will be able to offer a larger scope of speakers and cover a wider variety of general topics.

On Friday, before the Annual Conference, Mary Graper, Henry Kaplan, Jeff Eckland and I met with WDA's Medical Advisory Committee, Dr. Schilsky, Dr. Brewer and Dr. Askari. We had a very detailed meeting and the Committee has pledged to continue in its advisory role. Additionally, they will assist the WDA by helping to identify physicians to increase our treating physician list. If you know of a treating physician who you feel would be a great addition to this list, please send their contact information to the office and I will forward this information to the Committee for review.

I am pleased to report, as a result of the members of WDA's generosity, we were able to unveil our newest brochure: A Diagnostic Tool For Physicians. The brochure can be viewed on our website at www.wilsonsdisease.org. Or to receive a copy, please call the office at 1-330-264-1450. This brochure has already received positive praise from the medical community as being a great diagnostic tool. We encourage you to help us spread the word about Wilson's disease by distributing this brochure to your physicians.

Please keep in touch, and together we will make a difference.

Sincerely,
Kimberly Symonds
Executive Director

A Debt of Gratitude

Paul Rutherford

Growing up in a family of six children in the prairie city of Winnipeg, Canada during the mid 1960's life was simple, but good. That is until the fourth child, my sister Carol, suddenly and mysteriously developed

some type of troubling ailment. At this time, Carol was a young headstrong woman in her early 20's engaged to be married. It was at this time she began to exhibit some troubling tendencies, which we were all at a loss to understand. Along with some episodes of bizarre behavior, Carol began to come undone physically. She began shaking and her speech became distorted and slurred. Her life began to unravel as her symptoms grew progressively worse and her fiancé bolted. Her tremors became so severe that she was unable to do all those everyday tasks we all take for granted. When the shaking became uncontrollable, my mother even had to feed her. To mother's anguish, father's bewilderment and her sibling's astonishment something terrible had taken control of Carol.

The medical establishment was at a loss to explain her situation, little less control it. She was treated for, amongst other things, Huntington's disease, Parkinson's disease and finally for mental degradation. She was prescribed a plethora of various medications and as nothing worked and her condition continued to deteriorate, she was eventually admitted to an insane asylum in a small town just north of Winnipeg.

At the asylum, she was under observation while being prescribed various types of mind and mood-altering drugs. Nothing helped and they were at such a loss to understand her ailment they even resorted to sessions of shock treatment! This humbling and humiliating experience my sister had to endure dumbfounded my parents. Our household would never be quite the same again.

Carol was finally released from the insane asylum, certainly in no better condition than when she entered and probably worse. Her life continued to spiral out of control for some time until one day she went to visit an optometrist because her vision was deteriorating. By accident she was about to get a break.

The young optometrist had studied medicine in England and when he looked into my sister's eyes, he knew immediately what was tormenting her. He witnessed the copper rings surrounding her pupils, a direct symptom of the disease we know as Wilson's disease. This debilitating disease was coined after

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Evidence-Based Management of Wilson's Disease. The Dutch Experience

Tjaard Hoogenraad, MD, Dept. of Neurology,
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Wilson's disease is a rare, autosomal recessive, inborn error of copper metabolism. The gene for the disease, ATP7B, is located on the long arm of chromosome 13. Defective biliary copper excretion leads to increase of free-copper in the liver. Free-copper induces the copper-binding-protein metallothioneine resulting in copper retention and detoxification. As the liver can no longer detoxify free-copper, symptomatic copper intoxication follows. Symptoms are caused by liver or brain disease. Increase of free-copper, urine copper, and Kayser-Fleischer rings are important diagnostic signs. Analysis of DNA markers surrounding the ATP7B gene enables diagnosis in affected presymptomatic family members.

In the Department of Neurology of the UMC-Utrecht, we have based our opinions on treatment of patients following the rules of evidence-based medicine (EBM). Since 1978 we have treated all patients with zinc sulphate. Treatment target is normalisation of free-copper, correction and prevention of damage of the liver, brain and other organs. Fading of Kayser-Fleischer rings is seen with effective long-term treatment. The opinion that zinc is effective, safe and cheap is in accordance with the guidelines of evidence-based medicine.

Other treatments that are not in accordance with evidence-based medicine include BAL, penicillamine, trientine, and liver transplantation. However, the reasoning is false and the side effects of these therapies are severe. Data on the effect of ammonium tetrathiomolybdate are insufficient to base an opinion upon. There are no evidence-based data that justify the opinion that any of the alternatives is superior to zinc. Penicillamine is contraindicated at the start of treatment because of potential deterioration. Prevention of liver transplantation by zinc therapy has been reported.*

References:

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*J.van Hattum, personal communication, UMC-Utrecht, April 2003.

Population Screening For Wilson's Disease

Sihoun Hahn, MD, PhD
Biochemical Genetics Laboratory, Department of
Laboratory Medicine & Pathology and Pediatric &
Adolescent Medicine, Mayo Clinic, Rochester, MN

Wilson disease (WD) may be the most frequent and most preventable cause of chronic liver disease in children. WD is treatable and serious symptoms can be avoided if a diagnosis is made early. We developed an in-house sandwich ELISA assay to measure the ceruloplasmin (CP) in dried blood spots using specific monoclonal antibodies and are currently conducting a voluntary research study to determine whether a screening program for children is workable.

The goal of pediatric screening for WD is to identify affected individuals and begin treatment prior to the onset of life-threatening symptoms. In this study, we aim to analyze approximately 4000 children aged from 3 months to 18 years within a year. Eligible children whose parents have provided permission (and who have assented when appropriate for age) will undergo a finger stick for blood collection on filter paper. From the blood spots we will then measure the concentration of CP. Those with an abnormal value that is demonstrated after repeat testing will be contacted to arrange for further confirmatory testing and consultation if indicated. In order to get the better cut off value and for the purpose of confirmation, we also developed the DNA test to screen whole exons of Wilson disease gene by CSGE (conformation-sensitive gel electrophoresis) followed by direct sequencing if indicated. The frequent mutant alleles, H1069Q and R778L are also tested by Light Cycler assay. A new technology with HR-1, which offers extremely high resolution and

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“The Future of Wilson’s Disease: Cell Transplants and Gene Therapy”

Michael L. Schilsky, M.D.
Associate Professor of Clinical Medicine,
Medical Director Of the Center for
Liver Disease and Transplantation at
Weill Cornell Medical Center, New York.

There are a number of emerging techniques and therapies that may be applied to the diagnosis and treatment of Wilson disease (WD). The identification of the gene for WD has made genetic analysis, gene replacement therapy or even gene repair a future possibility for WD. Cell transplant therapy may be used for correcting the metabolic defect underlying WD.

Recent attempts at gene therapy for WD included two independent studies that utilized adenoviral constructs containing cDNA for *ATP7B* (the WD gene) and introduced these into an animal model of WD, the LEC rat. Both studies demonstrated transient protein expression of *ATP7B* and production of copper containing ceruloplasmin and increased biliary copper excretion. These studies provided proof of principal that gene delivery to the liver is possible, and that the delivered gene could be functional in the hepatocyte. The utility of viral-based gene therapy awaits further development and testing of vectors that can safely deliver the desired gene with prolonged and regulated expression.

Hepatocyte or liver cell transplantation is another technique that can be applied for the treatment of WD. For this method to work, integration of the transplanted liver cells into hepatic cords and communication with the biliary excretory system. It was also unknown how much cell replacement or growth of the donor hepatocytes was needed to provide effective clearance of copper into bile. In a study by Dr. Sanjeev Gupta and his colleagues at the Albert Einstein College of Medicine in NY and his collaborators, normal syngeneic Long-Evans Agouti rat hepatocytes were transplanted into the spleens of 2 week old LEC rats. Cell transplantation restored copper homeostasis, as demonstrated by increased biliary copper excretion, reduced hepatic copper, and increased ceruloplasmin levels in the circulation, and importantly reversed liver disease in the recipients. The success of these experiments relied on the ability of the transplanted cells to proliferate subsequent to the onset of liver

injury. The livers were repopulated over an extended period with an increasing proportion of the donor cells. Future studies in cell-based therapies are focused around how to achieve better selective repopulation with donor cells, and also how to achieve immune tolerance to prevent cellular rejection when allogeneic cells are utilized.

While we can treat WD, current medical therapies are not curative for this disorder. A “cure” has only previously been achieved by liver transplantation. The need for medical therapy is life-long, and the many reported instances of non-adherence with medical therapy have led patients to develop crippling disease, liver failure or death. Some fortunate patients with non-adherence have been rescued by liver transplant. However, the societal cost is high for those requiring transplants and life-long immunosuppression, or for those that develop crippling side effects of the disease. Therefore the development of a curative therapy would be potentially cost-effective, and certainly welcome to patients facing a lifetime of taking medication. While we are likely decades away from finding the one best cure for WD, given current evidence for the limited success already, this is a future goal that should be obtainable.

Liver Manifestations and Monitoring of Wilson’s Disease

Frederick Askari M.D. PhD.
Assistant Professor of Internal Medicine,
Clinic Director, Wilson’s Disease Center,
University of Michigan

Wilson’s disease can present with a broad spectrum of liver manifestations, including little or no liver disease all the way up to abrupt and fatal liver failure. Liver disease stems from the effects of excess copper levels accumulating in the liver and causing injury. The hallmark of the most advanced current therapy is directed toward lowering the copper levels to safe levels and maintaining copper therapy over a person’s life. Copper reduction therapy can lead to a cessation of liver injury and even a reversal of injury in many cases. Avoiding other liver injuries by viruses, drugs, or alcohol is important to allow the liver to heal. Immunizations are available for two common forms of hepatitis, hepatitis A and B, and

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these are recommended for everyone with chronic liver disease. Dilated blood vessels or varices can occur in the esophagus or food pipe of people with scarring in their liver, and at times these can bleed. People with significant liver disease should avoid using aspirin and other non-steroidal anti-inflammatory drugs, like Motrin, which can precipitate bleeding.

In addition to at least an annual physical examination, treatment monitoring includes measuring twenty-four hour urine copper and zinc, as well as serum copper, ceruloplasmin, liver profile, INR and CBC with platelets. People need to take responsibility for their care by keeping track of when their medication dosing and testing is due and being sure to complete it on time. For many, the future of Wilson's disease can include daily medication dosing and annual or semi-annual testing. Liver transplantation is occasionally necessary in the early stages of hepatic decompensation as treatment is just taking hold or fortunately transplant is only infrequently later in the course of the disease. Each person has a responsibility for treatment and monitoring vigilance as Wilson's disease is a life long issue which can frequently be controlled.

Historical Perspective of Wilson's Disease Diagnosis and Treatment

I. Sternlieb, MD, San Diego, California

The 20th century witnessed a remarkable series of discoveries starting with the identification of a peculiar pattern of neurological abnormalities affecting young people, resembling multiple sclerosis, curiously associated with cirrhosis which could not be ascribed to either alcohol or syphilis because of the patients' ages.

In 1912 S.A.K. Wilson published a monumental monograph describing progressive lenticular degeneration as a familial, but not hereditary, disease affecting young people, invariably fatal within 6 months to 5 years. Early indications of an association with excessive metal deposits of metals, namely corneal Kayser-Fleischer rings and chemical analysis indicating elevated copper concentrations in tissues (Rumpel 1913) were not appreciated. However, after the demonstration of excessive concentrations of

copper in the urine (Mandelbrote 1948) and tissues of patients (Cumings 1948) copper-chelation therapy was introduced, first as painful injections of dimercaptopropanol (British Anti-Lewisite or BAL) and later as oral penicillamine (Walshe 1956) and trientine (1982).

A paradoxical discovery (Scheinberg & Gitlin 1952) of decreased concentrations of copper and ceruloplasmin in the plasma of most patients facilitated diagnosis and, in turn, led to early recognition and to prophylactic treatment of affected presymptomatic subjects. The introduction of zinc (Schouwink 1961) and tetrathiomolybdate (Brewer 1991) has broadened the therapeutic armamentarium. New challenges have surfaced since the cloning of the Wilson's disease gene

Selected Topics Regarding Wilson's Disease Including an Overview of Therapy

George J. Brewer, M.D.

My talk will have four areas: 1) Nutritional concerns; 2) Practical concerns regarding our U of M programs; 3) Overview of therapy; and 4) Potential projects for the WDA.

In the nutritional area we'll briefly discuss nutritional supplements and remedies, alcohol, when to take zinc related to food, dietary restrictions, and water testing.

Regarding our U of M programs, we have concerns about their sustainability given the present climate, and these concerns will be discussed.

Regarding treatment of Wilson's disease, we will try to put the "brave new world" in perspective, focus on the best drug treatments for the various phases of the disease, and how to decide on the best treatment.

Potential projects we suggest for the WDA include:
1) Solve the 24 hour urine copper/zinc problem;
2) Subsidize the Wilson's clinic in a meaningful way;
3) Help develop a single dose zinc; and 4) Black box penicillamine for initial neurologic therapy in the PDR.

A History of Wilson's Disease From a Patient's Perspective

Ann Hunter, M.A.

The history of the identification of Wilson's disease as a specific medical condition and the development of treatments for it began quite recently, in the late 19th century. At that time several different doctors published their observations of patients who were suffering from neurological symptoms that were probably caused by Wilson's disease. In 1912, Samuel Alexander Kinnear Wilson gave a name to the condition and identified it as a disorder that involves both the liver and the brain. Between 1908 and 1948, researchers gradually came to understand that the symptoms of WD were caused by copper. This breakthrough allowed them to begin shortly thereafter to develop treatments based on chelation of accumulated copper and prevention of additional copper from accumulating. An important breakthrough for patients with advanced liver disease was the development of successful liver transplantation therapy over the last few decades of the 20th century. In 1993, identification of the malfunctioning gene that causes Wilson's disease opened up possibilities for earlier diagnosis and additional treatments.

From the point of view of WD patients, there have been other important developments that are not usually discussed in articles on WD. These include the increased understanding of the wide variety of presentations of Wilson's disease and the development of facilities with expertise in working with the condition. Patients are also affected by the state of communication among physicians and researchers around the world, education of treatment providers, and the challenges of getting orphan drugs distributed to WD patients.

Wilson's Disease Association Annual General Membership Meeting Minutes

The 21st General Membership Meeting of the Wilson's Disease Association was called to order at 10:35 a.m. on May 2, 2004 by Mary Graper, President. Mrs. Graper presented the 2003 Annual Report and fielded questions from the floor. Proposed amendments to the current by-laws were presented and discussed. A motion to approve the by-laws as amended was made and seconded. A vote was called for and the by-laws were approved unanimously. Copies of the WDA bylaws are available upon request by contacting the WDA office.

The Executive Director and the current Board of Directors were introduced. Three members: Jeffrey Eckland, Henry Kaplan M.D. Esq., and Stefan Sandler were presented as candidates for re-election for a three year term. Two new candidates, Parichehr Yomtoob and Jean Perog were presented for election to the Board for an initial one year term. The membership was asked whether there were any other nominations from the floor; there were none. Printed ballots were distributed to all members in good standing, the votes were tallied, and all five candidates were elected without opposition. Mrs. Graper welcomed the newly elected Board members and thanked them for their willingness to serve.

Additional questions and discussion ensued. Closing remarks were made, and the meeting was adjourned at 11:15 a.m.

Mark Your Calendars

*The Next Wilson's Disease Association
Annual Meeting will be held in
Coral Gables, Florida
April 29 – May 1, 2005*

“Under Construction”

Justine Lemoine

"That which does not kill you only makes you stronger." I am living proof of and a firm believer in this philosophy. Although my construction of self began after a life-altering event two years ago, the images remain vivid in my mind. Much has changed in these two years and my physical, mental, emotional, and spiritual self has been under construction. Throughout these years I have been building and rebuilding my body, mind and soul and I believe that now, looking back, I have overcome an obstacle optimistically and successfully. I believe that I am now a unique individual, which is something that two years ago I never would have imagined I could be.

The symptoms started the summer before my sophomore year. That is when my journey of life experience really began. I was always moody and irritable which was unlike my normal, happy-go-lucky self. Most doctors would say that I was just acting as a typical rebellious or angry teenager would, but I had nothing to be angry about. My mom knew better though, so she insisted on getting second opinions. She is the person that I owe my life to because if it were not for her, I am not sure that I would still be here to talk about my obstacle.

During several occasions in my sophomore year, I would begin to feel faint and dizzy, my hearing would become muffled and my breaths shorter, yet that was always the extent of my symptoms. After a few other abnormal symptoms appeared, such as missed menstrual periods for a number of months, my mom was through with hearing the same answers; "Nothing is wrong with her."

As the brisk snowy winter came around my conditions seemed to be worsening. Migraines and sleepless nights were beginning to tear away at me. On top of everything else, I had my grades to worry about and it seemed as though the subjects that once came easily to me were now becoming extremely difficult. I feared my weekly five question quizzes and even worse, trying to reason angles and degrees on a geometry test. I had always been a good student and this concerned my mother. However, doctors continued to give my family lame excuses about what was going on inside my now weak and frail body.

March has always been a depressing month for me, maybe due to the fact that the damp, rainy days bring down my normally high spirits or that some twisted yet tragic experience always seems to take place then. Whatever the reason may be, March of 2002 seemed to be no different. I remember the wet and cold day clearly, the droopy slush and sleet hit the windshield of my parents' jeep as my mom and I made our way to the gynecologist's office. This was the day my mom decided she had enough and took it upon herself to

seek other professional answers about my conditions. As we walked in to the receptionist area the walls were filled with advertisements of different birth control methods and the ballet-pink walls gave the room a very feminine appeal. Teenage mothers and menopausal women filled the seats of the waiting room. "What am I doing here?" I asked myself.

I wasn't promiscuous, I was just a naïve fifteen-year-old girl who had not had a menstrual period in ten months. When we finally walked in to the exam room and met with the doctor she seemed to agree that I did not belong there. She recommended that we visit an endocrinologist and suggested that maybe I had a hormonal problem.

We called the endocrinologist and had an appointment within the first week. The receptionists were very friendly which helped me become more relaxed and gave me a good first impression, but then I met the doctor. The middle-aged man's strawberry blonde hair was balding and behind his glasses, his grayish-blue eyes looked as cold as ice. After asking a few personal questions and trying to perform an exam he had come to his less than scientific conclusion with not too much evidence to support it.

"Justine, after visiting with you I have come to the conclusion that you are going through menopause." I retorted back snappily, "I am fifteen, I can't be going through menopause at fifteen!"

"Yes, for this to happen is very rare but it can happen to some women," he continued on, "Now Justine, this does mean you won't be having kids." He began to preach to me about my options including in-vitro fertilization but I did not want to believe him. I was on the verge of tears when my mom came back into the office to hear the awful news. I tried to be strong while my mom found out she would never be having grandchildren. As soon as I climbed into the car, I lost control and my emotions took the best of me.

The next morning we received an interesting phone call from the secretary at the Endocrinologists office. She had called in private to tell us to seek out yet another professional opinion because she did not agree with the doctor. She suggested trying a hematologist at either Massachusetts General Hospital or Rhode Island's Hasbro Children's Hospital because she seemed to think what I had was blood related, not hormonal. It is because of this lady that we ended up discovering what was wrong with my body. After that it seemed that my journey for answers was well on its way.

My blood platelets had become abnormally low during this year and blood tests had shown they were down by

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(CONSTRUCTION, Continued from page 9)

one hundred thousand compared to most people. This worried my hematologist, Dr. Charlow. Numerous blood tests and urine samples narrowed my illness to three things: Lupus, Leukemia, or a very rare disease called Wilson's disease.

The hematology center is shared with the oncology section so what I saw during my visits there was heart wrenching. Frail boys and girls played around the reception area hooked up to IV's that made a spine chilling sound. Drip, drip, drip went the fluid into their fragile, tiny bodies as they received Chemotherapy treatment. This is where my outlook on life began to change and it is these fearless young children I have to thank. This is the point when my spiritual, emotional, and mental construction went well under way. I realized from that point on that I was a changed person; I was not scared anymore of my own illness. I wanted to do better in my life and not take anything for granted. Without their knowledge those brave children changed who I am today. They made me realize life is too short to take things for granted and they made me realize that being unique is one of the greatest gifts of life.

Unfortunately, I needed a liver biopsy because the hematologist had ruled out leukemia and lupus. I was now at the point where I had switched doctors and was now regularly visiting a liver specialist named Dr. Sharlon. A liver biopsy came out positive and my questions were finally answered. Wilson's disease is what I had the whole time. It is a build up of copper in your body that affects your liver, kidneys and brain. The doctor's told me that if not treated daily for the rest of my life, it would be fatal. However, I wasn't scared anymore because the little children opened my eyes to what life is really about.

Much changed over the next year. I transferred from Mount St. Charles Academy to Burrillville High School. It seemed as though the private school could not satisfy my needs any longer and changes needed to be made. I was put on heavy doses of medicine called Syprine to flush the copper out of my system, and on vitamin zinc to counteract the copper. Only 1 in 30,000 people share my disease with me. These statistics, I believe, are just another part of what makes me unique.

In an emotional sense I am happy that I have Wilson's disease. Besides making me unique it also made me realize not to take little things in life for granted. For example, I consider every day how lucky I am to get up every morning, go to school, and play sports like a normal teenager. For a while my physical self disabled me from taking part in these daily activities successfully. I have been building and rebuilding my physical, emotional, mental and spiritual self for over two years now and I believe that I have become a stronger person because of this. As I take the next step forward in my life and continue to rebuild my whole self I

will never forget the life lesson that the disease I have has taught me. My disease has become a part of who I am, a unique individual.

(DEBT, Continued from page 4)

the British doctor who discovered its existence and cause during the early 20th century, which became part of the medical curriculum for medical students in England.

Carol was immediately put on medication to rid her body of copper, the nemesis in Wilson's disease, and her progression was dramatic. She could now once again control her motor skills and her speech. Her recovery was close to complete except for some residual neurological symptoms and minor tremors.

The doctors who were now entrusted with Carol's care understood that Wilson's disease was a genetic disorder that could affect other children in our family. All of us children were tested and the three oldest tested negative while the three youngest (this includes Carol) tested positive for Wilson's disease. Carol was already on treatment so when the fifth child, Patsy, and I, the 6th child, tested positive we were immediately put on maintenance therapy medication.

Once Carol regained control over her life, she married and lived a relatively normal life until her death, from Cancer in 1996 at age 53. Carol paved the way for my other sister and me to be able to live normal lives. She was the 'guinea pig' who endured all the misdiagnosis and mistreatments over and over again, until by chance, the true diagnosis was so obvious to the young English optometrist.

My sister, Patsy and I, owe an immeasurable debt of gratitude to our sister Carol who paved the way for the normal lives we have been able to live to this day. We are forever grateful.

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However, with the exception of genetic analysis, no individual test provides enough information to prove the diagnosis. En masse genetic screening is currently impractical given the numerous mutations (greater than 60) already identified and a high frequency of compound heterozygosity among affected patients^{7,8}. While other genetic diseases are routinely screened for at birth, even those with lower prevalence, there is no definitive test for WD where no single test which establishes the diagnosis of WD. A study in 1997 conducted by Cauza et al, looked at levels of serum ceruloplasmin for predicting WD in patients admitted for evaluation of a liver disease. They found a positive predictive value of only 5.9%⁹ which is inadequate for mass screening.

Serum ceruloplasmin is reduced in 95% of patients with symptomatic disease⁹, but overall, ceruloplasmin may be normal in up to 30% of patients with WD^{7,10}. Thus, even in the absence of KF rings and a low ceruloplasmin, additional studies must be undertaken. A 24 hour urine copper should be collected (normal value: <50 g/24 hours; WD >100 g/24 hours) in a metal free container. False-positive elevations in urinary copper may be seen in the setting of significant proteinuria, rarely in other causes of liver diseases, and with ALF. A liver biopsy may be performed, if not contraindicated, for quantitative copper measurement (normal value: <50 µg/g dry weight tissue; WD >250 µg/g dry weight tissue), histology and rhodanine staining. False positives can occur in the setting of long standing obstructive liver disease¹¹. Ultrastructural study by electron microscopy (EM) should be performed when hepatic copper concentrations are equivocal in order to distinguish carriers from homozygotes. Molecular diagnostic testing is currently not commercially available, but may be obtained in the research setting.

Age of onset of symptoms is typically under 40 years of age, however recently, two siblings have been described as newly diagnosed in their seventies¹². Presentation may be chronic, acute on chronic, or acute liver failure (ALF), a progressive neurologic disorder with or without obvious hepatic involvement, and/or psychiatric illness. Such heterogeneity can make the diagnosis terribly elusive. According to the combined data of Walshe, Sternlieb, and Scheinberg, prior to 10 years of age, 83% of patients present with liver disease and 17% with neuropsychiatric symptoms. Between the ages of 10-18, 52% present with hepatic and 48% with neuropsychiatric symptoms. Over the age of 18, 24% present with hepatic manifestations and 17% with neuropsychiatric symptoms⁸.

WD should be strongly considered in: patients between the ages of 3 and 40 years old with liver disease of unknown origin; young adults with unusual cerebellar and extra pyramidal symptoms, atypical psychiatric disease and some evidence of liver disease or unexplained hemolysis; and in siblings and first degree relatives of already identified patients¹¹. KF rings are present in 98% of patients presenting with neurologic disease, but only in 50% in patients with liver presentation¹³. WD should be considered in any child with hepatomegaly, elevated serum transaminases or evidence of a fatty liver. Patients may have chronic or acute symptoms including anorexia, fatigue, nausea, and abdominal pain. They may have signs such as jaundice, abnormal coagulation studies, hepatosplenomegaly, low albumin, ascites and other findings secondary to portal hypertension from the development of cirrhosis¹⁴.

Copper accumulation in the brain is most common in the basal ganglia and cerebellum, but is not limited to these sites². Neuropsychiatric symptoms typically present in the second to fourth decades of life. Initial psychiatric findings may be quite subtle including depression, labile moods, and deteriorating academic performance. Motor disturbances include resting and intention tremors, micrographia, dystonia, and Parkinsonian symptoms¹¹. Approximately 95% of patients with neurologic symptoms also have KF rings¹³. Uncommon presentations of WD include: renal disease, cardiomyopathy, thyroid abnormalities, osteomalacia and arthritis, and sunflower cataracts¹.

Patients may even present in acute or fulminant liver failure, which accounts for approximately 5% of all cases of acute liver failure (ALF) in the United States². Patients with WD are often clinically indistinguishable from other patients with ALF. Only 50% will have Kayser-Fleischer (KF) rings and ceruloplasmin will often be in the normal or elevated range¹³. Patients with WD may be characterized by marked elevations in serum and urinary copper and Coombs negative hemolytic anemia.

This past year, I was involved in my own investigation with Drs. William Lee and Michael Schilsky and the Acute Liver Failure Study Group¹⁰. We compared screening tests for WD in the setting of ALF in 138 subjects. We confirmed that low serum ceruloplasmin in the setting of ALF predicted the presence of WD with a sensitivity of only 20% or 60% by oxidase assay or nephelometry, respectively. By contrast, a ratio of alkaline phosphatase to total bilirubin (AP:TB) less than 4 is 86% sensitive and 96% specific for WD in this setting. Similarly, a high serum copper was found to be only 73% sensitive. The recognition of the AP:TB ratio being predictive of WD is significant since these are standard tests for liver disease used in all patients, while copper and ceruloplasmin are evaluated only when WD is suspected. Although patients with ALF due to WD require urgent liver transplantation, failure to recognize WD as the underlying cause of ALF precludes the screening and diagnosis of family members with the disease prior to the development of symptoms.

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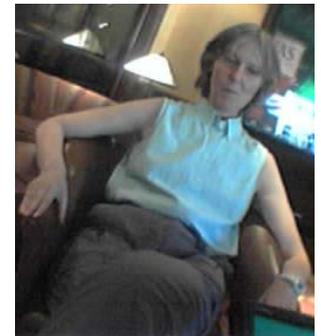
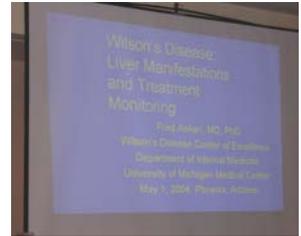
Though patients who present in ALF are a small minority of individuals with WD, the possibility of such an extreme manifestation of the disease underscores the need for new methods of early detection. We must allot resources towards improved genetic analysis, but in the interim, education and outreach should be actively promoted. Because there is no single best test for WD, select populations should be the focus of our efforts. Initially, liver transplantation centers should be targeted as a large population of patients with cryptogenic liver disease might be a suitable group for WD screening. We must initiate educational outreach programs to professional societies. Ophthalmologists should be trained in diagnosing KF rings on corneal exam. Pediatricians should be adept at recognizing the myriad of manifestations of WD. Psychiatrists, who often screen for liver abnormalities when prescribing medications, should be educated about the neuropsychiatric presentations. Gastroenterologists especially, must be trained to diagnose WD in its earliest stages as they might be consulted for liver enzyme abnormalities discovered by a general practitioner.

Investigations into cost-effective population screening in the pediatric population, similar to lead poisoning screening should be initiated. If a genetic disease such as homocystinuria, with an incidence of 1 in 100,000 live births is screened for in most states, then why not WD? Serum ceruloplasmin, although not sensitive, might be specific. Patients testing positive, can undergo a 24 hour urinary copper test to further narrow the diagnosis. False positives can be ruled out by a penicillamine challenge¹⁵. Of course, a cost-benefit analysis of any type of mass screening must be performed. Factors such as the cost of chronic liver disease, liver transplantation, varying degrees of neuropsychiatric disease, lifelong treatment, follow-up care, loss of productivity, and even death must be weighed against the cost of screening as well as the cost of false-positive results.

Perhaps in the future, with improvements in DNA analysis, we can develop better methods of mass genetic screening for the entire population. Then, all patients with WD will be identified early, when treatment is simple, effective, and life saving.

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