volume 3, winter 2004

LATE BREAKING news

from the **National Wilms Tumor Study**

Greetings from Seattle, the Emerald City

We hope that all of you who are participating in the Late Effects Study are filling out our forms, including the Pregnancy Questionnaire. For the first time since 1969 we are not conducting a clinical trial protocol (treatment study). The Children's Oncology Group (COG) will be doing this in the near future. This means that we will be concentrating exclusively on the Late Effects Study. Our plan is to put all our efforts into documenting and analyzing pregnancies and adverse late effects. This should improve our understanding of the therapies that have been employed and therefore help the COG develop better treatments. Again, thanks to **all** of you for helping us do this.

Thank you to everyone who sent comments, questions and suggestions regarding our first two newsletters. We have included in this edition some articles based on your input. We hope this newsletter continues to be helpful, and as always we welcome comments and suggestions. We are pleased to report that we now have some forms available in Spanish (please see box below). And finally we express great appreciation for the time you take to complete and return our forms.

Do You Speak Spanish?

Would you or someone you know prefer to receive our forms and documents in Spanish? We now have several of our forms available in Spanish. We regret that limited funding prevents us from having the newsletter translated. If you would prefer to receive these versions, please let us know. You can contact us by email **nwtsg@fhcrc.org** or leave a message on our toll-free message line, **1-800-553-4878**. There is now a Spanish option on this line. If you leave a message in Spanish, we will have a Spanish speaker return your call. We are pleased we can provide these services for our Spanish-speaking participants.

¿Habla Español?

¿Prefiere usted o alguien que usted conoce recibir nuestros formularios y documentos en español? Ahora tenemos varios de nuestros formularios disponibles en español. Lamentamos que la limitación de fondos nos impida hacer la traducción al español del boletín informativo. Si prefiere recibir estas versiones, avísenos por favor. Nos puede contactar por medio del correo electrónico en **nwtsg@fhcrc.org** o puede dejar un mensaje en nuestra línea gratuita llamando al **1-800-553-4878**. Ahora hay una opción en español en esta línea. Si deja un mensaje en español, una persona que habla español le devolverá la llamada. Nos complace poder proprorcionar estos servicios para nuestros participantes de habla hispana.

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Meet the Late Effects Study Staff

Before joining the Data and Statistical Center (DSC) in October 1997, Yevgeny (Gene) Grigoriev, MD, PhD, practiced internal medicine and nephrology for 25 years in his hometown, St. Petersburg, Russia, where he was an associate professor in the Medical Academy of Postgraduate Studies. There he conducted lectures, seminars and discussions, teaching students and physicians in continuing education. As part of the DSC staff, Gene has focused most of his time and effort on the fifth NWTS clinical trial: maintaining the data, answering data managers' questions on the phone, requesting and coding data. He has registered over 580 patients onto the clinical study, recalling, "In one working week I had registered 20 patients—an incredible record-breaking number!" Recently, Gene's efforts have included taking on new Late Effects activities such as finding participants for whom we don't have addresses, and documenting reports of late effects, while continuing to diligently code data and answer frequent calls to the main NWTS phone line. Gene especially enjoys being able to talk with people in the health professions on the phone, providing information or helping to retrieve important data.

Natalia Grigorieva, MD, has been part of the DSC team since November 2001. As Program Assistant she likes everything about her job. She says, "Here, I strive to help everyone and welcome the opportunity to learn new things and take on new projects." Natalia processes mail, maintains and updates the NWTS filing system and library. She has also been actively involved with the congenital anomalies and surgical projects as well the pregnancy project. Also a physician, Natalia's field of study is neurology. As chief of a neurology department in a city hospital in St. Petersburg, Natalia's work in administration involved supervising others and helping patients who were suffering from various neurological disorders. Her hobbies include cooking and gardening as well as sharing Gene's great enthusiasm for the arts.

In their leisure, both Gene and Natalia enjoy all kinds of art. They love opportunities to attend live performances whether they are the symphony, opera, ballet or theater. In the 5 years they have been Seattle Art Museum members, they have never missed an exhibit. During holidays they are very happy to visit with their daughter Annie, who is following in the footsteps of her parents, by attending Medical School at Ohio State University. Meeting at Medical University in St. Petersburg over 40 years ago, neither Gene nor Natalia imagined their work would bring them to Seattle. "Seattle is our home, and so is the DSC. Here our staff is committed to working together, helping others, and advancing research while regarding the interests and backgrounds of each employee." Both share a great enthusiasm for working with the DSC. "We feel very comfortable here and look forward to our work every day. Working here is like being part of a family as it brings us reward and has broadened our lifestyle." In March of 2004, Natalia and Gene will celebrate their 35th wedding anniversary.

Contact Us!

How should you give us your new address and phone number if you move? If you move, please call the project line at **1-800-553-4878**.

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Reaching Out, The WAGR Network

Fewer than 1% of children diagnosed with Wilms tumor have Wilms tumor as part of the WAGR syndrome. Parents of children with WAGR have created a support group, called Reaching Out, The WAGR Network, and a web site **http://www.wagr.org**. The following is an interview with Catherine Luis, whose daughter, Irma, has WAGR syndrome. Catherine and several other parents created this important support group.

Catherine, you and Kelly Trout started a support group called "Reaching Out, The WAGR Network." What motivated the creation of the group and the web site?

The group actually began with a little newsletter that was started by June Kuntze in Minnesota who found a couple of other WAGR families. Another mom, Annie Prusakiewicz, in Michigan took over the newsletter and expanded it. Kelly started an email discussion group, and I set up the web site. At that time, we had all of seven families in the group! WAGR syndrome really is quite rare, so the web site really helped other families to find us. Currently we have 68 families in the group, in 11 different countries (the United States, Canada, Australia, England, France, Germany, Greece, New Zealand, the Philippines, South Africa and Croatia)! So really, a number of parents "started" this group. We have all suffered in some way from the lack of information about this disorder, so we are all very motivated to help each other to help our kids. One great thing is that in addition to parents, many other people are also accessing our web site; physicians, therapists and students are using it, too. We're continuing to work on it to keep it up-to-date and user friendly for anyone interested in information on WAGR syndrome.

Please let our readers know what WAGR syndrome is:

WAGR syndrome is a rare genetic disorder. "WAGR" is an acronym. It stands for Wilms tumor, Aniridia (having no iris, the colored part of the eye), Genital or urinary tract abnormalities (like undescended testicles), and mental Retardation. Children with WAGR syndrome usually have at least two of these conditions. WAGR syndrome is associated with a defect in a certain part of a chromosome technically identified as 11p13. No one knows what causes this genetic defect.

Most children with WAGR syndrome are diagnosed at birth, or shortly after, because the aniridia is usually obvious. But thorough genetic testing (including a special test called the FISH probe) is important, because the other signs may not be present or obvious. If a child has two of the characteristics, such as aniridia or genital abnormalities or developmental delay, then screening for the presence of a Wilms tumor is recommended.

What difficulties do children with WAGR syndrome face?

Well, most kids with WAGR syndrome have some degree of vision impairment, although they often have a lot of functional vision. Aniridia can be complicated by cataracts or glaucoma, and these can cause further vision loss, so it's important for them to be followed by a pediatric eye doctor. More than half of the children with WAGR syndrome will develop Wilms tumor, usually at an earlier age. This is another reason why close follow-up is important, because it allows for early diagnosis. Treatment for Wilms tumor is difficult not only for the child with WAGR syndrome, but for the entire family. The good news is that most of our children are long-term survivors.

Many kids with WAGR syndrome also have mental retardation or developmental delay. In some cases, there may be behavior disorders, such as Attention Deficit Disorder (ADD), Attention Deficit and Hyperactivity Disorder (ADHD), and Autism or the so-called Autism Spectrum disorders.

Do WAGR children need special education?

Special education is a big issue for our families. Early intervention services, which are designed to help infants and young children cope with vision impairment and developmental delay, can be extremely helpful. Appropriate special education throughout their school years can make a huge difference for these children.

Do these children develop kidney problems?

In the last couple of years, we have become aware of another risk for kids with WAGR syndrome. The National Wilms Tumor Study Group found that older children with WAGR syndrome may develop kidney failure. In our group, about 60% of those over age 12 have some degree of renal failure, and five of them have had kidney transplants.†

What resources do you provide to families with children diagnosed with WAGR?

The wagr.org web site includes a "Just Diagnosed" parent information packet designed to explain the

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disorder in detail. The web site also has lots of information about how to get good medical care, and access to government agencies and special education. We publish a quarterly newsletter that has medical news and profiles of families and kids. We have an email discussion group that is really lively; parents find it is a great place to talk about everything from coping with cancer to where to get good quality sunglasses for babies.

We also offer assistance to professionals. Physicians often contact us for information about genetic testing, and our web site has a checklist of Guidelines for Health Supervision of Children with WAGR Syndrome. We're also working on a booklet now, called, "WAGR Syndrome: A Guide for Parents and Professionals." We hope to complete it sometime in the coming year.

What do you think is the greatest asset of the network?

Families! Moms and dads, grandmas and aunts and friends, we are all inspired by our precious kids and their desire to overcome their tremendous challenges. We're driven to help them and to help each other. Without each family's willingness to share there would not be a network. "New" families (those who have a new baby, or those who've just found out about us) often say that connecting with others is what helps them most. Our other great strength is that there are so many of us now. By getting together we really can make a difference for our kids.

What more can be done to find out about WAGR? You have conducted some surveys of your families. If these were expanded to be more scientific, would this be valuable to your families?

WAGR syndrome is so rare that the primary information about it in the medical literature has been case studies (reports of a single case or two). When the families began to communicate with each other, we found that our children had many things in common that had never been reported. So we drew up a list of health questions for parents to complete. The results of this survey told us a lot about what kinds of conditions to look for as well as some important ways to help our children.

The survey taught us that gathering this information is not only valuable--it's vital. We are constantly looking for ways to support and expand the research that will help our kids.

Your fourth annual WAGR Weekend is scheduled for next June. Please tell us what activities are being planned.

Our WAGR Weekends are just fun, informal gatherings where we finally meet each other in person. It's wonderful to spend time with other families who know just what your life is like. And meeting each other's children is the greatest! Our kids with WAGR get to meet other kids who are "just like me," and their siblings get to see that they're not alone either. For many families, it's a rare opportunity to just relax. The 2004 WAGR Weekend will be June 25-27, in Gatlinburg, Tennessee.

Your daughter Irma is now in high school. How is she doing?

She's thriving! What I've learned is never to say never. She attends a vocational technical high school in New Jersey. This is a wonderful place where she continues honing her academic skills and is learning different job skills to prepare her for entering the workforce. She loves this school and has never been happier.

† **Reference:** Breslow NE, Norris R, et al: Characteristics and Outcomes of Children with the Wilms Tumor-Aniridia Syndrome: A Report from the National Wilms Tumor Study Group. J. Clin Oncol 21: 4579-4585, 2003.

Are There Any Internet Chat Rooms the NWTS Can Recommend?

We have been asked this question a number of times. We have also received recommendations from participants for rooms that they have found to be very helpful. Unfortunately our organization cannot make any recommendation, as this would be seen as an endorsement of the site and all of its contents. Some contributions to chat rooms can be misleading or incorrect, and sound advice about your health and medical care is important, so we cannot endorse a source of information that may steer you in the wrong direction.

We are not discouraging you from finding helpful and supportive chat rooms. Many people do find these to be important sources of information and advice. Any recommendations regarding medical treatment should be reviewed with your doctor first. If you are looking for reliable sources of information, please check the links posted on our web site **www.nwtsg.org**.

Let Us Introduce You to Dr. Audrey E. Evans, Inspiration for the First Ronald McDonald House

Dr. Audrey Evans is a founding member of the National Wilms Tumor Study. She was born and educated in England and came to the United States as a Fulbright Fellow in 1953. For her entire career she has worked hard to provide each of her patients with the best treatment possible while steadily and consistently advancing the cause of all children with cancer. During her years of patient care she noticed that the patients' parents often also needed help, and Dr. Evans dreamed of providing temporary housing for families while their children received treatment.

In 1969 the three-year-old daughter of a professional athlete was treated for leukemia. Her parents camped out on hospital chairs and ate makeshift meals from vending machines. They noticed that other families did the same, and many who had traveled from great distances to seek treatment could not afford hotel rooms. They rallied support from teammates and, working with Dr. Evans and the local McDonalds restaurant chain, they established the first Ronald McDonald House in 1974 in Philadelphia. By 1979, ten more Houses had been opened, and today there are 212 Ronald McDonald Houses in 20 countries around the world. We are proud to have been long associated with an NWTS Committee member responsible for bringing such a significant contribution to the families of children with cancer.

Dr. Evans has dedicated her career to helping treat children with cancer. In the early years of clinical research, while living in Boston, Dr. Evans was responsible for some of the first trials of what are today's leading chemotherapy agents such as dactinomycin and vincristine. In addition, she developed the Evans Staging System that describes a system for staging neuroblastoma and helps design appropriate treatment based upon the stage. In 1969 Dr. Evans became the head of Pediatric Oncology at the Children's Hospital of Philadelphia (CHOP) and founded the now world-renowned Children's Cancer Research Center for patient care and research.

Because of her excellent and compassionate care of sick children and their families and her significant contributions to pediatric cancer research, Dr. Audrey Evans has been recognized with many awards. In 1976 she was presented the prestigious Janeway Medal of the American Radium Society. In 1989 her many admirers initiated a drive that established the Audrey E. Evans Chair in Pediatric Oncology at CHOP. In 1994 Dr. Evans shared the National Humanitarian Award with former First Lady Barbara Bush. Dr. Evans was also presented with the Sara Lee Foundation Frontrunner Award in the Humanities in 1995.

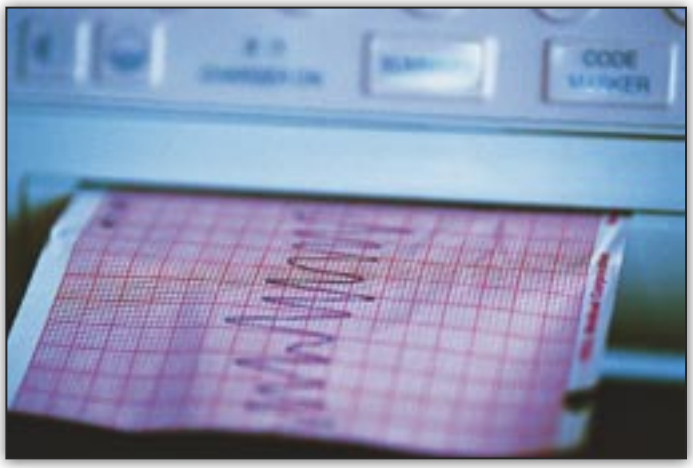
But, in the end, of all her many honors Dr. Evans has received, she is most rewarded by being able to help her many patients and their parents.

Can I Donate Blood?

A number of people asked us this question. In researching the answer we discovered that the American Red Cross (ARC) has rules that govern the circumstances under which people can donate blood at their facility, and your local blood bank however may not be governed by the ARC but by your state. Each state has its own rules governing the circumstances people can donate blood, and these may not agree with those of the ARC. Please check with your family physician or health care provider to determine if there are any factors that would prohibit you from donating blood.

The Story of Dactinomycin

by Giulio J. D'Angio, MD



Many of the major advances in science have been made serendipitously. What this means is that efforts directed towards one objective accidentally found something quite wonderful on the way. Columbus's discovery of America is an example. This can happen in science as well; for instance, the discovery of x-rays by W. Roentgen. While doing experiments in a darkened room, he noticed that a bit of paper covered with a certain substance glowed when he turned on his apparatus, and stopped glowing when it was turned off. This was a completely surprising phenomenon; and he reasoned that there were penetrating rays coming from the apparatus he was using. He did not know their nature and therefore called them "x-rays" meaning an unknown kind of ray.

Now about dactinomycin. In 1940, Selman Waksman, a professor at Rutgers University was trying to isolate antibacterial substances from melon molds that he was growing in his laboratory. This was an outgrowth of the serendipitous discovery of penicillin which also came from a mold.

Working with H. Boyd Woodruff of the Merck and Co. laboratories, Professor Waksman isolated a series of compounds that he called the "actinomycins" named after the type of mold he was growing. He found that these substances were extremely toxic to the mice in which they were tested. He noted his observations and closed the file because he believed the actinomycins to be too toxic for use in humans. In 1952, an investigator in Germany named Hackmann looked through the Waksman and Woodruff files, and noted that the experimental mice reported by them had small thymus glands and spleens. These organs are packed with lymphocytes, one of the components of the white blood series. Hackmann reasoned this was because the actinomycin compounds destroyed the lymphocytes. He further reasoned that if the chemicals killed normal white blood cells (lymphocytes), they might do the same for malignant white blood cells; namely leukemia.

The substance was included in the animal screening tests then being run in Washington at the National Cancer Institute. It was found not to be effective against the types of cancer used in the animal models that were included in those screens, those cancers being the kind that grow in adults. Childhood cancers are different, so actinomycin D, one of the series, was sent to Dr. Sydney Farber of the Boston Children's Hospital in 1955. It was immediately found to produce remissions in children with Wilms tumor! This was the birth of effective chemotherapy for the "solid tumors" of childhood like Wilms tumor; that is, the malignant diseases not originating from blood elements, such as leukemia. It was soon tested in children with various malignant diseases, and the first responses in other childhood "solid tumors" such as rhabdomyosarcoma, a muscle tumor, were soon recorded.

Also serendipitous was the observation that dactinomycin (as it has since been named) acted with radiation to produce reactions in normal tissues at much lower doses than when x-radiation was used alone. Studies showed that this combined effect was true not only in normal cells but also within cancer cells.

Thus, starting with a mold grown in a biology laboratory in the hope of finding a substance that would fight infections, there resulted one of the most useful chemotherapeutic agents in pediatric oncology. It was discovered through a series of chance observations. The important point is that an alert eye and a prepared mind used the information obtained serendipitously and directed that information to the fight against cancer.

The Genetics of Wilms Tumor

by Vicki Huff, PhD, Molecular Biologist

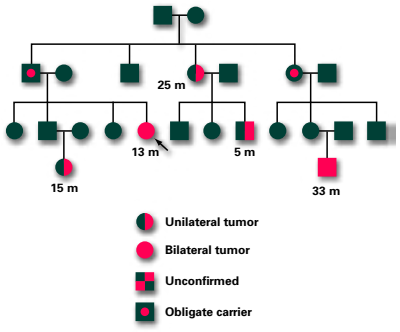
The development of Wilms tumor is thought to involve changes in a number of genes that normally function to control normal kidney development and growth. Cells that sustain alterations in these genes may multiply, develop abnormally, and accumulate additional genetic changes, ultimately resulting in a Wilms tumor. Understanding what genes have been altered in Wilms tumors will greatly aid in understanding how cancer develops, how kidneys normally develop, and how best to treat patients with Wilms tumor.

There are many approaches for identifying changed genes found in Wilms tumor. One way is to study the tumors themselves. However by the time a tumor is detectable it has sustained many genetic changes, and it is sometimes difficult to identify which changes were critical to the development of the tumor. Another approach for identifying Wilms tumor genes is to study people who have an inherited predisposition to Wilms tumor.

The vast majority of Wilms tumors are not due to an inherited genetic alteration, but rather develop as a result of genetic alterations that occur in just a few cells in the body (i.e., somatic alterations). However, roughly 2% of children diagnosed with Wilms tumor have a relative who was also diagnosed with Wilms tumor. Families with two or more Wilms tumor patients are considered Wilms tumor families. The occurrence of these rare Wilms tumor families suggests that the Wilms tumor patients in these families have inherited an altered gene that is important in the development of Wilms tumor. This altered gene alone will not result in a Wilms tumor; other genetic changes also have to occur. Some individuals may inherit a predisposition gene, but never develop Wilms tumor. However, the identification of that inherited altered gene will identify one critically important step in the path to tumor development.

To date, only one Wilms tumor gene called WT1, has been identified. WT1 is mutated in roughly a fifth of all Wilms tumors. Inherited WT1 alterations have also been observed in a few small Wilms tumor families, but studies of large Wilms tumor families have demonstrated that their inherited predisposition is not due to an altered WT1 gene. More recent studies have localized two familial predisposition genes, one to chromosome 19 and one to chromosome 17, but the actual identification of these two predisposition genes is still being determined. It is also known that predisposition in some families is not due to WT1 nor to the chromosome 19 or 17 genes, implying that other WT predisposition genes exist.

Hypothetical Wilms Tumor Family



The goal of the Familial Wilms Tumor Study is to identify genes that predispose individuals to Wilms tumor and to understand the function of those genes. Analysis of DNA from members of Wilms tumor families can help us localize more precisely the predisposition genes, a first step in the process of identifying the genes. The most important people to study in these families are those who have been diagnosed with Wilms tumor, their parents and any other family members who are the genetic "link" between the Wilms tumor patients. Further analysis of DNA from patients can help us determine if a particular gene within a localized region is, in fact, a predisposition gene. Since these genes likely will play a role in non-familial cases of WT also, this work will help in understanding the development of Wilms tumors in general.

GLOSSARY:

Gene alteration, gene mutation: A change in a gene that changes its function and may result in disease.

Inherited/familial predisposition genes: Altered genes that are present in the germ cells (eggs or sperm) and therefore can be passed through the generations, from parent to child. When an individual inherits a predisposition gene, all cells in their body carry that gene alteration, and the individual is at an increased risk of developing a particular disease.

Somatic alterations: Gene alterations that occur in non-germ cell DNA. This type of genetic alteration cannot be passed from parent to child since it has not occurred in an individual's egg or sperm cells. This type of alteration will be present in only some of the cells in the body.

Localized region: A small, unique part of the DNA in a cell that has been identified as being the location of a disease-causing gene alteration.

Non-familial: Wilms tumor not due to an inherited predisposition gene alteration.

A Celebration of Gratitude

A community in Glenview, Illinois, came through for Lilly Ludwig's family when Lilly was diagnosed with Wilms tumor in 2002. Neighbors helped with childcare and support for Lilly's brother Atticus and sister Grace. Their church organized meals for them, as did neighbors and members of Lilly's daycare center. This outpouring of help "truly depicts what the sense of community means in Glenview," observed Lilly's mother, Judy Zimmerman. To thank all these friends and neighbors and to celebrate Lilly's recovery Zimmerman hosted a **Celebration of Gratitude** on February 1, 2003. Lilly's family was thoughtful to also use this event as a way to raise funds for the NWTS.

Our office in Seattle was also especially grateful for the pictures of Lilly we received. We have a bulletin board in our office on which we post pictures sent to us over the years. Lilly's has added an additional special smile to our board. Do you have an extra photo of you or your family you would like to send us? We would love to have more to post. These are heartwarming reminders of why we do what we do.

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