Diabetes Mellitus
by Yevgeny Grigoriev, MD and Giulio D’Angio, MD

Diabetes mellitus is the most common cause of kidney failure, blindness and lower limb amputations and is a major cause of heart disease and stroke in adults. It is a group of diseases characterized by high blood sugar levels (hyperglycemia) from defects in insulin production, insulin action or both. Nearly 21 million people in the United States—7% of the population—have diabetes.

THE THREE MOST COMMON FORMS OF DIABETES MELLITUS ARE: TYPE 1, TYPE 2, AND GESTATIONAL DIABETES.

Type 1 diabetes was formerly known as insulin-dependent diabetes, childhood diabetes, or juvenile onset diabetes. It is an autoimmune disease that results when the body’s immune system turns against a part of the body. In diabetes, the immune system attacks and destroys the insulin-producing beta cells of the pancreas which then produces little or no insulin. A person who has type 1 diabetes must take insulin daily to live. At present it is not known exactly what causes the body’s immune system to attack the beta cells, but genetic and environmental factors, possibly viruses, may be involved. Type 1 diabetes accounts for about 5 to 10% of cases in the US. It develops most often in children and young adults but can appear at any age. Symptoms of type 1 diabetes may develop suddenly. They include increased thirst and urination, constant hunger, weight loss, blurred vision, and extreme fatigue. If not diagnosed and treated with insulin, a person with type 1 diabetes can lapse into a life-threatening diabetic coma, also known as diabetic ketoacidosis.

Type 2 is the most common form affecting about 90 to 95% of those with diabetes. This
form of the disease is most often associated with older age, obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity, and certain racial backgrounds. Notably about 80% of people with type 2 diabetes are overweight. When this type of diabetes is diagnosed, the pancreas is usually producing enough insulin, but for unknown reasons the body cannot use insulin effectively, a condition called insulin resistance. After several years insulin production decreases. The result is the same as for type 1 diabetes—glucose builds up in the blood and the body cannot efficiently use it. The symptoms of type 2 diabetes develop gradually, unlike the sudden onset of type 1. Symptoms may include tiredness, frequent urination, increased thirst and hunger, weight loss, blurred vision, numbness and tingling in the feet or legs. Slow healing of wounds and sores is another feature. Some people have no symptoms. Type 2 is initially treated by changes in diet and through weight loss. This can restore insulin sensitivity, even when the weight loss is modest, e.g. around 5 kg (10 to 15 lb). The next step, if necessary, is treatment with oral antidiabetic drugs: the sulfonylureas, metformin, or thiazolidinediones. If these fail, insulin therapy may be necessary to maintain normal blood glucose levels.

Gestational diabetes mellitus (GDM) is a form of glucose intolerance that occurs during pregnancy. It affects about 7% of all US pregnancies annually, resulting in approximately 200,000 cases a year. It is temporary and fully treatable, but if untreated it may cause problems with pregnancy, including macrosomia (high birthweight) of the child. It requires careful medical supervision during pregnancy. After delivery, 5-10% of women who had GDM continue to have type 2 diabetes. Women with a history of GDM have a 20-50% chance of developing diabetes in the future, and their children are at increased risk for obesity and diabetes during childhood and adolescence compared to other children.

Diabetes mellitus is diagnosed by demonstrating any one of the following:

1. Fasting plasma glucose level at or above 7.0 mmol/L (126 mg/dL);
2. Plasma glucose at or above 11.1 mmol/L (200 mg/dL) two hours after a 75 g glucose load; or
3. Symptoms of diabetes and random plasma glucose at or above 11.1 mmol/L (200 mg/dL).

**PREDIABETES**

This is defined as either impaired fasting glucose or impaired glucose tolerance.

Patients with fasting sugars between 6.1 and 7.0 mmol/L (110 and 126 mg/dL) are considered to have “impaired fasting glucose” and patients with plasma glucose at or above 140 mg/dL or 7.8 mmol/L two hours after a 75 g oral glucose load are considered to have “impaired glucose tolerance.” The latter in particular is a major risk factor for progression to full-blown diabetes mellitus as well as cardiovascular disease.

**SUMMARY**

Diabetes is a treatable but not curable chronic disease. The emphasis is on managing short-term as well as long-term diabetes related problems. The patient’s understanding and participation is vital as blood glucose levels change continuously. Treatments that return the blood sugar to normal levels can reduce or prevent complications. Other health problems that might accelerate the damaging effects of diabetes are smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise. Thus, good health habits are important for everyone. They are even more so for those cured of a childhood cancer like Wilms tumor who may already have partially damaged organs like the kidney, heart or liver secondary to the curative treatments they received.

The patient’s understanding and participation is vital.
Most patients who undergo treatment for childhood renal tumors undergo a nephrectomy. As a result, these patients are left with one kidney or half of their functioning kidney tissue. A very small percentage of patients have tumors in both kidneys and some of these children have even less remaining renal tissue after surgical interventions. One concern for patients undergoing treatment of renal tumors is the long-term effect on kidney function.

When physicians speak of kidney function they normally refer to the glomerular filtration rate (GFR). This is a test that can accurately measure the level of the kidney function. In most patients who have the kidney removed, the glomerular filtration rate by the remaining kidney will increase. This is a process of compensation in which the solitary kidney makes up for its missing mate. The adaptive response by the kidney is both beneficial and potentially harmful.

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The main function of the kidneys is to filter the plasma and to eliminate waste products. A normal solitary kidney can usually handle this task very well. Another function of the kidney is to help regulate the blood pressure. The kidney helps regulate salt excretion. It also produces some hormones that can affect blood pressure.

In addition to the surgical effects of removing kidney tissue, the treatments for childhood renal cancer can affect kidney function. Some chemotherapy agents can injure the kidney. This can occur temporarily but can also be permanent. Radiation therapy that may be needed to treat the cancer can also affect kidney function particularly if the remaining kidney was included in the radiation field. The effect of radiation is very dependent on the dose of the radiation therapy used. Fortunately, fewer patients currently being treated for Wilms tumor receive radiation therapy; those who are irradiated are given lower doses than in the past.

Overall, the incidence of overt renal failure where patients require active treatment for inadequate kidney function is very low, less than 1%. Patients who have treatment for a single renal tumor in one kidney rarely develop late renal failure. The rate is higher in those with tumors in both kidneys. In addition, some particular patients are at increased risk. These include children with certain genital anomalies or rare syndromes such as aniridia or the Denys-Drash syndrome. These latter patients have an inherent risk for renal failure due to an inherited specific disorder of the kidney.

All patients who undergo treatment for Wilms tumor should have long-term follow-up including annual measurements of blood pressure and urinalysis and blood test to assess kidney function. If there is elevation of the blood pressure, then prompt referral to a nephrologist, that is a kidney specialist, is warranted. Early intervention to lower blood pressure can prevent progression of kidney disease. Likewise, measurement of protein in the urine is extremely important because this a first sign of kidney failure. Again, referral to the nephrologist and early active treatment is recommended. The nephrologist may make specific recommendations regarding diet and avoidance of other risk factors that may affect kidney function.

Additional information can be found at the Children’s Oncology Group (COG) website. The COG has developed guidelines for follow-up of children treated for childhood cancer. These are risk-based, exposure-related recommendations for the identification and management of late effects due to therapies used for childhood cancer. They are designed for asymptomatic survivors presenting for routine medical follow-up two or more years after completion of cancer therapy. Patient education materials called “Health Links” accompany the guidelines; both the guidelines and Health Links can be downloaded from www.survivorshipguidelines.org.
Meet NWTS Chairman Daniel Green, MD

Dr. Daniel M. Green was born in Seattle, but has lived most of his adult life on the East Coast. After graduating from The Massachusetts Institute of Technology (MIT) in 1969, he went to the St. Louis University School of Medicine. He there was elected to the national honorary medical society, Alpha Omega Alpha, and attained his M.D. degree with honors in 1973. His subsequent medical training took him back to Massachusetts for five years, first as an intern and then resident in Pediatrics at the Boston City Hospital followed by a Fellowship at the Boston Children’s Hospital Medical Center in Hematology/Oncology.

His entire career thereafter has evolved in Buffalo, New York at the Children’s Hospital and the Roswell Park Cancer Institute, where he is the Professor of Pediatric Oncology. He is a man of extraordinary energy and matchless efficiency, perhaps reflecting his MIT education. Every minute matters. Precision and productivity are paramount.

An active clinician who treats children with cancer, he is also much in demand as an investigator, consultant and lecturer. To cite one example, he lectured in eight California institutions in five days as part of a program sponsored by the American Cancer Society. Dr. Green has been elected to highly responsible positions on national and international professional societies. These include the American Academy of Pediatrics, where he has been a member of the Executive Committee and Secretary-Treasurer; and the International Society of Pediatric Oncology where he was the re-elected Secretary General for two terms. He has in addition served on innumerable administrative and scientific commissions and committees for organizations in Buffalo, North America, and beyond our shores.

His contacts with the NWTS started during his time as a Fellow in Boston. One day, Dr. D’Angio, then the NWTS Chairman, received a letter from him asking for detailed data concerning a certain sub-set of patients. It was clear it had been written by someone with much more than a casual interest and knowledge of the issues involved. The letter left a lasting impression, so Dr. Green was made welcome when—years later—he volunteered to attend NWTS Committee meetings. It quickly became obvious that Dr. Green was deeply committed to answering the NWTS research questions being addressed. In 1991, he was the clear choice to succeed Dr. D’Angio as Chairman, a post he held with dedication and total commitment for 8 years during which time the 4th and 5th NWTS clinical studies were conducted. An important component of the 4th clinical study was based on observations concerning the efficacy of single dose chemotherapy Dr. Green made during his trainee years.

His association with the NWTS also gave him many opportunities to visit Seattle, the city of his birth, where the Data and Statistical Center (DSC) is located. In addition to attending committee meetings, he often visited the DSC to work with the data. Members of the DSC staff have always looked forward to his visits.

Dr. Green has long been intensely interested in the late complications of successful therapy given to children with cancer. He has written or co-authored many papers as well as two books on the subject. As a world-recognized authority, he has organized nine of what have become internationally-famous biennial late effects conferences. Dr. Green is a prolific author, and has published more than 200 articles, abstracts, books and book chapters during his career. These encompass the wide field of childhood cancers, not just Wilms tumor.

Dr. Green is direct in manner, tall, trim, and stays that way through regular visits to the gym to work out. He and his wife Lydia enjoy the theater, but his abiding hobby is tracing his family’s origins in Eire. Whenever in the vicinity of the Emerald Isle, he tries to find time to peruse county and village records, looking for entries concerning the Green family and its progenitors. One can only imagine the many adventures such a quest entails.

A devoted family man, he never fails to find time in an extraordinarily busy schedule to participate in family outings and school affairs. He recently drove 2500 miles in a few days. First, he took his son to an ice hockey event in New England; from there he drove to South Carolina to help his daughter pack-up at the end of the school year before returning to Buffalo.

He is a true philanthropist, and served on more than one board dedicated to advancing the welfare of children in the Buffalo region. Moreover, he has been a big booster of the city, and—as a volunteer—devoted time and attention to the bureau responsible for promoting its image. He recently moved—no doubt with a pang—from Buffalo to Memphis, TN to join the epidemiology team at the St. Jude Children’s Research Hospital.

Dr. Green brought much to the NWTS. His tenure as Chairman was marked by rigorous scholarship, accurate data collection, and high productivity. Children with Wilms tumor the world over have gained as a result.
Please Send Us Your Good News

The following article is a revision of an article in last year’s newsletter. We sent this out in a mailing to participants from whom we had not recently heard any news. We did hear from quite a few of you, and we thank you for that. If you are someone who has not returned our recent forms, please read the following and carefully consider the message. Your news, whether bad, good or no news, is an important contribution to study findings and subsequent advice about your health and welfare.

As the statistician and Principal Investigator for the NWTS Late Effects Study, I sometimes receive e-mail from former Wilms tumor patients who have just been diagnosed with a second tumor or who have had a problem pregnancy. What many former patients fail to recognize is the importance of hearing also from the great majority of you who have not experienced problems with your health. This enables us to report to you and to the physicians who treated you, via articles in the medical literature, accurate information on rates of occurrence of second tumors, low birth weights and the other endpoints we track. Such rates consist of both a numerator and a denominator. The numerator is the number of cases (e.g., of a second tumor or a low birth weight baby) that occur before a certain age. The denominator is the much larger total number of former patients who have been followed through that same age. We can only include you in the denominator if we receive news from you regarding your health status on or after the age in question. If we hear more frequently from patients in the numerator, we overestimate the rate and make it appear that the medical conditions following diagnosis of and treatment for Wilms tumor are worse than they really are. This is sometimes known as the principle that “bad news travels fast.” It can lead physicians to make treatment decisions for their current patients based on wrong information.

Please help us make sure that the advice we give all Wilms tumor survivors is the best medical and health advice possible. I urge you to keep in touch with us on a regular, annual basis. While of course we need you to report any adverse medical condition, we also need to hear your good news—of your good health, marriage, pregnancy or the fact that you are still at the same address and receiving our newsletters. If for any reason you need a new copy of one of our forms, please see our newly revised website: www.nwtsg.org. I hope to hear from you soon.

Good News / Bad News / Less News

FAREWELL AND THANKS TO THREE MEMBERS OF STAFF

This year we received the good news that the NWTS was approved for funding for another five years, thanks in many ways to your participation and contributions. Unfortunately we also received bad news—a dramatic reduction in funding. This required laying off three valued members of staff, our friends, Yevgeny Grigoriev, Blythe Hart and Ying Huang. We would like to take this opportunity to thank them for their work with us, for their dedication to the project and for their work with you, the participants.

Because of these reductions, this newsletter is shorter, but we hope still informative. You can help us compensate for the reduced funding by responding to our inquiries as soon as you receive them. Then we receive the important information from you, but we do not need to call you or write you a second time. Please make it a New Year’s resolution to respond promptly and thus strengthen the information we ultimately provide to you.

Who Can Report for Me?

“Can my mother complete and return the NWTS forms for me?” We get this question a lot. The simple answer is that anyone can report for you. If you are 18 years of age or older, we do need your written and signed permission for any other person to do this.

We realize that there are many reasons why adult participants would like others to report for them. Common examples are participants in their early 20’s who are away in the military, attending college, or just starting a new job and still receiving mail at their parents’ home. We often receive forms completed and signed by a parent of an adult participant. Unless the participant has already let us know that the parent has permission to report to us, we must send the participant a letter and form with the request that the form be signed and showing who may report for her or him. You may also simply send us an email to report this information.

If you would like someone else to report for you, you will find a short form on our website, www.nwtsg.org. Click on the “Participants, Family & Friends” link, then click on the Adult Consent Form. At this time it is not possible to complete the form online. Please print page 2, complete it and mail it to us. If you do not know your ID number, please leave this blank. We will be happy to send you a business reply envelope to use to mail the form; just send us an email requesting the envelope.
A participant asked how he can make a donation to the study...

Over the years we have received increasingly more inquiries about how individuals can make contributions to the study. We greatly appreciate these donations. They help support our research during these times of limited federal funding and allow us to conduct special research projects. All of these are designed to improve the lives of people diagnosed with Wilms tumor.

We are located at the Fred Hutchinson Cancer Research Center in Seattle, WA, which is a tax exempt 501c3 institution. Donations by check should be made payable to “National Wilms Tumor Study” and be mailed to our address which appears on the first page of this newsletter.

Electronic donations by credit or debit card can be made directly to Fred Hutchinson Cancer Research Center online at www.fhcrc.org/donating/donate_now.html.

Please visit us at www.nwtsg.org

We have recently completed an extensive revision of our website. We hope we have made it more useful and user-friendly for you. Please visit us. If you have comments, suggestions, even complaints, please let us know. The purpose of the website is to provide you, whenever possible, with what is most informative, helpful and valuable.

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