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Parent Empowerment Newsletter

Living with Inhibitors:

Five Families Tell Their Stories

by Sara P. Evangelos

Hemophilia patients take pride in managing their disorder with today's advanced healthcare options: convenient home infusions, choice of factor, safer products. Hemophilia is indeed easier to manage today — unless you have an inhibitor. Depending on the severity of the inhibitor and each person's response to treatment, some patients manage well. But many others continue to suffer. For them, having an inhibitor is almost like having a separate disorder. Because inhibitors are so different from 'normal' hemophilia, they represent the greatest challenge yet in treating hemophilia complications.

Inhibitors occur in approximately 20%–30% of people with severe and moderate hemophilia A, and in about 1%–6% of those with hemophilia B. An inhibitor is an immune system response: The body doesn't recognize infused factor, and produces antibodies to destroy it. Although treatments and products exist that can eradicate or bypass an inhibitor, the stories of five inhibitor families demonstrate that living with inhibitors is frustrating and challenging. Chronic pain, prolonged joint bleeds, missed school, changing levels of antibody response, varying reactions to factor products — and even rare allergies to some inhibitor treatments — all combine to produce a complex, painful and stressful condition. What's it like to live with an inhibitor, and how do families cope?

In March 2005, Jane and Chris Smith's son Leland had a bad hamstring bleed. "He wasn't walking properly because of it," recalls Jane, "and he ultimately stressed his left knee. The knee developed a bleed that we could not get under control. Over the next three months, Leland received factor daily and was admitted to the hospital twice for IV pain meds. He was in a cast and a wheelchair. Every time it would start to get a little better, he would bend it or use it, and it would flare up again. Although this knee had not previously been a target joint, this one bleed ultimately led to an open synovectomy at the end of June."

Leland, age 13, has severe hemophilia A and an inhibitor. "It showed up when he was 15 months old, when we were treating an intracranial hemorrhage," says Jane. Inhibitor screening done one month earlier at Leland's annual visit was negative, and the Smiths have no family history of inhibitors. "I knew what inhibitors were, but not much else," Jane recalls. "Honestly, we were more concerned about the head bleed, and didn't realize or process the full impact of the inhibitor diagnosis until later."

Leland's Boston medical team lost no time battling his inhibitor. "We immediately went into immune tolerance therapy (ITT)[1] ," says Jane, "and between the ages of 15 months and four and a half years, we tried

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[1] Immune tolerance therapy (ITT) is the scheduled infusion of factor, usually daily or every other day, for weeks or even years in an attempt to tolerize the immune system to factor. ITT can train the body to recognize factor and not reject it as a foreign substance.

inside PEN

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welcome

Sherrell Portrait Design

I've been active in the hemophilia community for 17 years as a consumer, educator and humanitarian. After meeting and interviewing literally hundreds of families, and traveling frequently to the developing world in search of patients who suffer, I thought I had just about seen it all.

Until I participated in the Inhibitor Patient Education Summit last fall, sponsored by Novo Nordisk, and met with 50 families who struggle with inhibitors. I witnessed an outpouring of raw emotion that I have not seen since the HIV litigation of the late 1980s, or since I read the first parent submissions to a new book about hemophilia I was to write in 1990. Emotions ran the gamut from bewildered, curious and grateful to angry, despairing and overwhelmed. At times I was speechless. The suffering of these inhibitor families was real and visceral. At one point I felt tremendous guilt, wishing I could slink away unseen. After all, my son *only* has hemophilia. How could I relate to what these families shared? But most of all I wondered, *Where have these families been hiding for the past 20 years?* Why is their pain so foreign to me, to us?

Inhibitors are one of the last great hurdles in proclaiming hemophilia a truly manageable disorder. It's now known that inhibitors, once thought rare, can affect up to 20%–30% of severely and moderately affected hemophilia A patients. In this issue of *PEN*, we share the stories of five courageous families who have inhibitors in common, but whose similarities end there. You may be amazed at the complications these families face, and the stoicism they exhibit – and come away, like I did, feeling intense respect and admiration.

Kudos to Novo Nordisk for recognizing an unmet need in our community by creating a forum where inhibitor families can meet and be educated. Learn the basics of inhibitors in *Inhibitor Insights* – our new column that reflects our recognition of these families' needs. Then read about the daily challenges and triumphs of five remarkable families. If you have an inhibitor in your family, please contact us. We'll put you in touch with companies and families who will welcome and educate you. I believe and hope that this is a new era for inhibitor families, when their voices will be heard loud and clear, and their needs readily met.

Clarification: In the February issue of *PEN*, "Johnny, drink your factor!" featured a picture of two pigs in an outdoor pen. This photograph does not depict pigs used in gene therapy research. It was meant only to emphasis that this research involves the use of pigs. Transgenic pigs are raised in near-sterile environments to prevent viral infections and are never allowed outside to play in the dirt or mud.

PARENT EMPOWERMENT NEWSLETTER MAY 2006

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PEN is a newsletter for families affected by bleeding disorders that is produced and edited by a parent of a child with hemophilia. It is a forum that promotes an active exchange of information and support among divergent groups in the national and international hemophilia community.

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letters

Project SHARE

THANK YOU AGAIN FOR THE GENEROUS DONATION OF FACTOR IX that I received on behalf of the hemophilia patients in Romania. The entire amount of 70,000 units arrived safely at Dr. Serban's hospital. It just happens that she has three patients currently in desperate need of factor IX. It is a godsend! Thank you for the privilege of working with you.

Adriana Henderson, President
S.T.A.R. Children Relief
CALIFORNIA

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Putting the Fun in Fundraising:

The Extraordinary Efforts of the Red Nose Club of Saguaro High School

by Susan Phillips

photos: Susan Phillips

Mark Phillips presents a camp sponsorship check to Michael Rosenthal of the Hemophilia Association of Arizona, accompanied by (left to right) Nick Guliano, Oley Moroz, Marissa Jacobs, Kelley Stapleton, Alicia Cormie, Oliver Buchanan, Marissa Mintz, Paige Russell and Ashley Simonson.

Mark Phillips, age 16, is an extraordinary teen. He found his mission in life early: easing the burden of children with chronic medical conditions. While most teenage boys are busy with school, sports and friends, Mark focuses much time and effort on helping organizations that benefit children in need.

Mark is president and founder of the Red Nose Club of Saguaro High School in Scottsdale, Arizona. The Red Nose Club is a school program dedicated to fundraising for non-profits that serve children in need. Mark's inspiration comes from his younger brother Eric, who was born with three life-threatening illnesses in addition to severe hemophilia B. Mark has witnessed numerous emergencies and horrendous bleeds, and has spent several hundred hours with Eric in the hospital. He knows firsthand how difficult it is for families with severe medical problems. For 11 years, Mark has volunteered for medical nonprofits everywhere he has lived–and now he wants to make a difference on his own.

As a freshman in high school, Mark decided to start his own club. The Red Nose Club takes its name from the 1998 movie *Patch Adams*, starring Robin Williams. The movie is based on the true story of the founder and director of the Gesundheit Institute, a holistic medical community that has provided free medical care to thousands of patients since 1971. Dr. "Patch" Adams often wore a red clown nose to boost the spirits of his hospitalized pediatric patients. Like Adams, Red Nose Club members put the "fun" in fundraising, and are eager to do their part to help children in need.

Mark's inspiration: Eleven-year-old Eric Phillips (left), who has hemophilia.

What has this group of teens accomplished? The club held a week-long cereal drive to aid a local food bank and collected 1800 boxes of cereal! To benefit a Romanian orphanage for handicapped children, the club held a "Romania Night" fundraiser at a local restaurant. Members waited on customers while wearing their red noses. A giant Romanian flag hung from the ceiling, Romanian music played, and Romanian handicrafts were displayed. The evening was a success, raising $975.

But the club's biggest accomplishment was helping children attend Camp Honor, a hemophilia camp in Arizona. A three-hour bake sale held in December 2005 generated an astonishing $1,160! The students, wearing red noses and big smiles, happily passed out free samples to holiday shoppers, who then returned to load up with goodies. When the teens shared their goal of sending one child to Camp Honor, shoppers opened their wallets and donated generously. On January 13, 2006 the teens presented a check to Michael Rosenthal, executive director of the Arizona Hemophilia Association. "This came from a bake sale?" asked Michael, stunned. "With this check, you have sponsored two children to camp." The club members were ecstatic!

Each month, Red Nose Club members generate new ideas to help children locally and internationally. With so many needy children in the world, the club's list seems never-ending. Mark's ultimate goal is not just fundraising, however. "Our Red Nose Club is helping children here in Arizona and internationally. As I see it, our story will inspire other teens across the country to put on red noses and help children in their area."

Susan Phillips is the proud mother of Mark and Eric, who has hemophilia. She and her husband Tim have been married 20 years. Tim's career in the military and Department of State has allowed the family to travel and live in many parts of the world. Eric's medical needs have required Susan to remain at home full time with him, which she does joyfully. She is a big supporter of the Red Nose Club.

by Paul Clement

Inhibitors: *The Hows and Whys*

Inhibitors are one of the most feared and challenging complications of hemophilia. Inhibitors interfere with the ability of factor to stop a bleed, increasing the risk of other complications, such as joint damage. What may be a minor bleed for someone without an inhibitor can turn into a major bleed for someone with an inhibitor.

Inhibitors are *antibodies* directed against factor VIII or IX. Antibodies are part of the body's immune system. They are designed to protect us from foreign proteins and invaders, such as bacteria and viruses, that try to "set up housekeeping" inside the body. Although the immune system typically does an excellent job of protecting us, it makes occasional mistakes, or becomes "confused." The immune system may mount a defense against substances, such as dust or pollen, that are essentially harmless; this results in allergies. Or the immune system may mistakenly attack the body itself, resulting in an *autoimmune* (*auto* means "self") disorder, such as lupus or acquired hemophilia.[1] In a patient with a hemophilia inhibitor, the immune system erroneously determines that infused clotting factor is a foreign and possibly dangerous protein, and mounts an attack. It produces custom-designed antibodies that attach to the outside of the factor molecule and prevent it from participating in the clotting cascade, ultimately preventing the blood from forming a clot.

How do you know if your child has an inhibitor? Often, there are no obvious signs. Inhibitors are sometimes diagnosed during routine checkups; however, most are discovered after factor infusions fail to adequately stop bleeding. A screening test called a *Bethesda inhibitor assay* measures the length of time it takes a mixture of patient plasma and normal plasma to form a clot. A prolonged clotting time indicates the presence of an inhibitor.[2] The results of this test are reported as *Bethesda Units* (BU) or a *Bethesda Titer*. Inhibitor levels lower than 5 BU are referred to as "low titer" inhibitors. Inhibitor levels greater than 5 BU are called "high titer" inhibitors. The Bethesda assay is not foolproof – some people appear to have high titer inhibitors but respond normally to factor; others have no detectable inhibitors, yet infused factor is rapidly neutralized and ineffective.

Once an inhibitor is detected, the person is tested to see how he responds to a dose of factor. If, after infusion with factor, the inhibitor level stays low and rises to only 5 BU or less, the person is classified as a "low responder." If the inhibitor level increases, and rises above 5 BU after infusion with factor, the person is classified as a "high responder." In high responders, the inhibitor level doesn't often remain constant – it may drop to low levels if these patients do not receive an infusion for a long time – several months to years. But after this time, the next infusion of factor will cause the inhibitor to jump again to high levels. Low-responding inhibitors may spontaneously disappear after weeks or months; these are known as *transient inhibitors*. High-responding inhibitors are usually permanent, unless the body learns to accept the factor as a result of a specialized treatment protocol called *tolerization*, or Immune Tolerance Therapy (ITT).

Bleeding episodes in low responders often can be treated with large doses of factor VIII that overwhelm the neutralizing effect of the inhibitor. A single large dose of factor may also be effective in someone who is a high responder, and who has low inhibitor levels as a result of not having been exposed to factor for months to years. Unfortunately, subsequent infusions of factor in high responders are rendered useless because the immune system mounts a vigorous attack against the factor: Inhibitor levels jump over a period of several days, neutralizing most or all of the factor, regardless of how much factor was infused. Normal factor concentrates are useless for treating bleeding episodes in patients who are high responders and who have high-titer inhibitors, because the infused factor is rapidly neutralized.

It's still not known exactly why some people get inhibitors and others don't – this is one area of active research. It is known that people with hemophilia A (factor VIII deficiency) are ten times more likely to get inhibitors than people with hemophilia B (factor IX deficiency). Between 20% and 30% of patients with severe or moderate hemophilia A will develop inhibitors, and between 1% and 6% of patients with hemophilia B. Most inhibitors occur in people with severe hemophilia A. This makes sense: If you have no functional factor, your body is more likely to consider factor a foreign

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[1] A form of hemophilia that may suddenly occur in women after giving birth, or in the elderly fighting cancer or an infection.

[2] The test does not directly measure the level of antibodies in the plasma, and results may be affected by other antibodies in the plasma.

Annual Report 2005

PROJECT SHARE

It's time to give back.

There is no word to express our feeling [to Project SHARE] for helping us and bringing hope for Boussad. Without you, Boussad's life could be something else. On many occasions his life was saved with the medicine that you sent him. You are a part of his life. God bless all of you!

~ Father of Boussad F., 16, Algeria

Introduction

Project SHARE℠ (Supplying Hemophilia Aid and Relief) is a humanitarian program devoted solely to donating life-saving antihemophilic factor to the hemophilia community in developing countries.

Founded in 2002, Project SHARE is the world's first private humanitarian hemophilia program to partner with corporations to ship medicine to patients who do not qualify for assistance from any other source. With Project SHARE, millions of dollars worth of factor that would be destroyed are able to reach deserving people with hemophilia.

Project SHARE donations not only save lives—they also help attract rural patients to treatment centers for care, and encourage patients to create hemophilia societies where none exist. Project SHARE also serves as a central advisory agency for all US HTCs, hemophilia nonprofits, homecare agencies, and patients seeking information about donating factor overseas.

Accomplishments

- Donated or brokered **3.74 million** IUs of factor (estimated value: $3.7 million).
- Brokered more than 2,150,000 short-dated IUs to Romania, the Dominican Republic, and Nicaragua in just three days.
- Brokered an emergency shipment to a four-year-old in Peru to alleviate a life-threatening head bleed.
- Shipped 30,000 IUs to a 15-year-old in the Bahamas to alleviate a limb-threatening bleed.
- Directed thousands of dollars worth of medical supplies to our partner organization, International Medical Equipment Collaborative (IMEC) for distribution to developing countries.
- Sponsored a 40-foot IMEC sea container packed with emergency medical supplies to Pakistan for earthquake relief.
- Welcomed **Grifols** to Project SHARE Board of Directors.
- Emailed 52 **weekly updates** on factor donations to the WFH, SHARE board members, and other interested parties.
- Visited **the Bahamas** to assist with the development of their national society.
- Expanded Project SHARE's outreach to **40 countries**, including **three new** ones (in bold):

- Afghanistan
- Algeria
- Armenia
- Bahamas
- Bangladesh
- Belize
- Bolivia
- Bosnia
- China
- Colombia
- Dominican Republic
- Ecuador
- Egypt
- El Salvador
- **Ghana**
- Haiti
- Honduras
- India
- Indonesia
- Iraq
- Jamaica
- Kazakhstan
- Kenya
- **Lebanon**
- Mexico
- Morocco
- Nepal
- Nicaragua
- **Nigeria**
- Pakistan
- Peru
- Philippines
- Romania
- Russia
- Serbia & Montenegro
- St. Vincent & the Grenadines
- Trinidad & Tobago
- Ukraine
- Vietnam
- Zimbabwe

Our Beneficiaries

Romania

Project SHARE brokered a donation of more than 1 million IUs of factor VIII Romania, providing hundreds of deserving patients with medicine.

Ghana

At our request and with our support, Ghana established a national hemophilia society and gratefully accepted the first Project SHARE factor shipments to their country.

Dominican Republic
Project SHARE co-sponsored the Dominican Republic's seventh annual hemophilia camp and donated most of the factor and toys.

India
Project SHARE sent enough VWD factor to India so that Sudha Rani Y. was able to give birth to her beautiful new son.

Belize
Peter D., a 12-year-old Mennonite boy, received his first Project SHARE shipment of factor VIII this year.

Bahamas
Nathanial, Rafael and Michael S. have received Project SHARE factor for more than five years.

Ancillary Supply Donations

Project SHARE's partnership with **International Medical Equipment Collaborative (IMEC)** allows non-factor donations and ancillary medical supplies to efficiently reach qualified medical personnel in developing countries. IMEC reports increasing numbers of inquiries and donations from Project SHARE referrals.

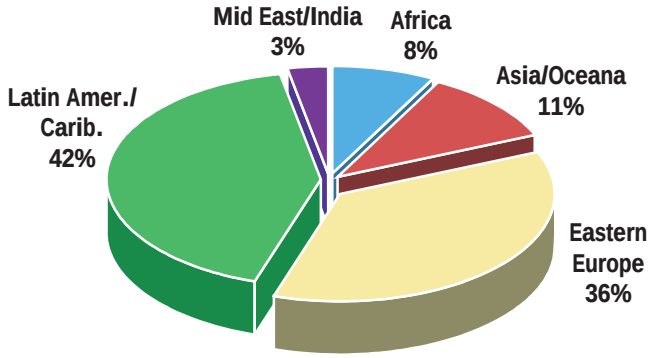
Through IMEC, Project SHARE sponsored an emergency relief shipment in response to Pakistan's devastating earthquake in October. IMEC volunteers packed a 40-foot sea container with enough supplies and equipment to fully stock twelve emergency medical tents.

Sources of Factor Donations

Project SHARE accepts donations of unwanted, in-date factor from all reputable sources. Our main sources of donations include US individuals, HTCs and hemophilia nonprofit organizations.

Project SHARE does not actively seek donations from factor manufacturers, which normally are donated to the World Federation of Hemophilia (WFH). Our goal is to recover excess or unwanted factor that would otherwise be destroyed. We accept any number of vials, in any assay size, up to within days of expiration.

Our Beneficiaries



Focus for 2006

Among our 2006 goals: increase public exposure and media coverage; develop board membership and collaborative partnerships; visit with one or more developing countries that receive Project SHARE donations; and ship or broker 5 million IUs of donated factor to developing countries.

In Gratitude

Project SHARE exists only through the support of our generous corporate partners. We would like to thank the following companies:

- Bayer HealthCare
- Baxter BioScience
- Hemophilia Health Services
- Grifols USA
- Novo Nordisk
- ZLB Behring

We give special thanks to New England Biolabs for their continued funding and management of our shipments, and to S.T.A.R. Children Relief for its help in Romania. Thanks to all who donated factor to Project SHARE, especially those who donated in memory of a loved one.

Our Vision

A global hemophilia community where life-saving factor is shared consistently and conscientiously, alleviating the suffering of patients in underserved countries, and empowering them to actively participate in their own healthcare.

Our Mission

Encouraging the hemophilia community in developed countries to donate unwanted antihemophilic factor (AHF) to developing countries, with the following goals:

- Attracting underserved patients to treatment centers.
- Supporting camps, surgeries and physical therapy.
- Establishing independent hemophilia care.
- Alleviating suffering and saving lives.

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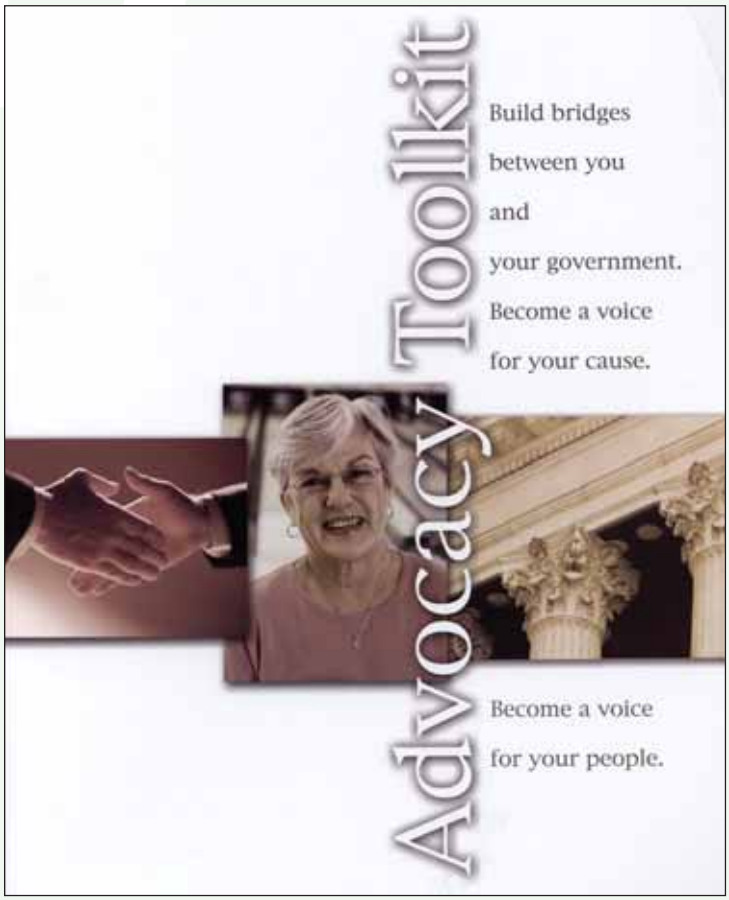
Become a Voice for Your Community

by Laurie Kelley

Today, changes in the reimbursement of factor products are affecting more states and more patients with hemophilia: "The Coming Storm" is now "The Current Storm." Our national organizations are working hard to ensure that our right to choice is protected. Our local chapters are working hard to protect our coverage of brand and provider. What can you do to help?

You are the most important player in this story, because all changes ultimately impact your own healthcare, and your child's. Partner with your local, state or national organization through grassroots efforts. Grassroots advocacy is the expression of popular support or opposition for a position, demonstrating popular solidarity among people in a certain geographic region or specific group. Grassroots advocacy lets political representatives and legislators know what's important to constituents. Legislators like to know that what they do in federal or state government is ethical, and popular with people back home. Popularity translates into voter support on election day!

Bayer's Advocacy Tookit is a resource you can use to work with your local, state and national organization. The toolkit will teach you how to write effectively to your legislator; organize meetings or speak at hearings; write for the newspapers or talk on the radio; and convey a strong understanding of the issues. You can use the strategies suggested in this brief but comprehensive, easy-to-read, colorful and insightful toolkit to help our community protect itself against threats to factor coverage.



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and request a toolkit in the "Contact us" field.

Inhibitor Insights... continued from page 4

substance. Surprisingly, it has been found that young babies exposed to factor on a regular basis have a much lower incidence of inhibitors, perhaps because their developing immune system recognizes factor as a "normal" protein. People with certain genetic defects in the gene for factor VIII are more likely than others to develop inhibitors. And race plays a part: African-Americans develop inhibitors at twice the rate of Caucasians. Scientists are even investigating environmental influences on the incidence of inhibitors, especially if factor was infused while the patient was fighting an infection, during a major bleed, or after an immunization. Different brands of factor may also affect the incidence of inhibitors. In the early 1990s, changes made in the viral inactivation steps of some brands have increased the *immunogenicity* of the factor, or the ability to elicit an immune response.

If your child is going to develop an inhibitor, this will probably happen within the first ten infusions. After 100 infusions, inhibitor development is very rare. Fortunately, regardless of when your child develops an inhibitor, help is available through various treatment options. Research is underway to determine exactly which parts of the factor protein elicit an immune response, and why some people develop inhibitors and others don't. Eventually we may be able to prevent the formation of most inhibitors by modifying the factor protein so it doesn't trigger an immune response. Inhibitors are still a feared and challenging complication of hemophilia, yet the outlook for people with inhibitors has never looked brighter.

NEXT ISSUE: Which treatment is right for your child with inhibitors?

Living with Inhibitors... continued from cover

ITT two different times." To begin an ITT program, an inhibitor patient's antibody titer (a measure of the strength of the inhibitor, denoted in Bethesda Units, or BUs) must be as low as possible, preferably zero. After the initial attempt at tolerization failed, plasmapheresis – the infusion of donated plasma without an inhibitor – was used to get Leland's antibody titer down to about two, and a second ITT attempt began when he was three years old. But even with daily high doses of factor VIII, Leland had bleeds throughout ITT and his inhibitor titer wouldn't come down. "After 18 months, Leland's immune system did not tire out; it just kept fighting and fighting. At some point you just have to admit that it isn't going to work, so we gave up on ITT." says Jane. "In hindsight, I now know that some patients continue ITT for up to three years, but at the time, everyone agreed that 18 months was a fair shot."

The Smiths continue to treat Leland's bleeds with either the plasma-derived product FEIBA® or the recombinant product NovoSeven®, depending on the type of bleed and time of day. Until he was almost 12, Leland was able to keep up with his regular activities, including school. But then, says Jane, "We noticed that pain issues were kicking in. Suddenly, every bleed had significant associated pain." Jane notes that the products used to treat bleeds for inhibitor patients aren't as effective for Leland as pure factor VIII. "We aren't replacing in his system exactly the puzzle piece that it needs; we're tricking it by using other products that can compensate. But this doesn't work as effectively for him. These products have a much shorter half-life[2], so they're not hanging around in his system long enough to work as well." For Jane, dealing with an inhibitor is almost like living in hemophilia's darker past. "I feel like we're managing Leland's hemophilia the way they did a generation ago – he has a lot of regular bleeds and the complications that go with them."

Coping with Pain

In November 2004 Leland developed an ankle bleed. After two weeks of treatment, the bleed was getting better, but Leland was still in pain. He was admitted to the hospital for IV pain management. "Oral medications weren't even taking the edge off," explains Jane. After the bleed subsided and the swelling was gone, Leland was left with significant *neurogenic* (nerve) pain in his ankle joint for months.

Leland and Jane must cope with the chronic pain of an inhibitor.

Now Leland copes with two different pain issues: the pain associated with an acute bleeding episode, and the neurogenic pain caused by swelling and irritation to nerve endings in the joint. During the painful period of November 2004 to March 2005, recalls Jane, "Even though Leland could bear weight on the joint, because he was in pain he didn't feel like he could walk, and chose to use crutches and a wheelchair."

Unfortunately, nerve pain doesn't respond well to narcotics and standard pain medications. "Leland would tell you that he's been in pain 24/7 for the last year and a half," says Jane. "Most days, he's able to work through the pain, but some days it's debilitating. Nighttime is difficult because when you lie down in bed, it's all you can think about." The Smiths found a psychiatrist who specializes in pediatric pain management, and who took the lead in this part of Leland's treatment, prescribing a variety of medications for both neurogenic and acute bleed pain. "At times, he's on a number of different meds; some are serious narcotics, including IV morphine when he's admitted to the hospital," notes Jane. "It worries me, but I don't feel that we have a choice right now." The Smiths are also working with a psychologist to develop distraction techniques to help Leland cope. "We're investigating visualization and meditation, and other non-narcotic ways to deal with pain. Having friends over, and video games, TV – all that stuff that parents would like to avoid – become a larger part of the picture because he's not mobile, and they provide distraction from the pain."

After his synovectomy, Leland spent a month in bed and then began physical therapy. But pain is still an issue. "There are days when he just can't go to therapy," Jane reports. "And because he's using crutches so much – our house isn't wheelchair accessible – he's stressing the other ankle, which bears all the weight. So now that right ankle is a target joint, and it bleeds regularly."

In January 2006, when Leland returned to school after winter vacation, he felt he could finally put weight on his knee. "It was the first time in over a year that he went on the bus," Jane says proudly. "He was walking around school feeling like a normal kid, blending in with the crowd – and the knee started bleeding again. I couldn't believe it: one day of 'normalcy' and he was back in the hospital." Leland was admitted to the hospital for two weeks of aggressive factor treatment and pain management. He spent January recovering, and has slowly improved. Currently, Leland is off the pain medicine and able to spend a full day at school. Still, Jane points out, "It's been a year and a half since he's walked independently, and just sitting in a classroom holding in his pain all day is exhausting. He's made good progress in the last two months, but we still have a way to go."

Out of 180 days of school in sixth grade, Leland missed at least 70. "Every activity has been affected by the fact that he's in pain all the time," says Jane. Add to that several in-patient hospital stays, and Leland has had

[2] Half-life refers to the time it takes for half the clotting ability of a dose of factor to be used by the body. For factor VIII, the normal half-life is 12 to 14 hours.

to drop even non-physical activities like Scouts and guitar lessons. He hopes to resume some of these activities soon. But in spite of the many challenges of living with an inhibitor, Leland maintains a positive attitude, does well in school, and enjoys his friends and the activities that he is still able to do. Jane notes, "I'm very proud of how well Leland has handled things. His strength and courage are amazing for a kid his age."

The Battle of Levels

Horbacz family

The Horbacz brothers, Matthew (right) and Justin, are on prophylaxis every other day to control their inhibitors.

Matthew and Justin Horbacz of New Jersey also have severe hemophilia, inhibitors and a positive attitude. But unlike Leland, the Horbacz brothers are on regular prophylaxis following successful ITT. Matthew has a low-responding inhibitor. Justin has no measurable inhibitor, but has an abnormal recovery[3] of his factor levels and very short half-life of infused factor. The main goal of treatment for the boys is to keep factor and antibody levels under control.

Eleven-year-old Matthew was diagnosed with hemophilia when he was five and a half months old. At ten months he had a port implanted, and one month later his parents Diane and Gary learned that he had an inhibitor. "We were still trying to understand hemophilia when we learned about inhibitors," recalls Diane. "We weren't prepared – just overwhelmed." Because Matthew's inhibitor was very low responding, he was put on ITT every other day. During the first year, his BUs dropped significantly.

Justin, age eight, had no measurable inhibitor when he was born. "So I thought that my first son had the inhibitor and my second son didn't," laughs Diane. "Later I learned that although there is no measurable titer, you can have either a transient inhibitor or an inhibitor that's low responding; but you don't measure an inhibitor solely on the BUs." Sound confusing? "It makes it more challenging," Diane admits. "It's like my boys are in a middle group. Their recovery studies are abnormal: They have a sudden drop in the first hour, bringing them down to a low level. And their half-life is abnormal: They use up factor every four or five hours instead of every eight to twelve. Part of their system isn't recognizing factor, and part is accepting it."

Matthew and Justin have used several recombinant factor products. On some products, Matthew has had a measurable inhibitor. Currently, both boys are on prophylaxis and use Advate®. "Prophylaxis means keeping their joints and muscles strong and healthy," Diane emphasizes. "But after attending the Novo Nordisk summit on inhibitors [see sidebar, above], I learned that it also means keeping their immune system familiar with factor. If I did not give them factor for a week, and then infused factor, they could develop an even stronger inhibitor. That's why we infuse every 48 hours." To keep a patient tolerized, a prophylaxis dose must be maintained.

Diane's primary concern is repeated needlesticks in the port or veins. Add to that worries about head bleeds, and controlling factor and antibody levels. Recently Diane treated Justin early one morning, and two hours later he hit his head. Diane's HTC instructed her to treat again immediately, and again eight hours later. "Knowing how the boys respond to factor," Diane explains, "and how levels can just drop, influences our treatment regimen. If everything's going smoothly, it's every 48 hours. But when the boys get injured, our HTC is very aggressive; there's no 'wait and see.'" The daily factor treatment needed to keep Justin's levels up, notes Diane, "put us in an aggressive mode, and required us to do repeated needlesticks. It was a very difficult time for us as a family. We were treating Justin every day for over a month. It was too much for his veins to handle, so we also had to rely on the port. But we learned that the port, too, couldn't keep up with all those pokes."

Groundbreaking Summits for Inhibitor Families

Novo Nordisk, Inc., manufacturers of Novo Seven® factor replacement for patients with inhibitors, held an innovative Inhibitor Patient Education Summit in Philadelphia in November. More than 50 families joined with advocates, doctors, social workers and educators to learn more about inhibitors and their treatment, and to share with each other. The families who attended this informative and inspiring meeting were invited from the Northeast and Mid-Atlantic regions of the US. In 2006, people who live in other regions of the country will have a chance to attend.

Inhibitor Patient Education Summits are planned for

- Dallas (August 4–5)
- Anaheim (July 28–29)
- Baltimore (September 22–23)
- Chicago (October 27–28).

Topics will include inhibitor basics, immune tolerance therapy, exercise and sports, joint health, pain management, and surgical considerations. The summits have been planned by a steering committee composed of physicians, nurses, advocates, patients, and representatives from physical therapy and social work. Agenda topics will be relevant, timely and unbiased.

Travel grants will be available through local chapters. To pre-register or to learn more about attending an Inhibitor Patient Education Summit, please call toll-free 1-888-706-6867 or visit www.inhibitorsummits.org.

Adapted from a Novo Nordisk press release.

[3] Recovery is a measure of effectiveness of a dose of factor; it represents the level of circulating factor activity in the blood after a certain amount of time has passed.

Both boys have their antibody titers and factor levels checked annually. "We're fighting the battle of levels," Diane says wryly, but notes, "I don't get hung up anymore on what the titer is. I just look at the boys and see how they are responding. I've tried to step aside from numbers because it freaks you out."

Like many parents of children with inhibitors, Diane yearns for a simpler life. "I wish they responded to factor the way other kids with hemophilia do. I wish they had 'normal' hemophilia." Still, she tries to keep a healthy perspective, and lives with a feeling of gratitude. "It's just another challenge, and there are other children with greater inhibitors that don't respond to factor who have more bleeds." How have Matthew and Justin adapted to life with inhibitors? "They don't feel different because they're both in the same boat," says Diane. "They only know hemophilia as they live with it. If they live with a low-responding inhibitor, then that's what hemophilia is to them."

The Treatment Spectrum

Kerry and Chuck Fatula of Pennsylvania have four sons – three with inhibitors – and share the Horbacz family's sense of gratitude. "How can we complain about any of this when we are so blessed with treatment, medical professionals and factor availability?" asks Kerry. "The future is always uncertain for people with hemophilia, more so for inhibitor patients. We've accepted the limitations that having children with hemophilia brings – and that includes dealing with inhibitors."

Paul, 16, Nathan, 14, and three-year-old Stephen all have severe hemophilia A with inhibitors. Six-year-old Collin doesn't have hemophilia. When Paul was diagnosed more than a decade ago, inhibitors weren't well understood. Kerry recalls, "I knew almost nothing about inhibitors. I felt like parents who don't know anything about hemophilia when their child is diagnosed. And all the wonderful new hemophilia treatment options, including home infusion, were suddenly no longer options."

Paul and Nathan were diagnosed with inhibitors at about the same time, when Paul was two and a half and Nathan was one. "We first noticed that when they received an infusion, the needle site bled," says Kerry. "Sometimes we ended up with a puffy little hand that needed another infusion to stop that bleed. When it looked like the bleed wasn't resolving, we treated again – only to end up with more bleeding." Both boys began ITT, receiving high daily doses of factor VIII. Paul was diagnosed with a high-responding inhibitor, but his treatment was successful. He's been tolerized for the past ten years, has an antibody titer close to zero, and is on prophylaxis every other day. Nathan's very high-responding inhibitor has resisted repeated ITT attempts. Right now he is again on ITT, and this time his body seems to be responding.

Because of a head bleed during delivery, Stephen needed treatment the day after he was born. "We continued him on prophylaxis," recalls Kerry, "and hoped we might prevent an inhibitor by suppressing it from the outset. The inhibitor rose anyway when he was three months old." Stephen's inhibitor is also high responding; ITT was reasonably successful, but his recovery time is slow. Recently, Stephen's inhibitor rose again despite daily infusions. After switching products, his levels appear to have dropped, but as of this writing the Fatulas are still waiting for test results.

Fatula family

The Fatula brothers (left to right): Stephen, Collin, Nathan and Paul. After Stephen's infusion, the two older boys mix their factor while Collin builds Legos.

Changing Products, Changing Protocols

Every inhibitor responds differently at different times, which often means switching products and treatment regimens. "The problem for Nathan and Stephen," explains Kerry, "is that although at certain points we've gotten their inhibitor down to zero, we haven't been able to keep it there on the same dose that most people are able to use. We don't know how high we'd have to go, or how frequently, to maintain it." Nathan initially used monoclonal factor since recombinant was not commercially available. His inhibitor was diagnosed when his parents realized that the product had stopped working. Several treatment options were available at the time, but unfortunately Nathan developed an anaphylactic reaction to the first product, Autoplex® T. The Fatulas tried a factor IX product, Konyne® 80, with some success, but Nathan developed a reaction to that, too. (Both concentrates are no longer produced.) "Our last hope was FEIBA," recalls Kerry. "We tried it and had success with the clotting, and he never developed a reaction to it. That's strictly for treating his bleeds, and he's been on it since he was about five."

Since Nathan was four, the Fatulas have been trying to tolerize his inhibitor with factor VIII products. On one product, says Kerry, "We would just get his inhibitor up, and it would start to come down and then reach a plateau. Twice we just gave up the program because we were wasting so much money in factor, and so much time infusing – and it was stressful for Nathan." So the family waited for new products and tried different protocols. Right now Kerry is optimistic about Nathan's new

treatment with Alphanate®. Since December 2005, Nathan has been using both FEIBA and Alphanate with some success.

In contrast to Nathan's difficulties, Paul tolerized well on Recombinate®. "We got rid of his inhibitor pretty quickly," Kerry recalls. "It was high responding with a relatively high titer, but within a year we had zero titer. His recovery time with factor isn't great, but he is still able to treat every other day. He has very few problems with breakthrough bleeding or re-occurrences of his inhibitor."

Stephen's inhibitor is another story. He tolerized on a high dose of Recombinate, and once he was tolerized the dose was reduced. "Then we backed off to every other day," says Kerry, "and his inhibitor came back while he was on that protocol. So we bumped it back up." But Stephen's levels didn't drop quickly enough, so he was switched to Alphanate. Recently, Stephen had a port infection and port replacement surgery. "Every time the boys have an infection," explains Kerry, "their inhibitors come up pretty high. I hope that we'll see Stephen's inhibitor come back down the way it did initially." Because right now Stephen has an active inhibitor, he uses FEIBA to treat bleeds.

Due to the high titer of their inhibitors, Paul and Stephen use a lot more factor than regular prophylaxis patients. The main concern is keeping them tolerized with frequent treatments and relatively high dosing. "That means for the foreseeable future almost *never* missing a treatment," emphasizes Kerry. "When their inhibitors are low, they seem like 'normal' kids with hemophilia. But we can't miss treatments because after 48 hours the inhibitor starts to activate. Treating on demand will never be an option."

Because Nathan isn't tolerized, the Fatulas worry about joint damage, pain, missed school and activities, sleepless nights, keeping bleeds stopped – things that non-inhibitor patients don't frequently face. Kerry wonders about Nathan's future: "Whether he is going to have a career and be productive in the work force, due to crippling joint damage and the workdays he'll miss because of immobility and pain from bleeding."

Quality of life, today and in the future, is a key concern for many families with inhibitors. The infusion process often claims a part of every day, affecting school, travel and activities. "Many things are interrupted by bleeds," Kerry admits, "It impacts all of us as a family, but it's getting easier as Nathan gets older." Still, she worries frequently. "I have little peace of mind when he goes off to do things, and even when we take him places. He can't walk through the zoo for a day without an ankle bleed. He has to have access to a wheelchair, and we have to be able to infuse him. We don't let the factor out of our sight." For Paul and Stephen, things are a little easier. "If we infuse in the morning, Stephen will probably be OK all day, and Paul will definitely be OK, although we always take factor just in case."

A Teen's Unusual Inhibitor Diagnosis

Ray Sowinski of Pennsylvania, age 17, was diagnosed with an inhibitor unusually late, at age 15. His parents, Chris and Raymond Sr., were amazed that their son, who has moderate hemophilia A, could develop an inhibitor. "For the first 15 years," Chris reports, "Ray's had only 18 infusions. He might get treated twice in a year, and then skip years." In September 2004, Ray was infused after an eye injury during a soccer game. "I had read that an eye bleed could press on the optic nerve and cause blindness, so I got worried," recalls Chris. "We had factor from a free product trial offer, and we infused Ray that night." During the next week, with their clinic's approval the family treated Ray five times with the same product, which they hadn't used before.

Sowinski family

The Sowinski family (left to right): sister Renee, brother Ray, parents Raymond Sr. and Chris.

At Ray's regular clinic visit in December, tests showed an antibody titer of nine BUs, but an inhibitor was not diagnosed. Then in July 2005, Ray injured his ankle in another soccer game. He couldn't walk, and was treated with recombinant factor for several days. At a subsequent clinic visit in September, Ray was found to have an inhibitor of 14 BUs.

Chris wanted to know what might have caused Ray's inhibitor: Treating Ray five days in a row, when he had received so few infusions in his life? Switching to a new product? It's often reported that if a hemophilia patient is going to develop an inhibitor, it will probably happen by the 100th infusion. It's also anecdotally reported that some new factor VIII products may cause an inhibitor to develop, or that switching products may trigger an inhibitor. Ray had received only 18 infusions in his life. Could his inhibitor have been dormant until his system was bombarded with the five daily doses? Or was it triggered by the new product? To date, no one knows why Ray's inhibitor developed.

Ray's doctors recommended daily ITT, but Ray is against the idea. "He's used to just treating when he gets injured," explains Chris. "ITT means prophylaxis for the rest of his life. Ray isn't willing to do that. He's active and doesn't get hurt often. Right now he's doing track, running, and he's a hurdler."

Chris wishes there were an easy answer for Ray, and notes that right now, he's unwilling to become involved with the hemophilia community. "He wants to just forget about it. When I ask him if his ankle is hurting, he says it's fine. And when I made him get an infusion after a car accident this past February, he thought that would make his inhibitor go up. So he's not going to tell me

when he thinks he's bleeding." Although she's explained to Ray that NovoSeven, the product he uses currently, is designed to control bleeds in inhibitor patients, "He doesn't really understand. He's a typical teenager. Cars and school – that's what he worries about."

Paying the Price

As if inhibitors weren't challenging enough, Dave and Shari's 11-year-old son Jay has severe hemophilia B with a high titer inhibitor – and an allergy to factor IX. About 30 days into Jay's treatment for a head bleed at age 11 months, he developed hives and an inhibitor, and his allergic reaction progressed to anaphylactic shock. The family was completely unprepared.

"We tried a plasma-derived factor IX product for nine months, hoping to desensitize Jay to the allergy," explains Shari. Then Jay developed nephrotic syndrome, or kidney disease. "We used NovoSeven on a compassionate-use basis, and Jay had to be hospitalized each time until the product was approved by the FDA when he was five." Shari reports that NovoSeven works well for Jay at high doses. "It absolutely is the only product he can use; the only one out there that doesn't have factor IX."

Jay shows his sense of humor during a knee bleed. That's Bob (left knee) and his friend Bernice (right knee).

Like other inhibitor parents, Shari and Dave are concerned about missed school, joint damage and surgeries. But their overriding concern is the exorbitant cost of treatment: Last year, Jay's medical bill was $4 million, mainly for factor. "One dose [of NovoSeven] for Jay is about $13,000," says Shari, "and when he has a bleed, we typically treat him with four doses a day for the first two days, then drop to two or three doses. A normal joint bleed means treating him anywhere from three to nine days."

How does the family manage to pay? "We have a $250,000 per year cap on Jay's prescriptions, and he maxed out his prescription cap mid-February," reports Shari. "So now we're using [a Michigan state healthcare program] to cover his factor cost." The family worries about the effect Jay's treatment costs will have on this state-funded program; a lot of people with hemophilia in Michigan rely on it, explains Shari. "We're nervous that it's going to fold. While we've carried the coverage and paid our premium, we've done everything in our power *not* to use the state system."

How did this situation develop? Nearly three years ago, the family's insurance carrier dropped Dave's employer, a hospital, from its coverage. "Jay was costing them so much money," notes Shari. The family found a new carrier with a $5 million cap per person on the major medical benefit.

But last May, Jay had knee surgery and needed a lot of factor. The family exceeded half of their lifetime cap. "From June until the end of the year I was panicked," recalls Shari: "What are we going to do if he caps out?" Dave and Shari were able to switch to their carrier's HMO plan, with no lifetime cap on the major medical benefit but a cap on prescriptions through the pharmacy benefit side. Dave called the carrier to confirm that NovoSeven would be billed to major medical. But two weeks later, their case manager told them that the company would no longer bill injectable drugs through the major medical side; injectables would now be billed through the pharmacy side. The HMO would have a $250,000 prescription cap per year. "I have said many times to many people that they're putting a price tag on my son's life," says Shari angrily. "First they tell me he's worth only $5 million. Now they tell me he's worth only $250,000."

Dave and Shari have explained their situation to the Michigan Hemophilia Foundation advisory board, which has offered its support in advocating for Jay and others facing similar circumstances. "I've written to our state representatives and senators," adds Shari. "The response is typically that they're very sorry for our situation, but there's nothing they can do."

While they feel fortunate to be living in Michigan because of the state-funded program, Dave and Shari have considered extreme solutions to the problem of treatment cost. "We've thought about moving to Canada or Sweden," Shari confides. "Our families are here, and we really don't want to have to make that choice. But we'll do whatever we have to do for our son to get the medical care he needs."

Stress Multiplied

How to handle the stress of fighting the battle of treatment costs while caring for a child with an inhibitor? "I

really think I was on the verge of a nervous breakdown last year," admits Shari. "I felt like our child was being singled out, and I was getting tense and short-tempered. It affected my ability to be a patient mother. I have since realized that it wasn't helping to be all tied up in knots. I had to take a step back – do what I can without pushing myself over the edge. I want to be proactive, and advocate for my son's quality of life and future, but without having it control my life."

Dave understands that the insurance companies view factor provision as a business, and now the family tries not to take things so personally. "But then again," notes Shari, "I think it needs to be *made* personal. The insurance companies need to see that this isn't just about business. This is about people's lives." So the family advocates for changes in the insurance industry and the pricing of pharmaceuticals. "My primary goal is to get the word out, and my ultimate hope is that we can get the insurance companies to raise their caps."

Shari reports that Jay has felt stressed during the past year. "For a while we were getting calls from our insurance company at dinnertime, and we'd be arguing with them," she says. "We took the attitude initially that we would be open with Jay, and teach him how to advocate for himself. But it became very stressful and upsetting for him, so we don't discuss insurance with him now. In hindsight, I wish we'd never discussed it in front of him. We need to shield him from that."

Shari and Dave worry about Jay's health, schoolwork and social life. "I think he has a hard time making close friends and keeping them because he's not in school all the time. He missed six weeks of school last year because of knee surgery. And I worry about the future," she adds. "Who's going to want to hire him when he's going to shoot up the cost of whatever they're paying for insurance? He can get state aid, but we want him to be a participating member of society. He has a lot of gifts to offer."

To keep his joints healthy, Jay stays active on the golf course.

Unfortunately, research into inhibitor treatment may not soon hold the key for Jay because of his allergy to factor IX. "I know there are new things on the horizon, but is there going to be anything that will benefit *my* son?" asks Shari.

Looking Ahead

While the future is uncertain for inhibitor treatment, hope is on the horizon (see sidebar, page 14). In the meantime, how do these boys view their health, their options and their future?

At 13, Leland is forming new concerns about life with an inhibitor. "Leland's perception of his future has changed," believes Jane. Until recently, Leland accepted his hemophilia and inhibitor, dealing with problems and then getting on with life. But now, Jane reports, after his recent challenges, "Every time he feels the symptoms of a bleed, he immediately starts worrying that it will be a bad one that gets out of control. His resiliency isn't what it once was; he doesn't have a lot of reserve left."

Jane admits that she and Leland "haven't talked much – because I don't want to stress him out – about what this means for high school, for college, for getting a job and being a productive adult. I hope that the impact this has on his day-to-day life will level out, but from a parent's point of view, I'm very concerned. He's a bright student, and has been able to catch up with his schoolwork; but he's missing chunks of the foundation that's built by going to school day after day." Thoughts of the increasing workload in high school and college fuel Jane's apprehension. "I have many more concerns about his future now. Having a good job, and the insurance that goes with it, is crucial. How do you hold down a full-time job when you have so many days that you're out of commission?"

Kerry reports that Nathan is frustrated by the repeated attempts to control his inhibitor. "We try to convince him how much better his quality of life will be without the inhibitor, and how important it is to try whatever comes up." But she points out, "Treating with FEIBA or NovoSeven isn't as effective for us as factor VIII products. We can't treat prophylactically. So although it sounds good to Nathan just to treat a bleed when it comes, it's not that simple."

At 17, Ray remains resistant to ITT attempts, and reluctant to discuss his disorder. Chris would like to connect with other inhibitor families for support and sharing. She hopes that through this article, she may learn of other inhibitor families facing similar challenges.

Finding Support

How do inhibitor families find strength to face daily challenges? Shari is comforted by prayer support from

An Optimistic Outlook: Future Strategies for the Eradication and Prevention of Factor VIII Inhibitors

by Donna DiMichele, MD

In view of the major progress made in the management of hemophilia A and its other complications during the latter part of the twentieth century, inhibitor development has emerged as the most challenging remaining problem. Long-term successful eradication of inhibitors has been achieved using strategies such as immune tolerance. Recently, for patients whose inhibitors will not go away on standard immune tolerance therapy, doctors have begun to add treatments that dampen the body's immune response to factor VIII or factor IX. One such therapy is called Rituximab™ (IDEC Pharmaceuticals, San Diego, California). This drug is an antibody that temporarily removes B cells (the inhibitor–producing cells) from the body. However, so far the effectiveness of this drug in severe hemophilia A and B inhibitor patients is limited. More studies will be needed before we can decide how beneficial this treatment may be. Fortunately, one such study will soon begin in the US.

Much of the exciting current research is now focusing on how inhibitors might be prevented. Several such promising strategies are being targeted at the body's immune response to factor VIII. One involves potentially using gene therapy as a method to once again train the body to accept factor VIII treatments. All are currently being tested only in the test tube or in laboratory animals. There are as yet no clinical studies in humans. Importantly, although factor VIII inhibitors are the target of much of this research, any information we obtain could be applicable to factor IX inhibitors as well.

Ultimately, future approaches aimed at inhibitor prevention, and derived from a committed collaboration between basic scientists and clinical investigators, will provide the long-awaited solutions to this vexing problem.

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photo: New York Presbyterian Hospital–Weill Medical College

"Much of the exciting current research is now focusing on how inhibitors might be prevented."

her church, but describes the juggling act required to get Jay and his two sisters, six-year-old twins Anya and Isabella, through a typical day: "When Jay has a bleed, for the first two days we set the alarm and treat every six hours, so we're up in the middle of the night to do the pokes. We're trying to figure out who can take the day off work, and who will pick up the twins from kindergarten. Pain management is an issue. Throw in getting to school, homework, gymnastics, church functions… We're as busy as everybody else, plus we've got to make time for infusions, doctor's trips and dealing with bleeds."

Kerry echoes the emphasis on day-to-day functioning. "At this stage in our lives," she admits, "it isn't really emotional support I need most, but practical support. My husband travels for a living and I'm usually by myself with the four boys. Someone ends up in the hospital for a week, or Nathan is laid up for days with a bad bleed. So I just say, 'I'm calling in the troops!' Close friends, neighbors and family take turns helping out. It's a mini-corporation – but strictly volunteer. Without them I truly would be lost."

Is there a well-defined inhibitor community that can offer support? "There hasn't been an inhibitor community until just recently," believes Diane. "The first time I had a sense of community was at the Novo Nordisk inhibitor summit in Philadelphia last fall. Typically, when you go to annual meetings it's just a hemophilia community." Diane also finds support through online chat groups. "Even if you aren't a mother of a child with an inhibitor, you're the mother of a child with hemophilia who's had a bleed, so you have the same thing in your heart. In that way, we're all connected."

Finding Inhibitor Information

Inhibitor information traditionally has been ignored or discounted in most hemophilia literature and on websites. "There is no collective source of information, no depository for new stuff," notes Kerry. "Almost everything I know I've learned through just living it." She explains that inhibitor families share concerns outside the realm of 'normal' hemophilia. "It can be difficult to relate both to non-inhibitor patients and to regular treatment and educational information. The inhibitor handouts in the HTC don't even skim the issues for us. They seem very simplistic."

To understand inhibitors, it's essential to first fully understand hemophilia. But as Diane notes, many families new to inhibitors are under-educated on even hemophilia basics. She observed this knowledge gap firsthand at the Novo Nordisk inhibitor summit: "I expected to get hot and heavy into the core of inhibitors, but they started giving 'hemophilia 101.' Then I looked around the room, and realized that a lot of people who were trying to understand inhibitors still didn't have the basic foundation of hemophilia. Parents of children with

Smith family

Leland and his sister Taylor share an affectionate moment.

inhibitors must go to the next step to understand hemophilia at a deeper level than the average hemophilia parent."

Sharing her challenges and hopes with a peer group at the summit, Jane found fundamental support. "That was huge for me – a program devoted specifically to inhibitors. I came away with some new information, but just as important for me was being with other families who share similar experiences, and who have that knowing nod of the head." She also talks to medical professionals outside her HTC. "I have great confidence and respect for my son's medical team, but because there are so many different approaches, and so much is unknown, it's crucial to find out what's being tried outside of our own little world. And I expect my son's doctors to be doing the same."

Seeking the Right Treater, Right Product

Are most hemophilia specialists well informed about inhibitors? "It's the same across the board," believes Diane, "whether you're talking about ports or inhibitors: You get a varying degree of expertise. Some doctors are in tune with the latest research and information, and some doctors don't know as much."

Finding specialists who are experienced in inhibitors is key. And because inhibitor treatment is highly individualized, Diane avoids making decisions based solely on the comments of other consumers. "During one breakout session at the summit," she recalls, "I heard very strong opinions from parents [about specific products]. Parents listened to other parents, and got the dickens scared out of them." She concludes, "It's best to make these decisions in conjunction with your doctor. With inhibitors, it's trial and error."

Jane notes that once an inhibitor has been tolerized, parents are sometimes reluctant to make any changes in treatment regimen, fearing that the inhibitor will return. "I think they're worried about rocking the boat: We're so lucky we got rid of it. We'd better not change anything because what if we do, and it comes back?" Parents worry about changing the frequency of treatment, changing products – changing anything. "What if the product used all these years is phased out because that company is introducing a new, better brand?" asks Jane. "Will the slight differences in that new concentrate tickle the inhibitor again?"

Chris advises avoiding the temptation to switch products based on lower price or free offers. "The clinics seem to leave all the decisions up to you: What brand do you want? You can get this for free. Want to try it?" She still has products in her refrigerator that she received through free offers, but worries that changing products might cause or reactivate an inhibitor.

"Parents are looking for answers," Diane says simply. "When Matthew was diagnosed with hemophilia, I was stunned. But the doctor reassured me, 'Listen, we'll put a port in him, he'll have factor, he'll have a normal life.' And I was at ease. Then I was told he has an inhibitor. Again I was looking for answers: You gave me a port and factor; what are you going to give me now? What do you mean, there are no answers? You gave me an answer last time." She warns, "With uncertainty, there is also fear – and then you're just listening to anybody and everybody. You have to be careful, weed through information, and not go on hearsay."

Finding Peace

For Kerry, accepting life with inhibitors has brought a sense of focus. "We have accepted the responsibility, both to the kids and to the community. That brings a kind of peace, an automatic ordering of our priorities." She concentrates on issues that she can directly influence, and ignores what can't realistically be changed.

Despite stressful times, Diane believes, "It's no different than having any other challenge in life. You take what is handed to you and do the best you can. There are no guarantees in life. My children are healthy and happy. I simply count my blessings and continue to face the challenges we face in life, whether it is hemophilia, inhibitors, insurance issues or getting my children to listen!"

Along with friends and family, Kerry concludes, "My main source of emotional support is God and my belief that nothing happens on this earth without a reason. When things are scary and painful and frustrating, I pray for three things: strength, courage and commitment. That's what I rely on and hope that I will pass on to the boys."

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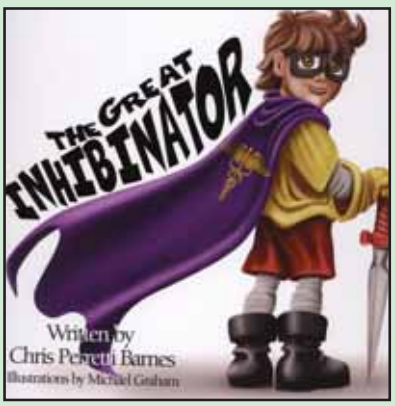
Bloodstone Mini presents the Welligan Hugsley gang in its own colorful magazine for children.

For more information: www.HemophiliaHealth.com

Meet *The Great Inhibinator*!

BioRX has teamed with Bayer HealthCare to present a children's book for school-age children about Nate, a boy who discovers he has an inhibitor. With colorful illustrations and a story centering on creating a costume for Halloween, this hardcover book is recommended for young school-age children.

For more information: www.biorx.net or 866-44-BIORX



nonprofit

Radical Changes Proposed at NHF

The National Hemophilia Foundation is proposing to unite the various and disparate state and regional chapters into a united national organization with a single budget and reporting structure. The goals of this proposed structural overhaul are to gain efficiency in an era of tighter budgets; to present a common voice, particularly in the fight against reimbursement restrictions; and to unite the community in general. It's estimated that currently about half the US chapters approve the historic proposal, and half do not. Negotiations are expected to continue between the NHF and chapters this year.

For more information: www.hemophilia.org

New Booklet for Hemophilia B Patients!

B2B Speaking from Experience is an inviting, colorful booklet for adult and teen "B" patients that shares the personal experiences of other factor IX deficient patients. Developed using recommendations by the Wyeth Consumer Advisory Board, this booklet is user-friendly and packed with information designed to reach those already living successfully with hemophilia B.

For a free copy and more information, contact The Coalition for Hemophilia B: hemob@ix.netcom.com or 212-554-6898

manufacturer

Humate-P Diluent in Convenient Size

Humate-P is now available with 50% less diluent in all assay sizes. The new formulation offers added convenience: Patients who use the new formulation spend less time infusing, and the smaller package size requires less storage space. Humate-P is the only factor concentrate approved by the FDA for use in treating patients with von Willebrand Disease. ZLB Behring is a company of CSL Limited.

For more information: www.zlbbehring.com

Grifols Adds Theft Deterrence Measure

Grifols is now voluntarily inscribing the lot numbers of all coagulation products, including Alphanate®, AlphaNine® SD, and Profilnine®, with a laser. The laser etching should correlate with the lot number on each vial's label as well as the number on the aluminum overseal on the vial's top. The lot number correlates with filed data, such as date of production, product expiration date and vial size. This should help deter counterfeiters from adulterating products and re-labeling.

For more information: www.grifolsusa.com and read "Hemophilia Thieves" by Laurie Kelley (*PEN*, Feb. 2006)

International Survey of Practices in Hemophilia A

A survey sponsored by Baxter Healthcare provides the first opportunity to compare treatment of hemophilia A in 16,115 hemophilia A patients from 19 countries. Key findings from the survey:

- 37% of patients were prescribed prophylaxis; 54% received on-demand therapy.
- The mean ratio of nurses to patients per treatment center was 1.6 nurses to 110 patients.
- Patient compliance was strongest during early childhood (0–12 years: 90%); this was most likely due to family supervision. Compliance fell with older patients.

Global Nurse Symposium Planning Committee developed the survey, which was designed to improve the global understanding of current hemophilia A practice patterns, factors that influence them, and changes over time.

Source: Baxter BioScience press release

Wyeth *Lifelines*

The Wyeth *Lifelines* program includes an informative and educational newsletter: *Lifelines* covers timely topics like reimbursement issues, and presents medical expert articles, personal stories from hemophilia patients, hemophilia news–and more.

For more information: Hemophiliavillage.com

"Coming Storm" Alert!

Reimbursement Alert On-line is a comprehensive review of current changes in health insurance reimbursement for plasma therapies and other relevant issues. To read the *Alert*, visit www.zlbbehring.com or have it emailed by registering at www.zlbbehring.com/zb/n968936/eNEWSSignUp.htm

Letters... continued from page 2

IT IS SO GOOD TO READ ABOUT THE positive things that people do in life. It's like a breath of ffresh air. I am a lay woman who is an associate with the Sisters of Notre Dame de Namur. Our mission statement includes making known "God's goodness and love of the poor through a gospel way of life" and "to work with others to create justice and peace for all." I believe that there are many people like you who live out our mission statement in their lives. If people are willing to share their factor with others, this shows that sharing our excess, whatever that may be, is what we all should be doing. So to you, Laureen Kelley and Julia Quigley Long, keep up this wonderful work and may our good God continue to bless you for all that you do.

Ann Crotty
MASSACHUSETTS

["JOURNEYS OF HOPE"] WAS SO moving. Thanks for all you do to help those who are less fortunate than ourselves. The world is a better place because of you!

Cheryl Hurst
NORTH CAROLINA

THANK YOU FOR ALL YOU DO FOR THE hemophilia community, both here and abroad. I am glad to donate factor that, instead of expiring in my home, can be used to help someone. God bless you!

Rebecca Lacey-Vorstenbosch
KENTUCKY

IN NOVEMBER 2005 I RECEIVED FOUR vials of NovoSeven® as a donation from your organization. Pakistan has one of the highest rates of maternal mortality (mothers dying during childbirth). The most common cause of this is massive blood loss. We have started using NovoSeven for these young mothers for whom all medical and surgical treatments have failed. I am usually called upon to treat these women as a last resort, hoping that I can do a miracle. So far I have managed to save 12 women in the last few months; four of them were saved because of you, from the donated NovoSeven. I consider saving one mother equal to saving one generation. Thanks for the great work you have been doing.

Dr. Tahir Shamsi
Bismillah Taqee Institute of Health Sciences & Blood Diseases Centre
KARACHI, PAKISTAN

Storm Watch

WE JUST GOT OUR 2006 OPEN enrollment information, and it's not good. Our premiums and deductible have doubled and we have been hit with a $1 million lifetime cap. We'll max out that cap quickly: Our claims to date for 2005 are over $600,000 and we were lucky this year – no hospitalizations or surgeries!

Needless to say, we are in a panic and are using any resource we can find to educate Nathan's employer and the insurance company about the impact this will have on our life. Not once in two years have I had such negative feelings surrounding hemophilia. When we got the diagnosis, Nathan and I literally hit the ground running to educate ourselves, and never even looked at our son Thomas differently. Then we got the inhibitor diagnosis, and after a deep breath, we pulled out the boxing gloves and were ready to fight. Although ITT has its ups and downs, we've stayed positive and continued to not see hemophilia as a burden. Now as we fight this new and entirely different beast, I feel so incredibly beaten – it's like we are being punished for something completely out of our control. But it's not going to deter me from being the alarm to wake up my fellow hemophilia parents. I'm probably going to be up on my soapbox even more than usual!

Sonji Wilkes
UTAH

"THE COMING STORM" SERIES [*PEN*, Nov. 2004, Feb. and May 2005] was one of the best-researched and most informative articles I have read on the topic. My first love is insurance/reimbursement as it relates to hemophilia patients; and I know what I'm talking about, based on 16 experiences in the hemophilia community. Take my compliment seriously – please continue to do the good work you do.

Bobbie Kincaid
Hemophilia Health Services

THANK YOU SO MUCH FOR publishing Ann Rogers' editorial "With Access For All" [*PEN*, Feb. 2006]. I have had the opportunity to work with both the Delaware Valley Chapter and the Western Pennsylvania Chapter of the NHF in the drafting and advocacy of the Pennsylvania Hemophilia Health Care Act (HB 1705). When approved and enacted, this legislation will be a significant step forward in the protection of the right to access for individuals with bleeding disorders. Further, this legislation will

increase recognition and proper treatment for the under-diagnosed condition of von Willebrand Disease. As stated in the editorial, it is estimated that nationally 30,000 women annually have unneeded hysterectomies. This legislation will serve to ensure that women with VWD in Pennsylvania will be screened prior to a hysterectomy. This should lead to an increase in proper treatment for VWD while reducing the number of hysterectomies and the psychosocial trauma that is far too prevalent with such a procedure.

In this time of growing insurance restrictions concerning access to care and provider, the two Pennsylvania chapters should be applauded for creating legislation that will be of benefit to people with hemophilia throughout the commonwealth of Pennsylvania. Moreover, just as the Pennsylvania chapters used legislation enacted in New Jersey to model HB 1705, I hope other state hemophilia chapters and organizations tailor HB 1705 to meet the specific needs of their individual states. With the onslaught of restrictive regulations and legislation being offered throughout the states in terms of access and the need to react to such proposals, it was refreshing to be part of a proactive approach to address this looming problem. I look forward to being part of the battle, being led by both Pennsylvania chapters, to obtain passage of HB 1705.

Patrick Collins, Sr.
Manager, Public Affairs
ZLB Behring
PENNSYLVANIA

"Hemophilia Thieves"

WHAT A GREAT JOB YOU ALL DID WITH "Hemophilia Thieves" [*PEN*, Feb. 2006]. Thanks for the diligent work, the kind words and, graphically, a very nice looking piece. Congratulations!

Katherine Eban, author,
Dangerous Doses
NEW YORK

FABULOUS ISSUE! THIS WILL BE AN eye-opener for most people. It was for me. Great work.

Elena Bostick, Executive Director
Hemophilia Association of New Jersey

FINALLY HAD A CHANCE TO READ this issue – very informative! You are really my idol for writing about and doing research and advocacy.

Ellen Kachalsky, MSW, ACSW
Adult Hemophilia Treatment Center Henry Ford Hospital
DETROIT, MICHIGAN

THE FEBRUARY ISSUE OF *PEN* is the same high quality to which we have grown accustomed. I want to second the remarks and thanks that Elizabeth Fung expressed to you last Thanksgiving [*PEN*, Feb. 2006, *Letters*]. Your efforts on behalf of the hemophilia and bleeding disorders community are greatly appreciated.

With regard to the letter from the family traveling in Mexico, I would like to draw attention to an online resource. The Hemophilia Emergency Care website (Region VI), while designed for physicians, does have English information available in Spanish. This information could be useful if someone needed to access an ER in a Spanish-speaking country: www.hemophiliaemergencycare.com/spanish/index.html

Dennis Penning
Clinical Services Coordinator
Hemophilia Foundation of Illinois

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