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Parent Empowerment Newsletter

Crossroads for Gene Therapy

by Kevin C. Kelley

Five years and five trials into the clinical testing of hemophilia gene therapy programs, the results are mixed. While the promise of a cure remains strong, proponents of gene therapy face a number of tough choices, and many unanswered questions. Do we really know enough about all the various gene transfer methods to be moving them into human testing? How can we balance the desire for progress with the need for safety? How will the necessary research be funded? Who will decide which programs move forward? How will participants in the trials be chosen?

In many ways, these unresolved questions have always been with us. Yet the events of the past few years have heightened the importance of facing each question head on, and coming up with workable strategies to keep gene therapy moving forward. During the early years of the first hemophilia trials, intense momentum was driving the trials, and optimism reigned. But that trend has reversed over the past several years. The current climate presents financial, regulatory and scientific conditions that are much less conducive to supporting gene therapy. Gene therapy today is at a crossroads, and decisions made now could determine the direction of gene therapy research for the foreseeable future.

Balancing Risk and Progress

"*Only those who risk going too far can possibly find out how far one can go.*" **– T.S. Eliot**

In 1998, Transkaryotic Therapies, Inc. (TKT) initiated its hemophilia A clinical trial, marking the beginning of human gene therapy testing for hemophilia. In all areas of medical research, human testing is an integral step in advancing from the laboratory to commercial products. The safety and efficacy of any product cannot be known until the product is actually tested in humans. However, the purpose of human trials is not simply to prove that products *work*. Rather, in most cases, human trials represent an advanced stage of clinical research. They provide additional knowledge that helps scientists continue to fine-tune and improve treatment methods– by adjusting dosing regimens and altering protocols, for example. Human clinical testing is often an ongoing process: results, both positive and negative, from early trials may be used to design improved methods for future trials. Particularly with a novel technology like gene therapy, the early trials are more likely to provide insights into how gene therapy works (or doesn't work) than to actually lead directly to a cure.

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inside PEN

LA Kelley Communications, Inc.

welcome

The past year and a half has been a tumultuous period for gene therapy research in general, and hemophilia gene therapy in particular.

There is meaningful progress to report, but there have also been significant setbacks in the majority of programs. Financial constraints, regulatory concerns and scientific obstacles have all contributed to a decline in the rate of progress and, perhaps more ominously, a decrease in corporate support for hemophilia gene therapy. In this issue of *PEN* we take a detailed look at the major challenges facing the future of gene therapy research. We'll examine why gene therapy today is at a crossroads.

One clear message is that the scientific basis underlying gene therapy remains solid, and our hope for a cure for bleeding disorders is still strong. But the development and commercialization of gene therapy will require more than good science–it will require ongoing financial support. In today's economic climate, institutional support for gene therapy is wavering. The decline in corporate support increases the burden on our community to keep gene therapy moving forward. In *As I See It*, Steven Humes, Director of Research for the National Hemophilia Foundation (NHF), describes the idea behind the NHF's second phase of the "It's Time for a Cure" campaign. As you read this issue, ask yourself what you, your family and your community can do to support the NHF campaign and continued gene therapy research. These monumental efforts can, and will, bring us closer to our goal: a cure for all bleeding disorders.

PARENT EMPOWERMENT NEWSLETTER AUGUST 2003

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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 an unbiased forum that promotes an active exchange of information and support among divergent groups in the national and international hemophilia community.

PEN does not promote individual products or companies, and will use brand product names and company names pertaining only to news and education.

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Are you interested in submitting articles to PEN?

PEN is looking for medical professionals, advocates and consumers with good writing skills to submit articles. *PEN* pays $800 for original feature articles and $50 for *As I See It*. For submission guidelines, contact us at info@kelleycom.com. *PEN* will work with authors on editing and content but cannot guarantee that submissions will be printed. Overseas authors welcome!

letters

I AM GRATEFUL FOR *PEN* AND ITS HELPFUL ARTICLES. *PEN*, and the friends I have met through it, have kept me going through some very rough times. My son Ryan was the first in our family to have hemophilia, and when he was diagnosed I felt completely overwhelmed, terrified, guilty and depressed. I wrote and asked for help, and received such a huge personal response from people it was amazing. I have many "*PEN*" pals now who are parents of older children with hemophilia, and they help me deal with problems. It was, and still is, very comforting to talk with others who have gone through the same thing. They are surviving, so I guess I can, too.

Ryan is almost three, and very active and healthy. Like most children with severe hemophilia B, he has good days and bad days. But when they are good, they are really good, and we have learned to calm down and enjoy our son. A piece of advice that changed my whole way of thinking was when one *PEN* pal told me, "Love the boy and then treat the disease." Those wonderful words of wisdom have really settled a lot of my terrified feelings about hemophilia. And we do just that–we love and play with Ryan like he's a normal little boy. We aren't so terrified that he might scrape his knee and bump his head. It has helped so much with his development, and with our stress levels.

Just thought I'd say thank you for such a valuable publication. We look forward to it every quarter!

The Malcolm Family, CALIFORNIA

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it's time for a cure...

www.hemophilia.org

by Steven Humes

"It's Time for a Cure"
Broadening the Focus

In 1998, The National Hemophilia Foundation (NHF) launched the initial phase of the new "It's Time for a Cure" campaign (ITFAC). The goal of ITFAC was to raise $5 million for research that would lead to a cure for bleeding disorders. At that time, the economic and scientific climate was vastly different than it is today: many biotechnology firms were engaged in preclinical research on gene transfer for hemophilia, and multiple clinical trials were apparently on the horizon. The US was in the midst of a frenzied economic boom that some analysts thought had erased the typical highs and lows of the normal business cycle.

That rather remarkable–and blindly optimistic–era is now a bittersweet memory. The stock market implosion and ensuing hard times dried up much venture capital. The death of Jesse Gelsinger, a patient in a gene transfer trial unrelated to hemophilia, slowed the regulatory process and discouraged many potential subjects from enrolling in studies. Other setbacks in research, primarily related to immunological issues, made it clear that a gene transfer "cure" is not imminent. The unsurprising result: both start-up and established biotech firms have folded up their tents and left the hemophilia gene transfer field, with only the Avigen trial (currently on hold) an oasis in a fairly barren desert.

The partial withdrawal of industry from promising research has left the burden of research on the federal government and private organizations, underscoring the wisdom of NHF's expansion of its grants program. What some saw as NHF's peripheral role in spurring important studies has now become prominent. NHF plays a major part in stimulating research into a cure for bleeding disorders. Its efforts include an annual gene therapy workshop; advocacy with Congress and the National Institutes of Health; and a growing portfolio of awards including three Laboratory Grants and ten Career Development Awards given to date under ITFAC.

Now, after the launch of the second phase of ITFAC in November 2002, NHF is poised to extend its sphere of influence by **doubling** its financial commitment to gene therapy research. NHF will raise $10 million by fall 2007, and has already received pledges of $3.3 million. Further, and equally important, the National Heart, Lung, and Blood Institute (NHLBI) has signaled its willingness to collaborate on a joint research venture, in which it would match any funds that NHF contributes. The NHF and NHLBI are currently working out the details of an arrangement that would devote $6 million of the second ITFAC campaign to a grant program administered by NHLBI for research in various "cure" related areas.

The scope of research being negotiated with NHLBI represents NHF's recognition that many potential paths lead to a cure for bleeding disorders, and gene transfer is only one of them. At NHF's last gene therapy workshop, at the Salk Institute for Biological Studies in April 2003, a new realism emerged among researchers about how to tackle systematically the substantial barriers to successful gene transfer. Equally gratifying was information shared about novel approaches in the following areas: stem cell therapy, factor production in transgenic animals, factor half-life prolongation, and translational bypass therapy. This broad spectrum of approaches characterizes NHF's strategy for the foreseeable future. NHF wants to achieve the equivalent of a cure for bleeding disorders–whether this means far less frequent factor infusions, oral delivery of factor proteins, customized gene repair or some other technique.

To develop a cure for bleeding disorders, NHF intends to champion the most innovative and high-quality science possible. The tools of this endeavor include the proposed arrangement with NHLBI, the ongoing series of gene therapy workshops, a variety of awards including the three-decade-old Judith Graham Pool Postdoctoral Research Fellowship Program, and public advocacy efforts. This is NHF's vision, and it is needed now more than ever.

Steven Humes, MPH, is Director of Research for the National Hemophilia Foundation.

by Paul Clement

Striving for Increased Safety

Second- and Third-Generation Recombinant Factor VIII Products

"*Safer factor concentrates.*" This has been the mantra of the hemophilia community since the early 1980s, when 60% to 70% of people with severe hemophilia A were infected with HIV and more than 90% with hepatitis C (HCV) from contaminated factor concentrates. As a result, the plasma collection and fractionation industries (companies that produce factor concentrates) were pressured by advisory committees, consumer groups and the US Food and Drug Administration (FDA) to improve the safety of blood plasma and blood products like clotting factor concentrates. These industries have now implemented many new processes, standards and tests to ensure the safety of their products. And in recent years, pharmaceutical companies have introduced factor concentrates that have no plasma-derived proteins in the final product, thus essentially eliminating the possibility of viral contamination of the final product.

What measures have improved safety? Since the mid-1980s, **purification**[1] and **viral inactivation**[2] processes have been implemented to remove and destroy, or "inactivate," most viruses. Plasma pools from multiple donors have been reduced in size from a high of 400,000 units to 60,000 units of plasma or less per pool.[3] New and more rigorous examination and screening of plasma donors has been implemented. In addition, new plasma donors are required to return for a second donation, and pass all health and blood tests again, before their plasma can be used. Fractionators have implemented a "60-Day Inventory Hold Standard." This standard requires that source plasma[4] be held in inventory (frozen) for a minimum of 60 days, to allow for the retrieval of any suspect donations before they are used in fractionated blood products. And new and more **sensitive viral blood tests**, such as Nucleic Acid Tests (NAT), have been introduced.[5]

The result of all these safety measures? There has been no transmission of HIV since 1987, no instance of HCV since screening began in 1993, and no instance of hepatitis A (HAV) transmission from factor concentrates since 1995.

Beyond the task of making plasma-derived factor safer, industry searched for a way to produce factor VIII without using blood plasma. The gene for factor VIII was cloned in 1984 and, by the late 1980s, the first **recombinant factor VIII** was produced–*without* using blood plasma as a source of factor VIII. By the early 1990s, two recombinant factor VIII products[6] were approved for the US market. Unfortunately,

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[1] Such as monoclonal antibody purification, chromatography, and nanofiltration. [2] Viral inactivation methods include heat (dry heat, pasteurization and "wet heat") and solvent/detergent washes. [3] Plasma donors, through plasmapheresis centers, donate a unit of plasma referred to as "source plasma." (See footnote 4.) To gain the advantage of economy of scale, fractionators would collect up to 400,000 units of source plasma and process the whole batch, or pool, at one time. Large pools increase the odds that one of the donors will have a disease that would be transmitted to everyone receiving a product produced from that pool. [4] "Source plasma" is a donation of plasma only. It is donated through plasmapheresis, a "continuous loop" donation process that removes plasma and returns red blood cells to the donor. [5] "Closing the Window: Virus Detection Technology Comes of Age," *PEN*, May 2003, p 4. [6] Recombinate™ (Baxter) and Kogenate® (Bayer).

A BIRTHDAY TO TREASURE

by Pamela Mosesian

Ifrad Tazik Ahmed

Ifrad Tazik Ahmed of Dhaka, Bangladesh, celebrated his fourteenth birthday in June with classmates, friends and relatives. This year's celebration was especially joyous since Ifrad had recently recovered from a debilitating hip bleed that almost kept him from enjoying his own party.

In April, Parimal Debnath of the Hemophilia Society of Bangladesh (HSB) contacted Project SHARE seeking help for Ifrad. Ifrad was suffering from a devastating psoas (hip) bleed, with crippling pain in his swelling hip joint. Ifrad wasn't able to stand or leave his bed. Thanks to Project SHARE, Ifrad received the 20,000 IUs of factor VIII that he needed to recover from the bleed, and was able to receive some physiotherapy. His pain subsided, and he returned to school. He was even able to attend his own birthday party.

Hemophilia affects Ifrad's life every day. Most 14-year-olds with hemophilia in the US lead very active lives, spending their boundless energy on sports and activities with friends. This isn't possible for Ifrad. Playing outside with his friends isn't an option. Frequent bleeds and little access to medicine interrupt regular school attendance and homework assignments. To complicate matters, Ifrad has a rare blood type that makes finding blood products such as cyro extremely difficult when factor is not available.

Ifrad says "hello" to the US hemophilia community, and is happy to share his experiences. "People with hemophilia in poor countries," he explains, "always hope that their counterparts in rich countries will come forward and help them– not only with logistic support when needed, but also by sharing their feelings and sending their encouragement."

Determined student: Ifrad reads diligently to make up for schoolwork missed due to frequent bleeds and little medicine.

A more normal life, for now: Thanks to Project SHARE, Ifrad recovered from a debilitating hip bleed and is enjoying his life.

Without donations of in-date factor from the US hemophilia community, this donation from Project SHARE to Ifrad would not have been possible. So far this year, Project SHARE has impacted lives in more than 22 developing countries with total factor donations of over 3.4 million IUs. Our goal of donating six million IUs of factor by the end of the year is reachable, but not without the help of the US hemophilia community.

To learn more about Project SHARE, please visit www.kelleycom.com/iha/projshare.html or contact director Annie Schwechheimer at (978) 352-7657 or annie@kelleycom.com.

Project SHARE[SM] is an international humanitarian program administered by LA Kelley Communications, Inc., in partnership with Aventis Behring, Baxter BioScience, Bayer HealthCare, Hemophilia Health Services and Novo Nordisk Pharmaceuticals, Inc. Factor donations are primarily from private sources.

Eric Dostie Memorial
College Scholarship Winners 2003

LA Kelley Communications is pleased to announce the winners of the Eric Dostie Memorial College Scholarship for 2003. The scholarship honors the memory of Eric Dostie, a five-year-old boy with hemophilia who was tragically murdered in 1994. Funds provide financial assistance to students and family members in the bleeding disorders community. The Eric Dostie Memorial College Scholarship is generously funded by NuFactor, of Temecula, California. We extend our deepest thanks to NuFactor and to the 2003 review committee for their hard work, compassion and dedication.

Adam Wilmers plans to pursue a pre-medical degree at the University of Michigan. He is considering a career as a pediatric hematologist to give back to the hemophilia community. Adam enjoys theater, photography and working with children. "My eventual goal is not to take care of patients; it is to take care of *people*."

"My eventual goal is not to take care of patients; it is to take care of people."

"The biggest obstacle in my life has certainly been living with hemophilia… but thanks to it, I have figured out what I want to do with the rest of my life."

Michael Reutershan will attend Bowdoin College as a biology major. He hopes to attend medical school and pursue a career in hematology. Michael enjoys reading, writing and spending time with friends and family. "The biggest obstacle in my life has certainly been living with hemophilia… but thanks to it, I have figured out what I want to do with the rest of my life."

"To help people enjoy life and reflect for the moment, and to possibly inspire someone."

Victoria Vieira plans to pursue a degree in graphic arts and illustration. She would like a career that allows her to apply her artistic talents. In addition to art, Victoria enjoys researching mythology, and bird watching. Through her creativity, she hopes "to help people enjoy life and reflect for the moment, and to possibly inspire someone."

Travis Ward attends the University of Texas, Austin. After graduation, he plans to pursue a career in special effects for the film industry. Travis enjoys computer graphics, drawing and outdoor activities. As a special effects artist, he hopes to "create the images that enthrall and inspire the imaginations of children."

"Create the images that enthrall and inspire the imaginations of children."

Rachelle Rubin is a business administration major at the University of Florida. She enjoys volunteering, soccer and photography. In the future, she hopes to start a company that will benefit the hemophilia community. "I want to work with families and patients, help them get medicine, and create outreach programs for those new to the community."

"I want to work with families and patients, help them get medicine, and create outreach programs for those new to the community."

Marcus Hurt is a psychology major at Hannibal-LaGrange College. He enjoys art, weight-lifting and playing drums. He plans to pursue a Master's degree in clinical psychology, and would like to work in a hospital counseling patients. "One day, school will be done, but learning will never cease."

"One day, school will be done, but learning will never cease."

Matthew LaPine is a music education major at Westminster Choir College of Rider University. He enjoys basketball, racquetball and writing, but music is his passion. "My true motivation is in knowing that, through music, I can help others."

"My true motivation is in knowing that, through music, I can help others."

Lindsey-Joy Gillian Hanson attends Tulane University, and plans to obtain a Master's degree in oriental medicine. She enjoys swimming, research and volunteer work. She ultimately hopes to open a clinic dedicated to helping those with chronic illnesses. "I don't want to simply treat diseases, I want to help others maintain good *health*."

"I don't want to simply treat diseases, I want to help others maintain good health."

With heavy heart, we inform our readers that George Gosselin, grandfather of Eric Dostie, passed away on April 14, 2003. He loved his grandson very much, was devastated by his loss, and worked to help honor Eric's memory through the Eric Dostie Memorial College Scholarship. George was grateful to NuFactor, especially to founder and CEO Patrick Schmidt, for funding a program that eased his family's suffering and helped so many in the bleeding disorders community. George will be deeply missed.

Applications for the 2004 Eric Dostie Memorial College Scholarship will be available through LA Kelley Communications, Inc. after November 1, 2003. For more information, please visit our website at www.kelleycom.com/finaid/finaid.html or call us at (978) 352-7657.

www.Xanodyne.com

Congratulations... Amicar's 40th Anniversary!

by Laurie Kelley

MANY PEOPLE ASK ME HOW I CAME TO WRITE MY BOOK *Raising a Child With Hemophilia*. Was I a professional writer? A nurse? No; just a mom with a newborn with hemophilia. Well, I was also an economist, but not a very good one. And I always enjoyed writing. So I had plenty of incentive to start a new career.

But my real push to write a book was due to my "Amicar® story." Tommy was six months old and teething, desperately chewing on everything. One night after I had placed him in his crib, I heard him cry sharply. When I turned on the light, he was sitting up crying and bleeding from his mouth. The poor baby had chewed on the crib rail and cut his gum. Blood oozed out at a steady pace, but by the time we called our HTC, the flow had stopped. Still new to hemophilia, we didn't know what this meant. Our doctor told us to just put him back to bed, which we did.

The next morning, a shocking sight met our eyes: our six-month-old, bouncing happily in his crib, one hand on the crib rail, the other on his bottle, completely covered in blood from head to waist. Blood was everywhere–on his sheets, pillowcase, hair, in his ears and nose. I recall just two white eyes blinking at me. Tommy was happy, and thankfully we understood the source of the blood. Had we not known, imagine the shock we would have felt! We bundled him up and whisked him off to the HTC, where he was monitored and released. Again, the bleeding stopped.

Some time later, I related this somewhat macabre story to another mother of a child with hemophilia, who asked, "Didn't your doctor tell you about Amicar?" She explained how taking Amicar® at the first sign of the cut in Tommy's gums might have helped neutralize his saliva; and might have prevented the saliva from breaking down any fledgling clot. Tommy's experience was a case in point. In fact, his blood had clotted by the time we had put him to bed. But in the morning, we found a clot on his sheets. Using Amicar at the first sign of a mouth bleed could have helped prevent the clot from breaking down. We might have avoided the subsequent trip to the hospital.

I appreciated then the extreme benefit of speaking to other parents, for their wisdom, experience and insight. *No* doctor had ever told me about Amicar–only another parent. So *Raising a Child With Hemophilia*, which represents the combined wisdom of 150 parents, was born.

This year is the 40th anniversary of Amicar, one of our least publicized products to help treat bleeds. I urge all parents to ask their physicians about Amicar. Read about it, check out the website of its distributor Xanodyne, and keep a bottle handy especially when your child is an infant. Mouth bleeds are tricky, and Amicar is a great first line of defense. It can be used before infusing, in case there is a fledgling clot; and after infusing, to preserve the clot that factor forms.

Parents today can benefit from the vast experience of many other parents. Order our books, visit websites, and have lots of face-to-face meetings with other parents. Your child can benefit from 40 sterling years of Amicar–a great product for our children.

tips for parents

Amicar® Popsicles

Recipe for: **Amicar Popsicles** Serves: _____

1. Defrost your child's favorite flavor popsicle.
2. Mix 1 ounce of defrosted popsicle with one dose of Amicar (follow medication label for proper dosage) and pour the mixture into one 2-ounce mold. *
3. Fill the remainder of the mold with additional popsicle juice.
4. Repeat the process for the remaining molds and freeze. You are now ready for the next mouth bleed!

* This puts most of the Amicar at the tip of the popsicle, the first part your child will eat.

Adapted from Karen Wulff's article in the Winter/Spring 2002 issue of hem-flo, *the newsletter of The Louisiana Hemophilia Foundation.*

Amicar is a helpful clotting medicine for both mouth and nose bleeds. Liquid Amicar is used primarily for mouth bleeds. It prevents clots from breaking down, so the tongue or gum can heal. When used properly, Amicar can reduce the need for further factor infusions. Amicar should not be used for joint or muscle bleeds.

For any mouth bleed, first apply ice. Popsicles have been a popular recommendation for years. However, parents of young children may find it challenging to get a child to swallow the subsequent doses of liquid Amicar. Enter an ingenious solution from several Canadian nurses: Amicar popsicles!

You can make your own Amicar popsicles by following the recipe and using 2-ounce plastic molds like the ones available at www.tupperware.com.

Crossroads for Gene Therapy... continued from cover

Still, we have certain expectations for any human trials. For example, it's reasonable to assume that all appropriate pre-clinical testing has been done, and that researchers have conducted the available laboratory and animal experiments that could help minimize the risks and maximize the benefits of human testing. (See related story, "Pros and Cons of Human Testing," page 13.) It's also reasonable to expect that the scientists, physicians and regulatory authorities that have approved and endorsed a trial believe that it will advance the program being studied–without posing excessive risks to patients. There are, of course, no guarantees in medicine. But we expect, and rightfully demand, that the relative risks and benefits be carefully evaluated before any trial is initiated.

With gene therapy, what makes the determination of risks and benefits so difficult is that the predictability of gene therapy methods is so uncertain. Both the introduction of new genes and the creation of vectors to carry those genes are radically new concepts. Compared to our experience with the administration of antibiotics, pain medicine, and most other types of oral or injectable drugs, we have much less history to draw on when dealing with gene therapy. To fully appreciate the complexity of predicting and interpreting gene therapy methods, it's helpful to examine a case that, while not involving hemophilia directly, has gained widespread attention in the scientific community and popular press: a gene therapy study in France that treated a group of children with an immune disorder known as SCID, or "bubble boy syndrome."

The SCID Story: Success or Failure?

For two years, the SCID program looked like gene therapy's first true success story. Patients with SCID normally have non-functioning immune systems, and are extremely susceptible to even the most minor infections. For patients who cannot be treated with a matching bone marrow transplant, SCID is frequently a fatal disorder, with a relatively short life expectancy and little hope of anything resembling a normal life. Surprisingly, the majority of children enrolled in the French trial showed nearly normal functioning immune systems after treatment with a retroviral vector carrying functional copies of their defective gene. Within two years, most of the children in the trial were living apparently healthy lives with no significant side effects from the treatment. Gene therapy, it seemed, had found a cure for SCID. However, in the fall of 2002, one of the nine children in the trial developed a form of leukemia, which was almost certainly a direct result of the gene therapy method employed in the trial. Then, a few months later, a second child developed leukemia. Once again, it appeared that the gene therapy treatment, which used a retroviral vector to transfer a therapeutic gene, caused the leukemia.

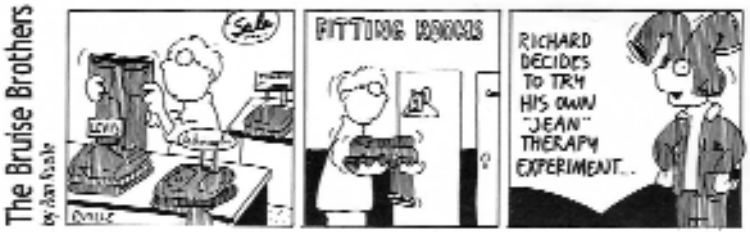
The questions raised by the results of the SCID trial are still being debated in the gene therapy community: With a severe disorder like SCID, is the risk of leukemia "acceptable," considering the lack of alternatives? Can these few cases be generalized to other SCID patients, or to patients with different disorders? Were there additional factors affecting these two patients, such as their very young ages, that could be avoided or circumvented when selecting future patients? And particularly important for patients with disorders other than SCID, how relevant are the SCID findings to other programs? Do these results imply that all patients treated with similar technology (retroviral vectors) are at risk? Or is the risk most likely confined to those who, like SCID patients, start out with a dysfunctional immune system?

Most experts believe that patients who, like those in the hemophilia A trial sponsored by Chiron, were administered retroviral vectors intravenously are *not* likely to be at risk. But for now, these questions remain open. The key points relative to hemophilia gene therapy are 1) that success or failure in gene therapy is hard to define; 2) that relative risk and benefit must be constantly evaluated; and 3) that long-term monitoring is needed, with an awareness that unexpected results can occur at any time. Indeed, as we look more closely at the individual hemophilia trials, it becomes clear that unexpected results *have* arisen in these trials. The need to be vigilant and cautious applies to all fields of research, including the hemophilia field. The extreme results from other trials (the leukemia detected in SCID patients and the death of Jesse Gelsinger [see *PEN*, Feb. 2000] in an OTC trial) may not pose a direct threat to hemophilia trial patients, but the lessons from those trials should not be lost. We must remain alert to real risks, even as we move aggressively forward toward a cure.

Results of the Hemophilia Trials

The results from the first five hemophilia trials reinforce the reality that gene therapy has potential risks and many uncertainties. It is important to evaluate each trial by balancing risks with signs of progress and efficacy. In some trials, the balance seems to tilt against pursuing the technology involved, or at least to suggest a return to the laboratory to re-examine important questions. In other

Bloodstone Gazette, Fall 1999, "The Bruise Brothers"



trials, the results warrant moving forward. Unfortunately, the scientific merit of each trial is not the only factor that determines whether a trial moves forward. Often business issues–particularly in corporate programs beset with limited financial resources or regulatory complications–can have a major impact on whether any particular program can advance to the next phase of testing.

After several years of testing, the first three hemophilia trials were proceeding well (see *PEN*, Feb. 2000). But over the past couple of years, some side effects have been observed that have slowed the trials. At the time of this writing, four of the five trials are complete, and the fifth is ongoing. The results are summarized in the table on page 11. Four of the five trials have reported measurable increases in levels of clotting factors, although some of the levels have been low and short-lasting. All of the trials have reported some signs of decreased factor usage among treated patients, although this may be a "placebo" effect rather than a real sign of efficacy. What is clear, however, is that while the first three trials consistently reported no significant safety issues, the two most recent trials have each encountered unexpected side effects that raise some concerns over the program's safety.

Each trial has its own unique profile. The TKT trial had an excellent safety record, and reported increases in factor levels up to 4%, with seemingly significant declines in factor usage in several patients for periods up to one year. All signs pointed to a possible Phase II trial, perhaps including more potent vectors.[1] But early in 2003, suffering from setbacks in some of its other major research programs, TKT announced that it was replacing its CEO, reducing its workforce by 30%, and suspending all research and clinical efforts related to gene therapy. Company representatives still state that they are committed to the hemophilia program, but they will probably not pursue future trials without financial support from a corporate partner.

In June 1999, Chiron began its trial using a retroviral vector to transfer the factor VIII gene to liver cells. There were reports that some patients appeared to have had fewer bleeding episodes during the trial, but in the end, researchers did not report any definitive signs of efficacy. At the end of the Phase I trial, Chiron announced that it would not pursue the program "for business reasons."

Avigen also began a Phase I trial in June 1999. This was the first trial to target hemophilia B, and used an adeno-associated viral vector (AAV) to administer the factor IX gene to muscle cells. Like the other trials, the Avigen trial reported slight increases in factor levels, less factor usage among some patients, and no significant side effects. However, at the conclusion of the trial its sponsors and researchers decided to switch gears, choosing to conduct another Phase I trial that delivered the vector to liver cells this time, rather than muscle cells. This decision was based on pre-clinical animal studies in hemophilic dogs that indicated that the liver was a preferred target over muscle cells.

Unfortunately, the scientific merit of each trial is not the only factor that determines whether a trial moves forward. Often business issues can have a major impact on whether any particular program can advance to the next phase of testing.

This second Avigen Phase I trial started in August 2001. Semen samples from one of the first patients showed traces of the vector used in the treatment, indicating that the vector may have traveled to cells other than the target liver cells. This did not lead to any detectable symptoms in the patient, but it did cause concern. There is a theoretical risk that if a viral vector gets into a patient's semen, it could eventually find its way into sperm cells and be passed on to future offspring–a process called "germline transmission."[2] Avigen halted the trial when it obtained the positive semen sample, but has since resumed the trial at a slower pace. After treating each group of patients, researchers are now waiting to demonstrate that sequential semen samples from those patients contain no traces of vector before advancing to the next group.

Even more significant, as the Avigen trial proceeded and the dosage increased, a sizable increase in factor IX levels was detected, reaching 10% in one patient. These levels persisted in that patient for several weeks. At roughly four weeks after treatment, however, the levels declined

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[1]There are three phases of clinical trials. A Phase I trial is a small study that focuses on safety issues and the detection of any notable side effects. Phase II trials generally examine dosage levels and therapeutic responses, as well as continuing to look at safety issues. A Phase III trial usually includes a large number of patients and follows the same protocol that would be used in a commercial process. Also see *Insights Glossary*, page 15.

[2]Although such "germline transmission" has never been documented in human studies, ethicists worry that if it did occur, it could some day open the door to the intentional genetic manipulation of sperm, eggs or embryos. Some fear that this could lead either to the creation of "designer babies," or to the inadvertent alteration of the genetic makeup of an unborn child. To most observers, germline transmission is more an ethical concern than a practical one, since short-term presence of vector in semen can usually be mitigated by the use of barrier contraceptives, or condoms, for sexually active patients.

HEMOPHILIA
Gene Therapy Clinical Trials
UPDATED JULY 2003

Sponsoring Company	Corporate Partners	Trial Site (Principal Investigator)	Date Begun	Type of Hemophilia	Treatment Method	Results	Status/ Future Plans
Transkaryotic Therapies, Inc., Cambridge, MA	None	Beth Israel Deaconess Medical Center *(Dr. David Roth)*	Dec 1998	Hemophilia A	*ex vivo* / plasmid vector	No safety concerns. Some signs of efficacy (up to 4% factor VIII level) in some patients.	Completed Phase I trial. Seeking corporate partner to help finance Phase II trial.
Avigen, Inc., Alameda, CA	Bayer Pharmaceutical	Children's Hospital of Philadelphia (*Dr. Catherine Manno*); Stanford University Medical Center (*Dr. Bert Glader*)	Jun 1999	Hemophilia B	*in vivo* / adeno-associated viral vector / muscular injection	No significant safety issues. Slight short-term increases in factor IX levels detected in some patients.	Completed Phase I trial. Currently conducting Phase I liver-directed trial.
Chiron Corporation, Emeryville, CA	NA	Trial terminated	Jun 1999	Hemophilia A	*in vivo* / retroviral vector / infusion targeting liver	One semen sample tested positive for vector. No other safety issues. No significant efficacy data published.	None. Trial terminated, no plans for future studies.
Avigen, Inc., Alameda, CA	Bayer Pharmaceutical	Children's Hospital of Philadelphia (*Dr. Catherine Manno*); Stanford University Medical Center (*Dr. Bert Glader*)	Jun 2001	Hemophilia B	*in vivo* / adeno-associated viral vector / infusion targeting liver	Several patients had semen samples test positive for vector. One patient had elevated liver enzymes that appeared to indicate an immunological response to the treatment. Increase in factor IX level up to 10% reported in one patient.	Trial is ongoing. Avigen is consulting with the FDA to determine protocol for completing the trial.
GenStar Therapeutics, San Diego, CA	Baxter Healthcare	Trial terminated	Jun 2001	Hemophilia A	*in vivo* / adenoviral vector / infusion targeting liver	Only one patient treated. Patient may have had slight rise in factor VIII level but also had an immunological response to the vector that included rise in liver enzymes and some cytokines, and short-term drop in platelets.	None. Trial terminated, no plans for future studies.

[1] Our update in January 2002 included information on two programs (Targeted Genetics and Cell Genesys) that had hoped to conduct hemophilia gene therapy trials, but both companies now say that trials are not likely in the near future.

[2] *Ex vivo* methods involve isolating cells from the patient, introducing DNA containing the factor VIII gene into the cells and re-implanting them into the patient. With the *in vivo* methods, DNA containing the factor gene is injected or infused into the patient and taken up by cells within the patient.

Crossroads for Gene Therapy... continued from page 10

sharply, at the same time that several of the patient's liver enzymes showed significant elevation. These elevations were not enough to produce symptoms in the patient, but they did indicate that the drop in factor levels might have been due to some type of immune response against the cells that carried the newly transferred factor IX gene. At present, the US Food and Drug Administration (FDA) and Avigen are discussing ways to effectively proceed with the rest of the trial.

The last trial, sponsored by GenStar Corporation, involved only a single patient. Initiated in June 2001, this trial used an adenoviral vector in an attempt to transfer the factor VIII gene to the patient's liver. It is known that adenoviral vectors can evoke strong immune responses in many patients, and many scientists believe that the response to the infusion of an adenoviral vector was a major factor in Jesse Gelsinger's death in September 1999. The vector used in the GenStar trial was a *modified* version of the common adenoviral vector used in the Gelsinger trial, and the scientists developing the GenStar program believed that this difference would make it safe. But many observers were concerned because the GenStar study was the first study in which *any* adenoviral vector had been approved for use in a clinical trial since Gelsinger's death. Why, they wondered, was this vector being tested again in relatively healthy patients with a treatable disorder, when the underlying cause of Gelsinger's death was still being debated? GenStar and the FDA apparently believed that the trial dose was sufficiently low to minimize risks. However, the first patient demonstrated side effects that, while much milder than those seen in Gelsinger, were similar enough to suggest that they involved some of the same mechanisms. The trial was placed on hold, but received FDA approval to continue when GenStar agreed to further reduce the dosage. Many members of the hemophilia community continued to express concern over the resumption of the trial, and further enrollment was delayed. In early 2003, before any more patients were recruited, GenStar merged with another biotech company. The newly formed company, Corautus Genetics, has announced that it will not be continuing its hemophilia program.

Lessons for the Future

What important lessons can be learned from these five trials? First, we must always remember that gene therapy is *experimental*, and at this point, no one knows exactly how any particular trial will play out. Second, we should recognize the clear signs that gene therapy *can* work. It *can* transfer working copies of factor genes to cells, and those cells *can* make factor VIII or IX, perhaps for extended periods. This is even more evident when we consider the extensive data from animal trials. Gene therapy can work–it's a matter of making it work well, and work safely. Third, we must remember that not all gene therapy programs are created equal. Each program must be evaluated on its own merits, and some may be more suitable for human testing than others.

Other lessons learned from gene therapy research are often underappreciated, having less to do with the science of gene therapy than with the business of gene therapy. The TKT example clearly shows that market factors and corporate business strategies can take precedent over even the most positive clinical results. We must remember that in the pharmaceutical industry, the bottom line is *developing marketable products*, not simply improving health care. If gene therapy research is to advance, we may need to look beyond industry and corporate sponsorship for funding. The NHF "It's Time for a Cure" campaign pledges to increase community-based funding for hemophilia research. This campaign, coupled with NHF efforts to obtain more government funding, are key elements in the attempt to complement corporate investment in hemophilia research. Additional factors that can influence the direction of a gene therapy program include the current regulatory climate and the overall business climate–especially toward biotechnology and the pharmaceutical industry. For advocates of hemophilia gene therapy, the challenge is to address all of the disparate influences, and create workable solutions through advocacy, education and direct funding of research.

Pros and Cons of Human Testing

by Kevin C. Kelley

In any drug development program, there comes a point where the treatment being developed must be tested in humans. No matter how many laboratory and animal studies are done, no one can know for sure how a drug or treatment will work in humans until it is actually tested in human trials. Even then, extensive testing over a prolonged period is needed for researchers to draw any statistically relevant conclusions. It's easy to see why some researchers or companies are eager to conduct human trials: trials may demonstrate most clearly whether new research methods will succeed.

Still, while some issues can be addressed only by human testing, many other issues can be addressed more easily and thoroughly by conducting animal studies. For managers of hemophilia gene therapy programs, one of the toughest decisions is choosing when to initiate a new round of animal studies, and when to progress to human studies. The decision is often one that combines science, ethics, economics and practical logistics.

Human Trials: Corporate and Government Views

Human trials, for gene therapy or any new drug, require approval from two government regulatory agencies: the US Food and Drug Administration (FDA) and the National Institutes of Health's Recombinant Advisory Committee (RAC). These two agencies don't evaluate the overall merits of a proposed trial, but rather focus primarily on those aspects of the trial that pose the most significant safety concerns. If a proposed trial contains no components that appear to pose a definite risk to patients, the trial is likely to be approved. FDA and RAC approval should not be seen as endorsements of a trial, but simply judgments that the trial poses no obvious and sizable risks to participants. The ultimate evaluation of a trial's scientific merits always rests with the trial's sponsors and the Principle Investigators.

Safety and scientific merit should always be the main criteria for deciding when the time is right to enter human trials, but other factors frequently play a role. Patent rights and legal issues, availability of suitable animal models, high cost and time requirements for animal testing, status of competitors' programs, current regulatory climate and prevailing attitudes in the investment community–these considerations can all influence a company's decision to conduct clinical trials. When TKT announced, in February 2003, that it would suspend its hemophilia gene therapy program, the decision had little to do with the scientific merits of its program. The Phase I trial had an exceptional safety record, and showed clear signs of efficacy in several patients. The trial warranted moving ahead with a Phase II study. But TKT suspended the program, for reasons that were almost exclusively business-related: the program had little chance of generating revenue for the company in the near future, and would require a financial and staffing investment that TKT concluded it was not in a position to make. TKT is not alone–Chiron ended its first trial with the comment that it would not be pursuing the research "for business reasons."

We live in a capitalist society, where health care and drug development are controlled primarily by companies whose main focus is not just improving health care, but making a profit from the development of new products. Phrases like "business realities" and "laws of the marketplace" appear frequently in the discussion of any drug development program–including gene therapy. Still, the laws of the marketplace can never prevail over the laws of nature. In the end, it is good science, not good business, that will determine which hemophilia gene therapy programs succeed or fail. Similarly, science should be given priority when shaping the direction of a research program. And science, not business, should determine when human trials are conducted.

The Scientific Issues

Scientifically, there are many reasons for conducting human trials. Animal models can never tell us everything we need to know about how people will respond to a novel drug or treatment. For example, hemophilic animal models (mice and dogs) are useful because the coagulation systems of these animals are quite similar to those of humans. Yet the immunological responses seen in mice or dogs may have limited value in predicting what will occur in humans, because the immune systems of different species vary greatly. Therefore, when immunological responses are the major concern in a research program, scientists often turn to studies in humans or non-human primates such as monkeys or apes. For programs that have addressed most of the basic research questions in pre-clinical tests, human studies are the single most useful indicator of whether a program will be useful on a commercial scale.

As useful and informative as human trials can be, they also have drawbacks, even in the best of trials. Phase I clinical trials involve a limited number of patients because they are always designed to address safety issues; this small sample size makes it difficult to draw statistically relevant conclusions. Also, it is frequently harder to extract data from humans than from animals. Except for the most ardent animal rights activists, most people accept the concept that sacrificing or performing invasive

procedures on animals is justified–if it improves our understanding of treating serious human diseases or disorders. But it is not acceptable to perform invasive procedures that would inflict unnecessary trauma on human subjects. Consequently, there are usually restrictions in human trials that limit a researcher's ability to obtain important data. For example, David Roth, M.D., the lead investigator in the TKT trial, was queried at a recent NHF-sponsored symposium: Did his team try to examine the cells implanted in the trial subjects, to determine whether the cells were still functioning at the end of the trial? Dr. Roth explained that his team considered it ethically inappropriate to perform this kind of invasive procedure on subjects, since they were not exhibiting any signs of problems with the implanted cells. Similarly, Mark Kay, M.D., Ph.D., one of the leading researchers behind the Avigen trials, noted that his team decided not to perform a liver biopsy on a patient who exhibited a short-term elevation in a few liver enzymes. Both research teams sacrificed potentially useful data, choosing instead the ethically responsible option of not performing invasive procedures on healthy patients. If the teams had used animals as subjects, they would have been able to surgically explore their "patients" to gain further insights.

Two Trials: Too Soon?

We accept the inherent limitations of human trials as part of a trade-off: the benefit is obtaining meaningful results in actual humans. But in some cases, when human trials are conducted prematurely, the limitations can dominate and the outcome can be even less informative. Two of the five hemophilia trials (those conducted by Chiron and GenStar) were initiated when serious questions remained about the basic biology of the techniques involved. The Chiron study used a retroviral vector to transfer the factor VIII gene to the subjects' *hepatocytes*, or liver cells. Study managers stated in their application to the RAC that they hoped to achieve circulating factor levels of 7% in their subjects. However, the few attempts made by the Chiron group to demonstrate lasting efficacy in hemophilic dogs were not successful, making the attainment of this 7% goal unlikely. In fact, many experts in retroviral biology believed (and still believe) that retroviral vectors could work only with cells that were rapidly dividing–a condition that would not exist for the hepatocytes in the trial's subjects. When completed, the Chiron trial had produced only minimal evidence that several patients may have received a slight benefit, but no hard data to address the fundamental question: Could (or did) the vector find its way into the desired target cells? Once the vector was infused into the human subjects, there was no way of tracking it to see where it ended up–or to determine which cells, if any, were *transfected*, or entered by the virus. If researchers had treated twelve hemophilic dogs instead, this question might have been answered.

The GenStar trial involved similar uncertainty about the ability of the vector to efficiently enter hepatocytes, but with an added element of risk. The 1999 death of Jesse Gelsinger (in a trial involving infused adenoviral vectors), and the subsequent autopsy, unfortunately provided a rare opportunity to extensively study a human subject. From the results of this one patient, investigators concluded that little of the vector actually entered the desired hepatocyte cells, and that most of the vector was found in macrophages (a type of immune cell). Researchers believed that the infection of the macrophages led to an uncontrollable immune response and the multiple system failure that ultimately proved fatal. Pre-clinical animal studies conducted by GenStar had shown that much of the vector used had ended up in the animals' livers. But at the time the trial began, researchers had not determined whether the vector was actually in the hepatocytes–or in the macrophages that also populate the liver.

When side effects were seen in GenStar's first patient, there was no easy way to determine whether there had been a problem with the distribution of the GenStar vector, as had been the case with Gelsinger. As with the Chiron trial, the use of a human subject ruled out the possibility of performing the risky, invasive procedures that could have provided important information about the vector's distribution in the patient's tissue. Once again, animal studies would likely have provided significantly more useful information for shaping future approaches.

Of course, it's impossible to state with certainty before any trial begins whether it will yield useful data. Often only in hindsight does a better alternative become clear. Yet a careful evaluation of a trial before it begins can help ensure that the individuals in the trial, and the hemophilia gene therapy field as a whole, can benefit to the greatest degree. As a community, it's vital for us to support research and trials, both by fundraising and by directly participating in trials when appropriate. In the long run, it's equally important that we carefully monitor all trials to help ensure that the trials that *do* get underway are truly suitable for human testing. While we need to accept risk if we hope to achieve progress, we also must recognize that accepting *unnecessary* risk is one of the surest ways to push the progress we all seek even further out of reach.

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Insights... continued from page 4

factor VIII is an unstable protein. It degrades rapidly unless it is protected, or **stabilized**, by another compound. These **first-generation** recombinant products used human **albumin**, a blood plasma protein, to stabilize factor VIII. But to many in the hemophilia community, adding a blood protein to a product not made from blood was a step backward. In fact, the added albumin makes up more than 99% of the protein in the final product in both plasma-derived and recombinant products.

Despite an excellent safety record, concentrates derived from plasma, or containing plasma proteins such as albumin, still have the potential to transmit viruses. Every few months, it seems, a new or emergent virus makes the headlines–viruses like West Nile Virus, Monkeypox and SARS. Each headline raises new concerns about blood product safety. (Fortunately, current viral inactivation methods are effective on all three of these viruses.) In addition to viruses, other novel infectious agents, such as prions[7], might potentially be transmitted through blood products.

In response to these concerns, the blood products industry has been working for several years to remove all blood proteins–even albumin, which has a long safety record–from recombinant clotting factor concentrates. Two recombinant factor VIII products[8] are now available containing sucrose (a sugar) as a stabilizer instead of the blood protein albumin. These products are referred to as **second-generation** recombinant products, to distinguish them from first-generation recombinant products that contain albumin added as a stabilizer. While second-generation products do not use albumin as a stabilizer, they still use human or animal proteins in the manufacturing process. However, second-generation products contain virtually no extraneous human or animal proteins in the final product, greatly reducing the potential for viral or prion contamination. Baxter Bioscience was just awarded FDA approval of a **third-generation** recombinant factor VIII product, Advate–which contains *no* extraneous human or animal proteins in the manufacturing process *or* the final product.[9]

The newest recombinant clotting factor concentrates eliminate albumin as a stabilizer, and essentially eliminate (second-generation) or completely eliminate (third-generation) other plasma-derived proteins from the final product. These products essentially bring to an end the possibility of viral contamination or CJD transmission through the concentrate. They offer a new level of viral safety, finally meeting the level of safety promised by recombinant products introduced over a decade ago.

[7] "Rogue" prions cause the brain-wasting Creutzfeldt-Jacob Disease, or CJD. [8] ReFacto® (Wyeth) and Kogenate® FS/ Helixate® FS (available from Bayer and Aventis Behring, respectively). [9] Wyeth has had a plasma protein-free factor IX product, BeneFIX®, on the market since 1997.

INSIGHTS GLOSSARY

Recombinant DNA (rDNA) Technology
Techniques for isolating genes or other DNA from one source or organism and "re-combining" them with DNA from another source. For example, the gene for insulin has been isolated from human cells and re-combined, or cloned, with bacterial DNA so that bacteria containing this cloned or recombinant DNA can now produce human insulin.

Recombinant Factor VIII
Human factor VIII produced by animal cells when (as in rDNA technology) the factor VIII gene is isolated from human cells, and re-combined with the DNA in animal cells. The factor VIII made by these cells is called "recombinant" to distinguish it from factor isolated from human plasma, even though both products are biochemically similar, and both are derived from the human factor VIII gene.

Cell Culture
The process by which animal cells are grown in large tanks, where they become "factories" for the production of factor VIII. The tanks contain a "growth medium" with nutrients that the animal cells need to survive and multiply. The animal cells secrete factor VIII into this growth medium. Factor VIII is then extracted from the growth medium and purified into its final form.

First-Generation Recombinant Factor VIII Products
The first type of factor produced through recombinant DNA technology. The growth medium contains human and/or animal plasma proteins; and human albumin (from blood plasma) is added to the final product to stabilize the factor.

Second-Generation Recombinant Products
Similar to first-generation, but with *no* human albumin added to the final product. Second-generation factor VIII products are stabilized with sugar instead of human albumin.

Third-Generation Recombinant Factor VIII Products
Similar to second-generation, but with no animal/human plasma proteins like albumin, in the cell growth medium *or* the final product.

correction

Prince Leopold: The Untold Story of Queen Victoria's Youngest Son (*Book Corner*, *PEN*, May 2003) is currently out of print and no longer available at www.amazon.com. Look for it instead at www.abebooks.com.

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Bruises and Inquiring Minds:

What Would You Say?

What can I say when strangers ask about my son's bruises? I don't have a thick skin when it comes to others' comments, especially about my children. I know they will probably say "poor baby." I don't want my daughter to hear strangers' comments either, but I know we can't avoid this forever.

My son's legs are covered with bruises now. It's getting hot, and I'll miss the shelter of long pants and sleeves. Even my own family members comment. Every time my mom holds him, she makes a big deal about taking off her glasses so he won't bump him and cause a bruise—even though I tell her not to worry. None of the other babies get this treatment, and my son understands more than she thinks he does. My mother-in-law makes up excuses so she doesn't have to hold him. She worries that if she babysits him and he gets hurt, we will never forgive her. She has made it clear that she won't babysit until he is much older.

Mary (last name withheld)

[A] I USUALLY ACKNOWLEDGE the bruise, saying, "He bruises easily," and leave it at that. If there is more interest (positive or negative), I explain simply that the bruising is caused by a bleeding disorder, and my son is quite healthy. Then I change the subject. Most people get the point. There's not much you can do about "poor baby" comments. Just smile and go on, because it isn't worth your energy.

As for your family–your mother-in-law is afraid, and your mom is over protective. (I used to remove my jewelry, too.) The only way to make a change is through open, honest communication and a lot of exposure. If that doesn't work, at least be glad that you know where they stand.

Kathy Mackay
GEORGIA

[A] I USUALLY JUST IGNORE people who stare at my children's bruises or bracelets. If they ask about the bruises, or say "poor baby," try explaining that it's due to hemophilia. If they wonder what that means, try making a joke! I feel strongly that others can sense our own fears and anxieties. If we are continually worried, anxious and afraid, those around us will be, too–especially our children. If I felt embarrassed, or worried about what others say, I'd be afraid that my children would sense those feelings.

My children have had bruises everywhere, and have scars and lumps from their port surgeries. We wear those marks with pride. I'm grateful that my sons, ages seven and five, have never been shy about their bodies or sharing that they have hemophilia. To avoid a false sense of security, we didn't use kneepads or elbow pads; many say that kneepads actually cause bruises! We didn't use a helmet, or pad shopping carts and strollers, because of the attention this draws. If fear or shame is guiding your lives and dictating how your family deals with hemophilia, maybe it's time to change treatment options.

Have you considered prophylaxis? It gave us a comfort zone, eliminated the bruising, and reduced our worries about bleeds. It also let our families see that our kids can lead normal lives.

Jill Lathrop
WISCONSIN

[A] I SIMPLY TELL STRANGERS that my son bruises easily. Lots of children have that problem. Or I just laugh and say, "Boys will be boys, and he is 100% boy!" If people continue to be rude, feel free to tell them the truth–his blood doesn't clot correctly. The shock of hearing that will most likely quiet them.

We have raised our daughter to know about Benjamin's hemophilia so that she will be careful with him, and will help us. As for the "poor baby" comments, this is a good opportunity to teach your daughter about empathy. Many people in the world are worse off than our sons. Teach your daughter about disabilities and differences. My six-year-old daughter has a great understanding of such things, thanks to her little brother.

I am glad to say that my mother has come around. Since she made a speech last year on hemophilia, she has lightened up considerably. She recently babysat by herself for five days–a huge step for her! Benjamin is now four, and she has seen how well he does. We ask our parents to treat him like a regular kid–which he is, except for his blood. When we go out, I leave my parents with detailed instructions, and permission for them to seek medical treatment. My in-laws are different: they've been alone with Benjamin for only an hour. It will be interesting to see what happens next month when my baby is due, since my in-laws plan to watch the other three kids while I'm at the hospital and at home recovering. My advice is educate, educate, educate!

Mindy (last name withheld)

[A] THERE IS AN ADJUSTMENT period. The word "hemophilia" pulls people out of their comfort zone, mainly because they don't understand what hemophilia entails. Grandparents will become more comfortable in time, as will neighbors and friends. Our friends and neighbors realize that Ian is, for the most part, a normal little boy. They also know to inform us if he sustains a hard knock. No two people are the same, and it will take time to get a handle on your child's particular needs in relation to hemophilia. But this will become second nature, and the grandparents will take their cues from you.

Prophylaxis has been fabulous for us! My son is an active, rough-and-tumble boy. I like knowing that he is "dosed up" and can take a hit. Of course, we watch him and inspect him for injuries as any parent would, but with extra attention to any potential hemophilia-related injuries.

Grant (last name withheld)

[A] REMEMBER TO BE POSITIVE. Every time my son Colton is treated for a bleed, my mother-in-law thinks it's due to something *she* did. I keep reminding her that I have him more often than she does, and we'll never know the cause of all of his bleeds. You can't dwell on how he did it–just that he gets better!

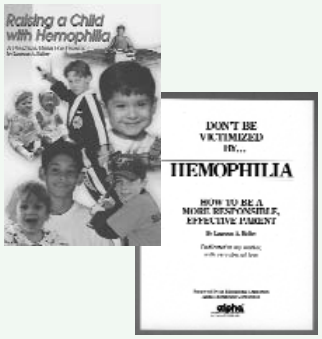
Randi (last name withheld)

[A] I MADE A JOKE, AND THE person matched me line for line! People certainly respond to our attitude; they can learn to be matter-of-fact if *we* are. And indulging in humor gets me through the day.

Think carefully about treatment options. My HTC staff talk a lot about comfort levels, and are willing to give extra factor if it will make me feel better–occasionally this does help! I felt better when we found a workable way to treat hemophilia aggressively; things improved when we started giving factor regularly, even with the inhibitor. The comfort zone helps me. I'm not worry-free, but I worry less.

Ziva Mann
MASSACHUSETTS

For more information on handling unwanted comments from neighbors and relatives, please order *Don't be Victimized by Hemophilia* and *Raising a Child With Hemophilia*. These publications contain sections explaining why such comments are made, and how to give helpful, non-defensive responses. They are available to patients **free** from LA Kelley Communications, Inc. at www.kelleycom.com, or by calling 1-800-249-7977.



The information provided in Parent-to-Parent should **not** be construed as medical advice. It is advice from one parent to another. Please consult your HTC for information on any medically related questions.

Wyeth to Increase Protein in ReFacto® by 20%

Wyeth Pharmaceuticals will recalibrate its standard for determining the potency of ReFacto, and increase the amount of ReFacto protein in each IU by approximately 20%. The price per IU and prescribing information will remain the same. Patients transitioning to ReFacto calibrated with the new standard (when available) should initially use the same dose previously prescribed. The recalibrated ReFacto will be available in the US, and will feature new, distinctive packaging.

For more information, call the Wyeth Hemophilia Hotline, (888) 999-2349.
Source: Wyeth Pharmaceuticals

New Recombinant Factor VIII Product Wins FDA Approval

The FDA has approved **Baxter Healthcare's Advate*, the first and only recombinant factor VIII medicine made with no added human or animal plasma proteins or albumin in the cell culture process**. Advate will be available in super-high potency (1500 IU/vial), with a smaller infusion volume (5ml diluent), and will be priced slightly higher than Recombinate.

For more information, visit www.advate.com.
Source: Baxter International, Inc.

New Screening System for Blood Supply?

UK-based **Blood Analysis Limited** is filing for US marketing clearance for its *DECAN* screening system. *DECAN* detects and quantifies bacteria in donor blood. The company believes that *DECAN's* ability to provide "accept/reject" results within one hour is a powerful advantage over current technologies, which require a culturing period of 24 to 48 hours.

Source: International Blood/Plasma News, May 2003

Now Obtain Medicine During Insurance Lags

Aventis Behring recently launched **Choice Assurance**SM, a new program designed to help ensure that qualified people with hemophilia on recombinant and plasma-derived therapies can continue to receive these products even during a lapse in insurance. Patients enrolled in Choice Assurance for one year can earn up to four months of free product, and up to a year of free product after three years' enrollment. Patients wishing to enroll must be using an Aventis Behring product and have third-party, private health insurance.

For more information, visit www.ChoiceAssurance.com.
Source: Aventis Behring

* Advate (Advanced Factor VIII) is registered by Baxter as ADVATE rAHF-PFM. As an editorial policy, LA Kelley Communications does not capitalize entire names of any product.

New Software Program Helps Patients Visualize Bleeding History

The Infusion Tracker is a unique software program that helps patients record, analyze and visualize bleeding episodes for any selected range of dates, on a color-coded map of the body. The program was designed by **NuFactor**, a California-based home health care company, to help home infusion patients more accurately document their factor usage and bleeding history. The Infusion Tracker helps patients…

- identify target joints instantly
- track prophylaxis schedule effectiveness
- learn seasonal bleeding patterns
- document factor usage
- record lot numbers permanently
- review statistical information, including average time between bleeds and average dosage
- print usage reports.

The program, which is PC compatible and soon to be Mac compatible, is free to clients and non-clients.

For more information or to register for the program, call NuFactor, (800) 323-6832.
Source: NuFactor

SARS Poses Little Transmission Threat to Blood Products

The FDA believes that SARS **cannot** be transmitted through clotting factor products manufactured from human blood plasma. Lipid-enveloped RNA viruses (such as the coronavirus, which is believed to cause SARS) should be removed or inactivated during intentional and effective viral clearance procedures like filtration, heating, acidification and detergent treatment. Under normal blood-bank procedures, donations would not be accepted from anyone exhibiting SARS-like symptoms. Symptoms include temperature above 100.4°F/38°C and signs of respiratory illness.

Although plasma-derived clotting factor products appear to hold little risk of SARS transmission, concerns remain about blood components such as red cells, platelets and plasma. This also applies to cryoprecipitate if viral inactivation procedures are not in place. A plasma quarantine of 10–14 days should be effective in minimizing the risk of SARS from cryo.

For more information, visit www.wfh.org/ShowDoc.asp?Rubrique=30&Document=344.
Source: World Federation of Hemophilia

US Hemophilia Camp List No Longer Available

LA Kelley Communications, Inc. has removed the US Hemophilia Camp list from its website. For a detailed list of camps in the US, please visit the National Hemophilia Foundation's website at www.nhfyouthworld.org/camps.htm.

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Readers respond to *PEN*, May 2003:

I REALLY LIKED THE ARTICLE ABOUT THE AV FISTULA. ["ANOTHER OPTION FOR VENOUS Access in Children with Hemophilia: The Arterio-Venous Fistula"] I wish we had known about this prior to the placement of our son's second port. It would have given us another option to consider, but for now he seems to be doing well with his new port. Thanks for the great information!
Candi Nakatani, CALIFORNIA

I FOUND THE MAY ISSUE OF *PEN* VERY INFORMATIVE. WE HAVE BEEN FACING SOME TOUGH decisions regarding venous access options for our son, and the timing of your article about the AV Fistula was uncanny. I have been in touch with Dr. Valentino via email, and our hematologist is further exploring this option with several other hematologists across the country. My father was one of the first people with hemophilia to have this procedure. It served him well for many years. I have attempted to discuss the AV Fistula as an option with my son's doctors in the past, but they never seemed to see it as a possible alternative. Thanks for the article. It helped open our physician's eyes and mind to this possibility. I am not sure how it will work out for us, but the information is greatly appreciated.
Debbie Porter, CALIFORNIA

THE NATIONAL HEMOPHILIA FOUNDATION (NHF) TOOK SERIOUSLY THE RECENT LETTER to the editor from a member of a local hemophilia association who feels that NHF chapter dues are too high. In the last several years, NHF chapter dues have been lowered to ensure that dues will not be a significant obstacle to affiliation. This is one reason that the number of NHF member chapters is at an all-time high of 44. More recently, we've taken this process a step further by establishing a means by which very small chapters have been granted full membership at an even lower rate. At least one group has already joined under this provision.

Finally, we feel that affiliation is important because it makes us a stronger, more effective advocate for the needs of people with bleeding disorders. However, we want the community to know that NHF research, education and advocacy programs exist for the benefit of the entire community, regardless of whether a person is a member of an affiliated organization.
Gina Shreve, Ph.D., PRESIDENT, NATIONAL HEMOPHILIA FOUNDATION

THE HEMOPHILIA FEDERATION OF AMERICA (HFA) WISHES TO STATE THAT OUR ANNUAL membership fee is $750.00, and includes a voting seat on our Board of Directors. If an organization is unable to raise these funds, we welcome the opportunity to review the situation and accept the challenge of trying to identify financial support.

Our organization offers myriad programs designed to enhance the lifestyle of those within the bleeding disorder community. We believe in choice because we are better able to promote unity and representation within our community, on the local and national levels, when choice is left in the hands of the consumer–where it belongs.
Bob Marks, PRESIDENT, HEMOPHILIA FEDERATION OF AMERICA

ALTHOUGH I AM NOT A PARENT, RATHER AN AUNT AND A PERSON WITH VON WILLEBRAND disease and Hepatitis C, I truly enjoy your newsletter. My husband and I both look forward to reading *Prince Leopold: The Untold Story of Queen Victoria's Youngest Son*. Since I care about all children, I look forward to learning about the issues facing children with bleeding disorders, and was glad to learn about Project SHARE. I also enjoyed the article "It's Not Like Hemophilia Camp: Creating Partnerships with Schools." I felt badly about school staff who thought that a mom was exaggerating her daughter's VWD symptoms, and the overreactions against children with hemophilia. Being 43 with VWD, I have had to educate many health care workers, and I'm sorry to know that educators are not better informed at this point in history. Having a bleeding disorder should not cause children and their families to face ignorant prejudice. I was glad to read your *Insights* column on blood safety. As someone infected with HCV in 1982 through cryoprecipitate, I always hope to hear of advances, and NAT sounds great. I think you should send the *Parent-to-Parent* letter regarding sterile technique, and its answer, to all HTCs. I was formerly in nursing and was saddened to hear how lax some caregivers are regarding asepsis. Thanks so much for a fabulous publication that appeals to a broader audience than you intended.
Marianne Squire-Maszer, NEW JERSEY

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