The Parent Exchange Newsletter

February 2002

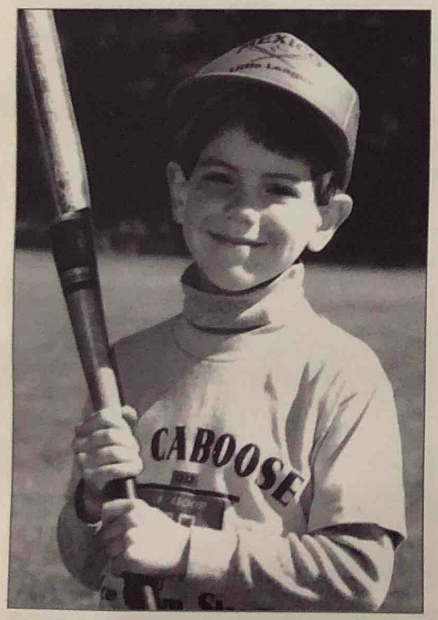
Volume 12
Issue 1

GENE THERAPY 2002

SETTING THE STANDARDS

by Kevin C. Kelley

Current standards of care may shape future expectations for hemophilia gene therapy



The young generation of hemophilia patients in the U.S. can aspire to active, full lives.

In the U.S. and other highly developed countries the bar is raised, and expectations for gene therapy allow little margin for error. However, for the majority of the world's patients, current standards of care are deplorable, and gene therapy may hold the last, best hope for meaningful care in the forseeable future. Will it be possible for gene therapy to meet the expectations of the entire global community? Or will the strict requirements of the market in the developed world effectively limit access to gene therapy in developing countries?

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Photo: Laurie Kelley

But for most of the world, care is sporadic or nonexistent, with traumatic bleeds, crippling joint damage and premature death all too common.

in this issue...

From the Editor

THIS ISSUE MARKS *PEN*'S FIFTH ANNUAL REVIEW OF HEMOPHILIA gene therapy. Although obstacles have occurred in each of the human clinical studies conducted to date, progress has been real. We are still optimistic that we will someday find a lasting cure. This hope is particularly strong among patients in the developing world, where hemophilia treatment is minimal, if it exists at all. In many countries, gene therapy may be the last hope for effective care. In this issue we ask the question no one has yet asked publicly: If gene therapy does lead to a cure, who will benefit? Only the rich? Or is a plan being prepared for the 80% of the world with no access to hemophilia care?

Will gene therapy repeat the pattern of past technological advances in hemophilia? Recombinant factor concentrates that we enjoy here in the U.S. have not trickled down to the developing world. Do we wait to see if gene therapy will someday reach people in urban slums or remote villages in developing countries? Perhaps it's too soon to expect answers, but it's not too soon to raise questions.

Find out what's happening in current trials that may affect your children. *(See United States Remains Focused on Safety, page 4.)* But share our concern that the time to look ahead is **now**. We must guarantee that gene therapy fulfills its potential—not just for select patients in the most developed countries, but for our global hemophilia community, which remains desperately dependent on us. *(See Risk-Benefit Considerations Far Different in the Developing World, page 7.)* The sooner we begin to ask questions, the better our chance to get the answers we want.

To the Editor

I MET A THREE-YEAR-OLD BOY IN THE ER WHO HAS FACTOR VIII DEFICIENCY, AND HE JUST stole my heart. He came in because of abdominal pain. He is full of bruises from bumping himself, and his right ankle feels like a sponge. His mom, who is a carrier along with her mother and daughter, is open to ideas and help. She is pregnant again, and doesn't know the sex of the child. She had a little brother who died at age three due to his bleeding disorder. I asked if she was giving her son his infusions; she said that in Georgia, she was told he is too young for her to learn give the medication. The little boy has already had two PIC lines in his arms, and numerous IV sticks. While he was in the ER waiting for a room, I infused him, and he helped me—he thought he was doing something good for himself, which he was.

This mother has nowhere to turn for education or answers. I told her about *PEN*, and she wants to be put on the mailing list. She could benefit from any information you have for her and her family. *—Cheryl and Allen Spencer*

I AM A PROFESSOR OF HEMATOLOGY AT THE UNIVERSITY OF SAN MARCOS IN LIMA, PERU, and am also advisor at the navy hospital here. With the help of the administration of the Hospial Rebagliati in Lima, I organize the delivery of information to patients with hemophilia treated here. I receive *PEN*, which is very useful to medical students, and to my patients. *—Alejandro Padron Bernal MD, Peru*

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The Parent Exchange Newsletter

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Gene Therapy and the Developing World

by Ashok Verma

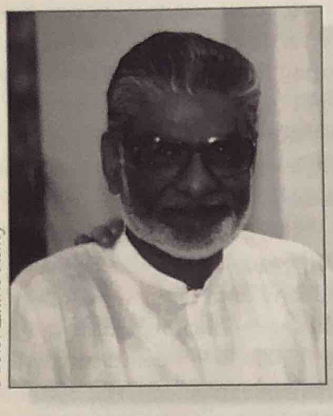

Photo: Laurie Kelley

Medical awareness differs from country to country, and from community to community. In the developing world, varying economic levels also make vast differences between people's medical knowledge and expectations, and the new advances in medicine.

However, even in the developing world, educated people with hemophilia keep asking, "When will gene therapy be available to cure hemophilia?" This question implies three things:

1. These people have no doubt that gene therapy will provide the cure for hemophilia.
2. They believe that gene therapy will be available to them.
3. It is only a matter of time before gene therapy arrives on their door steps.

I believe that these three statements also represent the attitude of the entire developing world on the question of a cure for hemophilia through gene therapy.

But how will this technology reach people? The developing world has neither the resources nor the will to invest in pure research. It did not invest in other fields of research either, but sooner or later received the techniques. I think that gene therapy will happen in exactly the same way. There are research centers in many developing countries that have created some basic infrastructure for work on genetics. When the time is right, and research in the developed world has reached a certain level, these research centers will start developing the right technology, applicable to their own countries.

The developed world is not designing gene manipulation and transplantation techniques with the constraints of the developing world in mind. The primary concern today is to develop safe and effective methods of gene transfer, with maximum speed. Money is not a major deciding factor just now. But once the basic research has attained a certain level, cost will become a major concern. At that time, the developing world will come into focus as an emerging and evolving market. And in this era of the global village, the time lag between advanced technology being available in the developed world, and in the developing world, is constantly shrinking.

In the worst possible scenario, from the date gene therapy first becomes available anywhere in the West, I do not foresee it being available in India for more than a decade. And in India, where most of those with hemophilia still live (or die) on plasma and cryoprecipitate, it isn't too much to wait ten years for gene therapy. It is possible that people may never be able to afford gene therapy. What really matters is the belief that one day we will be rid of hemophilia because of gene therapy. It is this belief alone that gives hope to many with hemophilia—hope to carry on with their lives from day to day.

Ashok Verma, who has severe hemophilia, is Founder and Executive Director of Hemophilia Federation of India, the world's largest registered hemophilia society. In 1983 Ashok founded the HFI, which has grown from one to 65 chapters nationwide. Ashok serves on the WFH Executive Board, and in December was honored as L.I.G.H.T.'s Leader of the Year.

First Book on vWD Now Available!

A Guide to Living With von Willebrand Disease is the first book devoted exclusively to helping people manage the issues of living with the world's most commonly inherited bleeding disorder. Until now, no comprehensive resource has been available to the approximately three million Americans suffering from vWD—most of whom remain undiagnosed and untreated, due to lack of awareness and misconceptions about bleeding disorders.

A Guide to Living With von Willebrand Disease is written by Renée Paper, R.N., in collaboration with Laureen A. Kelley, and made possible by a grant from Aventis Behring, L.L.C., a leading manufacturer of treatments for bleeding disorders.

Free copies are available from several sources: LA Kelley Communications, Inc., (800) 249-7977, or the company website at **www.kelleycom.com**. Call the Aventis Behring Choice Member Support Center at (888) 508-6978. Or see the first comprehensive website devoted exclusively to the education, guidance and support of people who have or suspect they have VWD, at **www.allaboutbleeding.com**.

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United States Remains Focused on Safety

Researchers and companies in the U.S. hoping to develop gene therapy as a treatment or cure for hemophilia face numerous scientific obstacles. They also face stringent regulatory and marketing requirements to develop a product with exceptional safety and efficacy. Because infusion therapy (treatment with recombinant or plasma-derived factor) has proven so effective and, for the past fifteen years at least, extraordinarily safe, the bar is raised for anyone hoping to replace either on-demand or prophylactic factor treatment with gene therapy.

As human trials of several different gene therapy methods proceed (*see table title, page x*), a number of positive signs have emerged that offer continued hope that gene therapy will eventually work as a cure for hemophilia. Yet much attention has focused on setbacks in each of the trials. Fortunately, no severe side effects or deaths have occurred in the hemophilia trials, but no trial has proceeded without interruption. Each of the five trials initiated has been halted for a time, to address safety or regulatory concerns. Both of the trials begun within the past year were halted after unexpected findings in the first patient treated in each trial. This scrutiny of ongoing trials clearly demonstrates that safety standards for the trials are very high, but also indicates that many unresolved issues remain.

Advocacy groups, most notably the National Hemophilia Foundation (NHF), are closely monitoring the ongoing trials, as are government agencies like the Food and Drug Administration (FDA) and the Recombinant Advisory Committee (RAC) of the National Institute of Health (NIH). Additionally, each institution conducting trials has its own internal Institutional Biosafety Committee (IBC) overseeing each trial. The NHF's dual objective is to aggressively support and encourage research toward a cure, while taking steps to ensure that all safety risks are adequately addressed. This is not always a simple task; it is often difficult to determine which risks are reasonable and unavoidable, and which risks are excessive, or better addressed by additional laboratory experimentation. Some risks can't even be anticipated until they occur, and the decision becomes whether to terminate a trial or allow it to proceed. In an effort to minimize risks in future trials, the NHF's Medical and Scientific Advisory Committee (MASAC) has issued guidelines for conducting human gene therapy trials.[1] The NHF has also expanded efforts to educate consumers, especially prospective trial participants, on the risks and benefits of human trials.[2]

The focus on safety in gene therapy trials was emphasized in September 1999, when Jesse Gelsinger, a teenage patient in a non-hemophilia trial, died as a result of the gene therapy procedure.[3] Yet for hemophilia, the commitment to safety probably owes more to the impact of HIV and hepatitis within our community. Devastated by products that were once thought to represent the safest and most advanced treatment available, our community is now committed to ensuring that another *iatrogenic* (treatment-related) disaster does not occur. In recent years, for example, the NHF has consistently advocated for limiting the release of factor products that may, even theoretically, have been contaminated with Creutzfeldt-Jakob Disease (CJD).

While recognizing that such restrictions might reduce the availability of donors and, eventually, factor itself, the NHF has argued that this risk is not worth taking until safety is proven—essentially establishing a "zero tolerance" policy regarding risk of contamination in factor. At an April 2000 WFH conference in Montreal, NHF President Mark Skinner explained, "The essential elements of our current effort can be captured in three concepts: safety, availability and affordability... It is imperative that safety is always the first and foremost consideration in our decision-making process. Until persuaded otherwise, we will not accept risk, even at a theoretical level. We simply have no other choice."[4]

While these comments were directed specifically at factor concentrates, most hemophilia advocates in the U.S. are similarly convinced that safety must play a primary role in gene therapy. However, some researchers worry that we may become too restrictive, arguing that gene therapy trials should be called clinical "research" rather than "trials," to emphasize the experimental nature of the work. NHF President-elect Glenn Pierce, MD, Ph.D., explains, "We may need to accept a significant level of risk if we ever hope to achieve the ultimate goal of curing hemophilia." According to Pierce, gene therapy "clinical research" differs from the clinical trials for factor products in which many community members participated: the nature of the clinical trials offered limited risk and almost guaranteed efficacy. "Entering a clinical trial to test a new recombinant factor VIII," says Pierce, "patients fully expect it will work and cause no side effects. In contrast, gene therapy is a novel technology for which the only way to identify and quantify some risks is through human experimentation."

To Pierce and others, the key is to conduct appropriate testing in animals before treating humans, whenever possible. More important, it is essential that all trial participants give "informed consent." We will never be able to eliminate all risk in gene therapy trials, but as long as the risks are identified as clearly as possible to patient participants, believes Pierce, "the ultimate burden

[1] MASAC recommendation #120, issued August 2001, available from HANDI (1-800-42Handi) or on the NHF website at http://www.hemophilia.org

[2] Call HANDI or visit the NHF website for resources on hemophilia gene therapy

[3] *PEN*, Feb. 2000, "How Safe is Gene Therapy?" Available on-line at http://www.kelleycom.com/pencont.htm

[4] *Proceedings of the WFH Global Forum on the Safety and Supply of Hemophilia Treatment Products*, Montreal, April 2000

of choice rests with the individuals in the trial and their physicians. If we put too much emphasis on trying to guarantee safety, we may impose restrictions that can never be met, effectively derailing gene therapy or, perhaps, discouraging researchers from choosing hemophilia as the disorder to study. That would significantly delay scientific breakthroughs that will benefit those of us with bleeding disorders."

Philosophical arguments aside, specific issues raised by the human trials have required regulators to make concrete decisions about when to allow gene therapy clinical research to begin, or continue. Some issues appear minor, even trivial. Others raise important questions about what level of risk we, as a community and a society, are willing to accept as part of our progress toward attaining gene therapy's promise. With the potential benefit so high—perhaps the cure for hemophilia and a multitude of disorders—our willingness to accept some risk seems appropriate. The question, theoretically and practically, is *how much risk?* And should the level of risk we accept depend on the likelihood and degree of benefit?

With the potential benefit of gene therapy so high, our willingness to accept some risk seems appropriate.

The first interruption in a hemophilia gene therapy trial occurred in the hemophilia A trial sponsored by Transkaryotic Therapies, Inc., conducted at Beth Israel/Deaconess Hospital in Boston. This "hold" came in early 2000, after the death of Jesse Gelsinger in late 1999 focused a spotlight on gene therapy trials around the country, including another unrelated trial at the Beth Israel/Deaconess in which regulatory irregularities were uncovered. Perhaps in response to negative publicity, and apparently hoping to demonstrate their commitment to patient safety, the authorities at BI/Deaconess announced the suspension of the hemophilia trial to review its safety profile. Ironically, this hold only cast further suspicion on the entire gene therapy field. In fact, the BI/Deaconess hemophilia trial was proceeding with no safety incidents, and with small but significant efficacy findings. Ironically, the suspension of the TKT trial was imposed at a time when no new patients were being recruited, so the announced suspension had no real impact on how the trial was proceeding. Fortunately, hospital administration moved quickly to lift the hold, and the trial was allowed to proceed as planned. The suspension was a front page story in *The Boston Globe*; the trial's subsequent resumption, a footnote buried deep inside the same newspaper. While it appears that no real safety issue was ever involved, suspicion was cast on a trial that could instead have been used as an example of the proper way to conduct a gene therapy trial.

The second hold of a hemophilia gene therapy trial occurred in the summer of 2000. A routine test of a semen sample from a patient in the Chiron trial showed traces of the viral vector used in the procedure to transfer the factor IX gene. In pre-clinical animal studies, this vector had never been found in the semen of treated animals, so the result led the FDA to request a temporary halt of the trial. The presence of vector in semen raises the possibility that the vector could infect sperm cells, and eventually be passed through the *germline* (eggs or sperm) to future offspring. So far, no one knows exactly what effect this might have, but to date the scientific community and regulatory authorities have never allowed a trial to take place involving intentional germline transfer. The possibility of unintentional transfer is still seen by most as an unacceptable risk.

Fortunately, investigators for the Chiron trial reported that additional testing of the sample in question produced negative results, as did subsequent sampling from the same patient. It was concluded that the initial test result was probably an error, or "false positive." Chiron received FDA permission to resume the trial, but stopped it soon after, for what Chiron called "business reasons."

The third trial to be put on hold was Avigen's trial for hemophilia B, involving intramuscular injections of adeno-associated viral vectors. In this trial, as with the TKT trial, the suspension was not directly related to a specific side effect in any of the patients. In Avigen's case, reports from other adeno-associated viral studies in mice had yielded some initial evidence that the mice being studied were more likely to develop tumors after being treated with the vector. However, a review by the FDA and RAC concluded that these results were unlikely to be relevant to the Avigen trial, and this hold, like the others, was also lifted.

It's apparent from these examples that putting a trial on hold doesn't mean that any patients are actually at risk—but there is enough cause for concern to pause and resolve uncertainties before moving ahead. Caution remains the guiding principle in all trials. The interruption of a trial is often a business or logistical setback, rather than a real scientific problem. However, in the two most recent holds, both of which occurred in 2001, actual side effects were observed that truly warranted the suspension of the trials, at least temporarily. Regulatory authorities now had much more complex decisions to make about allowing the trials to proceed.

The issue of positive semen samples, first occurring in the Chiron trial, has reappeared in the second Avigen trial for hemophilia B. Like the first Avigen trial, this trial utilizes an adeno-associated viral vector; but in this case, the vector is infused into the hepatic (liver) artery, targeting the liver, rather than injected into muscle. In general, infused vectors (like the retroviral vector used in the Chiron trial) are more likely to travel through the bloodstream to remote sites in the body, and get into various tissues and organs. This is usually considered insignificant, since

the amount of vector that ends up in various tissues is small, and normally persists only briefly before it is "cleared."

It is hoped that little harm will be done by this roving vector. However, several sequential semen samples from the first patient treated in the liver-directed Avigen trial were positive for vector. Once again, the remote possibility was raised of vector getting into a patient's sperm, and being passed on to sexual partners or offspring. Once again, the FDA requested the trial be put on hold. But since the samples were truly positive this time, decisions had to be made: Was the presence of vector in the semen reason enough to permanently halt the trial? Still determined to minimize the risk of germline transfer, investigators continued testing—until several sequential samples showed that the vector did indeed clear from the semen. They also tested for signs of the vector in actual sperm cells, and found no detectable traces of vector in the patient's sperm.

After reviewing the data, the FDA decided to allow the trial to resume, but with some alterations: additional steps to monitor patients' semen and sperm would be incorporated into the trial; and participants would be advised to avoid unprotected sex until it was demonstrated that their semen was free of vector. It is likely that this trial will proceed more slowly than originally planned, but if no further problems arise, it should proceed to completion. If additional persistent traces of vector are detected in semen samples, or if traces of the virus are found within future patients' sperm, the trial may be subjected to additional holds.

The final trial to consider is the hemophilia A trial conducted by GenStar Corporation. This trial raises the most serious questions to date. Utilizing a modified adenoviral vector, the trial was initiated in June 2001, after numerous animal studies were conducted to evaluate its potential safety. Some of the tests (particularly a series of experiments studying non-human primates) were designed to look specifically at the effects of the vector in animals whose immune responses were most likely to resemble what might be seen in humans. The GenStar trial, just like Jesse Gelsinger's trial, uses an infused adenoviral vector targeting the liver. Some scientists and hemophilia advocates were concerned that the issues raised by Gelsinger's death could be relevant, particularly since the exact cause of death has never been pinpointed. However, it is important to note that Gelsinger had a genetic defect that affected his liver; this may have made him particularly susceptible to toxic effects of infections. Studies conducted by GenStar indicated that even at a dosage of vector 100 times greater than the first patients in the trial would receive, the primates showed no significant side effects. Based on this information and other extensive pre-clinical data, GenStar received FDA approval to initiate its trial.

Unfortunately, the first patient treated with the GenStar protocol quickly developed unexpected side effects, including a drop in platelets and factor VII levels, and increases in several liver enzyme levels. These effects were transient, and the patient's levels soon returned to normal. But the results raised enough concern that GenStar, in consultation with the FDA, placed the trial on hold. GenStar noted that, even at this very low dosage, a measurable rise (up to 3%) in circulating factor VIII levels was observed in a patient whose factor levels were previously undetectable. The levels have apparently been sustained at about 1% over several months. GenStar stressed that all the side effects were transient, and while the deviations in blood chemistries were real, they were never severe enough to cause a health threat to the patient. Also, the patient had a high, pre-existing antibody response to the adenoviral vector, raising the possibility that patients with lower antibody levels might respond differently. After reviewing the protocol and the patient's lab results, the FDA agreed to allow the trial to resume with modifications. GenStar agreed to lower the starting dosage ten-fold, to minimize the chance of repeating the first patient's side effects. To date, no new patients have been enrolled or treated, and the NHF and GenStar continue to discuss the best way to move forward with this research.

Unquestionably, the envelope has been pushed. The debate over what level of risk is acceptable has intensified. Not all experts agree with the FDA ruling allowing the GenStar trial to continue. Some feel that until the immune response to adenoviral vectors is better understood, it is too risky to use them for anything other than life-threatening disorders. Some consider it premature to use these vectors for hemophilia, in relatively healthy patients who have viable alternatives in existing therapy. On the other hand, many proponents of gene therapy clinical research point to the overall safety of gene therapy, believing that we must accept some level of risk if we hope to achieve true progress.

It is unknown whether the immune response seen in the GenStar patient is related to that seen in Jesse Gelsinger. It is also unknown whether future patients face a real risk of repeating either the effects seen in the first GenStar patient, or those seen in Gelsinger. What is beyond question is that the decision to conduct trials, and the decision to enroll in them, has become more complex, requiring greater consideration by all involved—regulatory authorities, trial sponsors, doctors conducting the trials, advocacy groups like NHF and, perhaps most important, the patients themselves.

Identifying, quantifying, and accepting risk is an inherent part of the discovery process in medicine. As it does in all new areas of medical research, the debate over risk will continue, not just in the hemophilia trials, but across the field of gene therapy. Additional risk factors will emerge, or shift from theoretical risk to real risk. So it's possible that the closer we get to seeing the fruits of gene therapy and realizing its benefits, the more difficult the decisions will become. As we wind through this process, our guiding principle must be to ensure that we not take excessive, unnecessary risks during the trials, and that we understand any process thoroughly before allowing it be used on a broad commercial basis.

Risk-Benefit Considerations Far Different in the Developing World

Most adults with hemophilia in the U.S. are living with HIV or hepatitis. Teenagers, for the most part, live active, nearly normal lives, largely unaware of how fortunate they are to have escaped the HIV 'holocaust' of the early 1980s. Younger children with hemophilia are often treated prophylactically—many have never been treated with plasma-derived factor concentrates, and have no concept of the physical and emotional trauma that older people with hemophilia have endured. But what unites these groups, their families and caregivers, is the conviction that they will never again accept any compromise in the safety and efficacy of the treatment they receive.

The proactive U.S. hemophilia community has demanded, and received, products with ever-improving safety profiles: extensive screening of plasma donors; plasma quarantining; monoclonal purification; viral inactivation (even *double* viral inactivation of some plasma-derived concentrates); recombinant factor concentrates; and now, even recombinant products free of all human albumin and/or animal proteins. Considering our history, if gene therapy is to succeed in the U.S. it will need to achieve extraordinary levels of safety, and prove more effective than current treatment. Why would we settle for a therapy that is less safe or less effective than what we already have?

But not everyone can afford to insist on such high standards of safety or efficacy. Not everyone has safe and effective treatment readily available. In fact, the World Federation of Hemophilia (WFH) estimates that *worldwide, three out of every four people with hemophilia receive no care or sporadic care*. And the chance is slim that most of these people will *ever* gain access to meaningful care in the form of factor concentrates. For approximately 200,000 of the world's 270,000 with hemophilia, treatment consists of little more than ice and rest—assuming that ice is available, and rest is a possibility.

Not surprisingly, many patients in developing countries view gene therapy differently than we do in the U.S. For them, gene therapy is not just one more step forward in the search for a cure; it is the last, best hope for meaningful treatment in the foreseeable future. Yet because most of the gene therapy programs are being developed in the U.S., they are designed in accordance with the regulatory standards and economic realities of the U.S. market. As a result, any processes developed may remain inaccessible to most patients in developing countries, long after the scientific obstacles to successful gene therapy have been overcome.

Medicine is not the only arena in which accepted standards vary from country to country. What is unusual is the degree to which medical standards of the most highly developed countries, like the U.S., dictate what care is, or isn't, available to the rest of the world. When it comes to housing or general public health issues like water quality or food inspection, developing countries clearly cannot be held to the same restrictive standards that are justified in industrialized countries. Most Americans support the "watchdog" efforts of domestic agencies like the Environmental Protection Agency, the Food and Drug Administration, and the Centers for Disease Control. Yet no one would suggest that villages in Ethiopia or Cambodia should be required to conform to the same housing or public health standards expected in the U.S. In most policy areas, local communities or individual countries determine which regulations, if any, are warranted, weighing the economic, cultural and technical factors affecting each community. Unfortunately, when it comes to medical care, the choice for developing countries is often all-or-nothing: conforming to the standards of highly industrialized countries, or providing no care at all. Except for regional herbal medicines and a few locally manufactured pharmaceuticals, the developing world is almost entirely dependent on the developed world for producing the drugs and medical devices it needs. Frequently the options are limited: either pay dearly for these expensive treatments, or choose not to treat at all.

Clearly, millions of patients around the world have benefited from vaccines, antibiotics, and other drugs that have saved countless lives. But as advanced technologies, including recombinant drugs, are developed, they are often targeted for consumers in highly developed countries—consumers who can afford expensive treatments. Part of the problem is that U.S. drug companies prefer to focus on lucrative products like PROPECIA® (to treat hair loss), VIAGRA® (to treat sexual dysfunction), and a host of obesity drugs, all targeted to bald, impotent, fat American men—rather than conduct research on vaccines and drugs that could ease the many infectious and parasitic diseases that go untreated in developing countries. Even without considering economic motivation, the very structure of the pharmaceutical industry and the design of drug development programs in the U.S. make it unlikely that the end products—factor concentrates or gene therapy—will readily reach the hands of the patients who need them most.

Many factors affect the availability of drugs and other medical products in developing countries. Two of these, high cost and stringent safety requirements, are particularly relevant to hemophilia products—existing factor concentrates or, potentially, future gene therapy products. In the U.S. and other highly developed countries, cost is a concern, but not usually a critical factor in a consumer's decision process. Most consumers are covered by either private insurance plans or government health programs. Healthcare cost containment is an important topic of political debate in the U.S., but at present few patients actually are denied access to high purity concentrates due to cost alone. This is not the case in the developing world, where people are rarely able to obtain product on their own, and where government expenditures needed to secure factor for patients are impractical. According to the WFH, the per patient cost to provide factor for patients in developing countries would be a

minimum of $9,000 per year—a completely unrealistic figure in many countries.

Will gene therapy cost as much or more than factor concentrates? The final cost is unknown, but gene therapy is unlikely to be inexpensive. A novel technology that has required years of research and development to reach its current status, gene therapy will probably require years more before becoming commercially available. The methods currently being studied don't appear to be simple to manufacture on a large scale, and some of the programs will be difficult to distribute or administer globally, without incurring extraordinary expense. Right now, greater emphasis is on safety and efficacy than on the eventual affordability of a gene therapy process.

The emphasis on safety in the U.S. and other industrialized countries is understandable. Devastated by viral contaminants like HIV and hepatitis in factor concentrates, the U.S. hemophilia community is united in the conviction that safety must be a dominant consideration for all products, including gene therapy. The depth of this feeling was conveyed by Mark Skinner, President of the National Hemophilia Foundation, at a WFH Forum in April 2000.[1] Referring to the theoretical risk of CJD in factor concentrates, Skinner said, "Safety is always the first and foremost consideration in our decision-making process," noting, "Our community has made too great a sacrifice to allow history to repeat itself."

Although these comments were directly aimed at factor concentrates, a comparable sentiment exists in the U.S. community regarding gene therapy. Even in initial human clinical studies, where risk is unavoidable, great effort is made to minimize risks and respond quickly to any perceived risk factors that emerge. It is unlikely that, on a commercial scale, any gene therapy process will ever be widely accepted if it carries even a minimal risk of transmitting harmful viruses, or increased risk of inhibitor formation. Expectations in the U.S. are great, and the bar is raised high for researchers hoping to introduce new treatment methods.

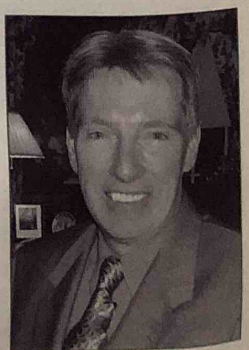
By comparison, the majority of the world suffers from conditions that most Americans can barely imagine—untreated bleeds; severe arthropathy and crippling joint damage; frequent internal bleeds leading to brain injury or damage to other organs; infections from bleeds leading to amputation; even premature death from bleeds easily treated in more highly developed countries. Under these circumstances, the emphasis on safety that seems so appropriate in the U.S. is untenable.

> If we require all nations to adhere to the standards we demand in developed countries, we may effectively eliminate the chance for developing countries to access treatment of any kind.

According to Mark Skinner, "Until persuaded otherwise, we will not accept risk even at a theoretical level." Yet Ashok Verma of India, another presenter at the WFH Forum, used similar words to express a very different view: "In developing countries, there is usually no choice. When faced with an acute complication because of hemophilia, and with no access to safe concentrates, *any* form of replacement therapy has to do."

Neither side is wrong. Each simply deals with differing realities in differing communities. However, we must keep in mind that the decisions made in the U.S. and other developed countries have a great impact on lesser developed countries. Our decisions about which products to develop or sell can directly determine whether care is—or is not—available to the rest of the world. If we require, directly or indirectly, all nations to adhere to the standards we demand in developed countries, we may effectively eliminate the chance for developing countries to access treatment of any kind. "If the developing world accepts the safety standards applied in the developed world," notes Ashok Verma, "there would not be any therapeutic material available, and 80% of people with hemophilia in the world would be condemned to permanent crippling and premature death."

So far, it is too early to predict which gene therapy methods will work, and whether they will be globally accessible. But it is not too early to begin examining how global access to gene therapy might be made more feasible. For gene therapy to ever be considered a real success, it must reach the tens of thousands of patients who need it the most—patients in developing countries who have little hope of ever gaining access to meaningful care in any other way. We must expand our current dialogue on issues that might affect global access, and search for ways to make global access to hemophilia gene therapy a viable goal. It is too soon to hope for clear answers, but not too soon to begin asking questions.



Kevin C. Kelley is DNA Products Manager at New England Biolabs in Beverly, MA, and father of a fourteen-year-old with hemophilia. He has published articles on blood safety and recombinant factor products previously in PEN. *You can reach him with comments or questions at* (800) 249-7977 *or* info@kelleycom.com.

[1] *Proceedings of the WFH Global Forum on the Supply and Safety of Hemophilia Treatment Products*, Montreal, Canada, April 2000

Hemophilia
Gene Therapy Clinical Trials

Sponsoring Company	Corporate Partners	Trial Site (Principal Investigator)	Date Trial Began	Hemophilia Type	Treatment Method*	Future Plans
Transkaryotic Therapies, Inc. Cambridge MA	None	Beth Israel Deaconess Medical Center *(Dr. David Roth)*	Dec. 1998	Hemophilia A	*ex vivo* / plasma vector	Completed treatment in Phase I trial; may initiate Phase II in 2002
Avigen, Inc. Alameda CA	Bayer Pharmaceutical	Children's Hosp. of Philadelphia *(Dr. Catherine Manno)*; Stanford Univ. Med. Ctr. *(Dr. Bert Glader)*	June 1999	Hemophilia B	*in vivo* / adeno-associated viral vector / muscular injection	Completed Phase I trial; may postpone decision on next phase until liver-directed trial results available
Chiron Corp. Emeryville CA	NA	Trial terminated	June 1999	Hemophilia A	*in vivo* / retroviral vector / venous infusion	None
Avigen, Inc. Alameda CA	Bayer Pharmaceutical	Children's Hosp. of Philadelphia *(Dr. Catherine Manno)*; Stanford Univ. Med. Ctr. *(Dr. Bert Glader)*	June 2001	Hemophilia B	*in vivo* / adeno-associated viral vector / infusion targeting liver	Trial suspended when vector detected in semen; given FDA OK to resume, with modifications
GenStar Therapeutics San Diego CA	Baxter Healthcare	Univ. of N. Carolina *(Dr. Gilbert White)*; Univ. of Washington *(Dr. Arthur Thompson)*	June 2001	Hemophilia A	*in vivo* / adenoviral vector / venous infusion targeting liver	Trial suspended due to unexpected side effects in first patient; given FDA OK to resume at lower dose
Targeted Genetics Seattle WA	Genetics Institute	NA	NA	Hemophilia A (and possibly B)	*in vivo* / adeno-associated viral vector / liver-directed	No definitive timetable for human trials
Cell Genesys Foster City CA	None	NA	NA	Hemophilia B, Hemophilia A	*in vivo* / lentiviral vector (FVIII), or adeno-associated viral vector (FIX)	May file FDA application to begin one or both trials in 2002

* *Ex vivo* methods involve isolating cells from the patient, introducing DNA containing the factor VIII gene into the cells, and reimplanting them into the patient. With *in vivo* methods, DNA containing the factor gene is injected or infused into the patient and taken up by cells within the patient. Updated January 2002.

Family Success Story

Adopting a

One April day in 2000, Kathy and Tom Kuklish were in their garage, unpacking boxes after their retirement from the Army. Their son, Thomas Pat, has hemophilia. Three of Kathy's four brothers were also born with hemophilia, and two have since died. "We found an old *PEN* article," recalls Kathy, "on international adoption of children with hemophilia.* After prayer and soul-searching, we e-mailed Laurie Kelley to ask if she knew of any children with hemophilia available to adopt."

On May 7, 2000, Laurie responded. "Unbelievably, an adoption agency has called wondering if there are any U.S. families looking to adopt an adorable Korean baby with hemophilia. He is ready to go!"

Realizing that life was about to change dramatically, but believing that this was meant to be, Kathy e-mailed Tom, who replied, "I don't know what we're getting into, but I will support you, and we'll make it work."

The Kuklish family lives in an Alabama suburb of Pensacola, Florida. Laurie put Kathy and Tom in touch with Americans for International Aid and Adoption (AIAA) in Troy, Michigan. They learned from AIAA that a 21-month-old boy with hemophilia (born Dong Joon Lee) was in foster care in Seoul, South Korea, awaiting adoption. The Kuklish family saw photos of the baby on the Internet, and communicated with AIAA mainly via e-mail prior to the adoption. "He is really an e-mail baby!" laughs Kathy.

Michael Paul Kuklish was 28 months old when he was welcomed from Korea by his new family, three days before Christmas, 2000. Michael Paul (now age three) joined his new siblings Thomas Pat (age 11), Mary Louise (age 13), and Kathleen Elizabeth (age nine).

PEN asked Kathy and Tom to talk about the adoption, and describe how the family has adjusted to its newest member.

PEN: Why did you choose to adopt a child with hemophilia?

Kathy: While we have our three biological children, we were advancing in age—and we have been touched by the hemophilia community. To us, hemophilia was not a show stopper. Hemophilia is really no more of a challenge than dyslexia or poor eyesight. It's no more limiting than any other challenge a child today faces.

PEN: Did you discuss adoption with any hemophilia specialists beforehand?

Tom: No. We get our comprehensive care from the hemophilia treatment center at Vanderbilt University Haemostasis and Thrombosis Clinic in Nashville, Tennessee—an eight-hour drive. So we didn't consult with anyone. We were comfortable enough raising a child with hemophilia. It's really not much different, having one child with hemophilia, or two; although there are some differences in physiology, bleeding patterns, and in the way Thomas Pat and Michael Paul react to pain.

PEN: Did you have any concerns or fears about the adoption process?

Tom: The length of the process! We wondered if it would ever really happen. We felt we were just stabbing in the dark. But once we decided that Michael Paul was the child we wanted, if we hadn't gotten him, I don't think we would have pursued adoption any further.

PEN: You felt he was the child for you?

Tom: Yes, it was intuitive.

Kathy: As we went through the process, it became obvious to us that he was the intended child for our family. Michael Paul has the same kind of hemophilia as my brothers and our son [factor VIII severe]. When we looked at his pictures, we felt that this is the child God wants us to have.

PEN: What happened when Michael Paul was diagnosed in Korea?

Tom: He was in a foster home, and was diagnosed at seven months. Shortly after the diagnosis, he was taken by his foster parents back to the orphanage in Seoul. Hemophilia is a daunting disorder in a baby and toddler! There was a lot of concern, so I think they pretty much kept him in the crib. At about 21 months, when we first learned of him, he was bruising so much that the agency permitted him out only when he was with his special volunteer, one-on-one. He was later placed with another foster family until just before he flew to America.

Kathy: Our adoption was delayed significantly by misplacement of INS [Immigration and Naturalization Service] paperwork. As we understand it, Michael Paul was virtually forced to stay in his crib during those weeks that paperwork was misplaced. That is a terrible waste of a toddler's life. Intentions were good, and I'm sure the people at INS worked as hard as the people at the adoption agency and in the foster home and orphanage, but that was a very harsh fate.

PEN: Did you receive sufficient medical information from Korea? Any surprises once Michael Paul arrived?

Tom: It was pretty well on target. We received a short videotape of him, and complete medical and personal history. We had a translated doctor's report, which we felt was very accurate. We had statements from social workers describing his visible physical condition: he had bruises, and was infused once a month.

Kathy: When we received his medical papers, we sent them to Vanderbilt. The nurses who helped diagnose Thomas Pat ten years ago said, 'Are you sure you know what you're doing?' We said, 'It's going to work. God intends us to have this child.' At one point, medical records indicated that Michael Paul might have an inhibitor, so we faxed the paperwork to Vanderbilt. Those people were so good—they reviewed the information, and suggested some questions we should ask. As it turned out, no inhibitor has been detected in Michael Paul.

Child with Hemophilia

by Sara Prisland Evangelos

PEN: Any problems with insurance related to Michael Paul's hemophilia?

Kathy: We struggled to 'break the code' with medical insurance with DEERS (the Defense Enrollment Eligibility and Reporting System for the armed forces), since we are both retired Army and receive our medical care at Pensacola Naval Hospital. We were in limbo: we didn't finalize the adoption in Korea, since Alabama required a six months' stay before we could finalize. The term 'legal guardian' became a concern to the Navy. But after several months of wrangling back and forth, it was finally recognized that Michael Paul was in the military eligibility system. It was a tough challenge with the pre-existing condition, but Tom accomplished the impossible by convincing the Navy to authorize him medical coverage *hours* prior to driving to New Orleans to meet the plane from Korea. Even then, we were told, 'You can't have him on your high tier of medical care because there's a three-month waiting period. You don't have his paperwork done at the right time of the month, so you have to wait for the next quarter of the calendar year.' Our supplemental insurance would not recognize Michael Paul until the adoption was finalized; neither would Tom's medical reimbursement plan.

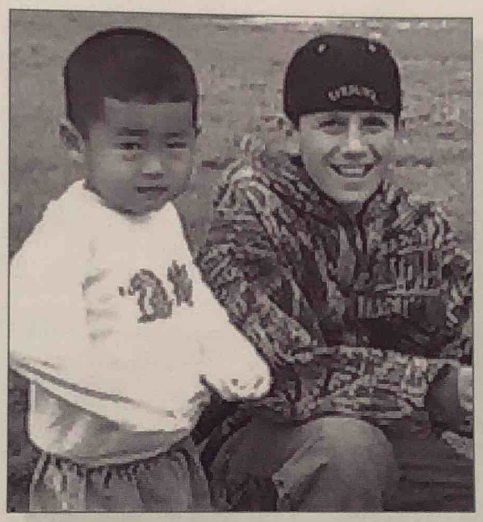


Photo: Tom Kuklish

New Siblings: *The Kuklish brothers, Michael Paul and Thomas Pat, now have a lifetime to learn from each other.*

We were blessed that nothing serious happened during that waiting period, and that we are nine miles away from Pensacola Naval Air Station Medical Center. The military doctors deserve praise for their ability to help us. Michael Paul has very special guardian angels—his health has been excellent.

PEN: What was it like to meet Michael Paul at the airport?

Kathy: It was a humbling experience to stand in the New Orleans International Airport, and see him come to us with nothing but a child's lost face and one set of clothes. Michael Paul turned to Tom in the airport, looked up to him, held out his arms and said '*Apa, Apa*' ['dad']. He was obviously out of his element, but he had a commanding presence, and he went instinctively to Tom. That has never changed.

PEN: If you hadn't adopted him, what do you believe life would have been like for Michael Paul?

Tom: I don't think anybody else would have adopted him. I think his chances would have been very slim.

Kathy: He was already stigmatized as an orphan. To have that against him socially, and then to have a chronic condition and continually be treated with human product—he would have had too many things against him to develop the way he has the opportunity to develop here in America.

PEN: How have your other children adjusted to their new brother?

Tom: I hear stories about adoption, about adjustment periods—but it has been minimal, even with hemophilia. It's been very positive for all of them. To be frank, there's a little jealousy because he's the baby, but they're all very protective of him. They have fully accepted him as a sibling, and that was quite amazing to me. Yes, we're helping him, but our family is also getting something out of it. In the Army, we had the opportunity to travel around the world, and although we've told our children about people in other countries, there's a lack of appreciation for what we have. When they saw Michael Paul come to our family, it became real for them. He was a child who had nothing.

Kathy: Our older daughter looks at Michael Paul and says, 'Mom, I love this kid! How could they ever have let him go?' You don't pick what you're going to get when you have biological children. Children have no choice when they get a new brother or sister. But we all fell in love with Michael Paul the first time we saw his picture.

One year after his arrival, Michael Paul is doing well in his new family. "He finds it interesting to see his older brother do his own infusions," Kathy notes, "and Thomas Pat is a big help with Michael Paul, helping him get his infusion done."

Any regrets? "Every life, every child is a gift," says Kathy. "They all have their own challenges. As I look at him, my regret is that his birth mother, whoever she is and wherever she is, doesn't know what a blessing she has brought into this world, to our family, to everyone. Michael Paul has a special way with people, a special smile. He is a godsend, and he touches people's lives. He is a blessing."

** The article "Adopting a Child with Hemophilia" appeared in* PEN, *May 1997. Visit the LA Kelley Communications, Inc. website for the text of the article:* **www.kelleycom.com/pen_adopt.htm**. *If you are interested in adopting a child with hemophilia, contact us and we'll see if we can help.*

Sara Prisland Evangelos is a free lance writer, editor and poet. She and her husband have a 12-year-old daughter, and a seven-year-old son who was adopted from South Korea.

Gene Therapy: Reaching a Star

by Nicolás and Ana Rosa Rangel

I will be born in a little less than a month. I have been inside my mother eight months and, believe me, after hearing all that I have heard, I think it would be best to stay right here.

I am going to be born in Mexico, which worries me. Soon I will be Mexican number 100,847,251. We are already more than one hundred million, and to be born in Mexico is in itself a great adventure.

I am happy that I already know my name. I will be called Yair Alexis. Well, at least that is what my mom said. My father's name is Alejandro and my mother's is Anna Karina. I am fortunate because here, all the boys are called José and all the girls are called Maria. I am going to be born in a new Mexico, one that never stops changing. Things are still not moving at the rate we would like—but I am going to be born, and that is a blessing.

During these months inside my mother, I have learned that I have hemophilia. That means that my blood will not clot adequately, and I will depend throughout my life on a special medicine called factor VIII.

One of the talks I have enjoyed the most was the one I heard the other day. It was my Tata (my maternal grandpa) speaking. He spoke to the whole family about the Mexican Health and Social Security System. Here's what he told us:

"In Mexico, 52 million people belong to the IMSS (Mexican Institute of Social Security), or 48% of the total national population. The IMSS is the largest decentralized public institution in the world.

Twelve million Mexicans, or about 10% of the total national population, are members of the Health and Social Security Institute for State Employees (ISSSTE).

Almost 2% of Mexicans belong to Mexican Petroleum Company (PEMEX) hospitals. Mexicans also receive treatment in the hospitals belonging to the National Defense and Naval Secretariats.

All these institutions provide first-class medical attention, and people with hemophilia, mainly children, have the opportunity to get factor VIII and factor IX concentrates.

But what happens to the rest of the Mexicans? What happens to the almost 40 million Mexicans who do not have access to health services in any of these institutions?

For this large number of people, there is the Health Secretariat; through its national system of hospitals, clinics and health centers, people with hemophilia are treated with cryoprecipitate and plasma.

In some of the major Mexican cities, like Guadalajara, Monterrey and Puebla, people can get treatment at the municipal medical services. These are health centers with very limited resources, so it is unlikely that patients will obtain factor concentrates. Unfortunately, the lack of knowledge about hemophilia means that patients are unable to get treated even with cryoprecipitate.

Finally, we have the Mexican Red Cross, which is responsible for emergencies arising from accidents or natural disasters in our country."

Now you know the reason that I prefer to stay here, inside my mother.

It is my wish that my parents belong to the IMSS. I wholeheartedly hope that they do everything necessary to give me the chance to develop with equal opportunities, because—and I want to state this loud and clear—I am no different, I am equal. My potential is great, and I want to live. I want to give my country the best of myself, to leave a mark, and not to pass unnoticed.

Today I learned two new words from my Tata: *gene therapy*. Today I felt my mother's heart beat with new hope. *Gene therapy*.

My Tata read an article about gene therapy. He told my mom that this is the hope for people with hemophilia. Of the three clinical trials already initiated, only one company's appears to move forward: Transkaryotic Therapies, Inc.

My Tata read, "The trial has an excellent safety record, and has produced the most impressive therapeutic benefit yet reported in a hemophilia gene therapy trial... At least two of the patients (both severe) have had no apparent spontaneous bleeds for more than a year." [*"A Long and Winding Road," PEN, Feb. 2001*]

And today, my Tata and my Tati (my maternal grandma) have great news: the Hemophilia Information Centre has just begun operations; this is a place where information about the hemophilia world will be available to all.

Although no one can see me, my mother can feel me, and today, I feel very happy. Soon I will be born to a responsible, interested and informed family. I will be loved by all.

It is very possible that when you read this, I have already

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To the Editor

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Gene Therapy Research

WITH GREAT INTEREST, I READ THE LETTER FROM LISA O'CONNOR [*PEN*, May 2001], which supports research to help those with hemophilia live better. This letter has obviously struck a common chord with many people with hemophilia, parents, and others impacted by this condition. I believe that gene therapy is a wonderful thing, and will be a spectacular boon for most of us. It might be the "silver bullet," but it might not, and may take a long time to come. We should not give up on other possible gains that research might offer just because things will be better in the future.

I was privileged to meet with the leaders of Genetics Institute in 1992 as a representative of the hemophilia community. The discussion was whether to continue the development of BeneFIX®. Some had predicted that gene therapy would be available in five years, or at the most ten. If this were the case, then GI would probably have bankrupted itself developing this product. It was a big risk. All of us should be eternally grateful that the company took the chance and continued its development. Without BeneFIX®, the hemophilia world would be much worse off.

We should follow GI's example. Research means expanding knowledge, and we can always gain from more knowledge. Things are better now than they were ten years ago, and we should work to make them better tomorrow. I support research to improve all of our lives, and I thank Lisa and the many others who also feel that way. *—John R. Taylor, Jr. Coalition for Hemophilia B, New York*

I READ THE EDITOR'S RESPONSE TO MY PREVIOUS LETTER [EDITOR'S note, *PEN*, August 2001], and it seems that I was misinterpreted. My main point was that the vast majority of research dollars are going into gene therapy. While gene therapy may represent the best hope, it may not be the only viable hope for a real cure.

The August issue of *PEN* reports on an experiment involving the use of a common antibiotic as a means of treating hemophilia. Hundreds of different methods of delivering large proteins are being explored worldwide, using technologies that did not exist even five years ago. Any explorations made "several decades ago" should not be our reference point.

It is true that factor IX is much smaller than factor VIII. Limited success has already been reported in achieving small amounts of circulating factor IX after subcutaneous administration. There are problems associated with subcutaneous administration of factor, and the day it may result in actual treatment is far in the future. It is, however, a viable area of research, and worthy of more investment by the hemophilia community.

Currently, it may seem that research on alternative delivery systems will never benefit factor VIII patients, but this may not be the case. I am reminded of the days when recombinant factor IX was developed without using any blood products, including albumin. At that time, albumin was thought to be a required element in recombinant factor VIII formulations for stabilization. Yet with advanced generations of recombinant factor VIII formulations, albumin has been eliminated from the final formulation, and in the future will probably be eliminated from the manufacturing process as well.

Although there are fewer factor IX patients, research into alternative delivery systems may ultimately benefit all our community. Gene therapy may—and probably will—be the way of the future. But at least some of the vast research money spent should be allocated to other areas, including delivery systems currently being researched for insulin. We have no way of knowing if these other systems will work if we don't try. It doesn't make sense, from a risk management perspective, to pursue only one avenue of research, which may lead to a dead end. A good investment strategy incorporates diversification of resources. And research dollars are nothing if not an investment in our future. *—Lisa O'Connor, New York*

Consumer's Guide to the Shortage

IN OUR MOST RECENT NEWSLETTER, WE REFERRED OUR READERS TO your splendid coverage of the issues connected with the factor VIII shortage ["A Consumer's Guide to the Shortage," *PEN*, Nov. 2001]. As I have come to expect from *PEN*, your article was timely, comprehensive, well balanced and much needed. We have distributed copies to members of our Board of Trustees.

Because your feature article is generally right on target—covering vital issues with well-researched and well-written essays—we have suggested that our readers subscribe to *PEN*. This is a first for us. I don't recall a time in the ten years I have been involved in preparing *Hemophilia OUTLOOK* that we have made such an endorsement of another newsletter.

Having often grappled with writing on the same subjects, I can especially appreciate the superiority of your balanced coverage. You provide me with the information I need to help my clients, and to write for our newsletter.

Please continue to provide the hemophilia community with this intelligent publication. It is much needed and very much appreciated. *—Isabel Brach, Program Director, Hemophilia Association of New York, Inc.*

ANOTHER GREAT ISSUE! YOU COVERED ALL THE BASES IN YOUR great article on the shortage. I'm sending it to our U.S.-based field team. *—Michael J. Dwyer, Senior Director of Sales, Novo Nordisk BioPharmaceuticals*

I COMPLIMENT YOU ON YOUR INFORMATIVE ARTICLE ON THE Kogenate® FS shortage. I am moved to add some additional reasons to the section "Why are we shipping to Canada and Europe during a time of shortage?"

1. Recombinant factor VIII usage in New Zealand is 36% of our total factor VIII volume used, but some 80% of our recombi-

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Baxter Produces Record Levels of RECOMBINATE™ rAHF

Baxter Healthcare Corporation announced that in 2001 it shipped more than one billion units of RECOMBINATE™ Antihemophilic Factor (rAHF, the company's recombinant factor VIII therapy) from its BioScience facility in Thousand Oaks, CA. Baxter began constructing this facility in late 1992, and licensed it in 1996. Since then, Baxter has invested more than $200 million in its continued expansion, and has produced more than 4.5 billion units of RECOMBINATE™.

Baxter is also preparing to submit its protein-free method recombinant antihemophilic factor (rAHF/PFM) to the FDA for licensing approval. The rAHF/PFM is a new category of rFVIII therapy, prepared without adding any human or animal raw materials (like albumin) in the cell culture process, purification or final formulation.

Curative Health Services Acquires Apex Therapeutic Care

Curative Health Services, Inc. has entered into an agreement to acquire **Apex Therapeutic Care, Inc.**, a specialty pharmacy services company based in Los Angeles, California, for a total purchase price of $60 million.

Founded in 1998, Apex is a leading provider of pharmaceuticals, therapeutic supplies and disease management services to people with hemophilia and related bleeding disorders throughout the U.S. Apex currently serves approximately 200 hemophilia patients with an annual revenue that exceeded $45 million in 2001. Curative anticipates that integrating the two companies will take 30–60 days, and Curative's current manufacturer agreements assure an adequate supply of factor.

Aventis Behring Announces Prion Testing Research

At the December annual meeting of the American Society of Hematology, researchers from **Aventis Behring L.L.C.** announced a new, highly sensitive, specific and rapid test being developed for prions. Prions are the infectious proteins thought to be responsible for Bovine Spongiform Encephalopathy (BSE) and its human form, variant Creutzfeldt-Jakob Disease (vCJD).

This unique test is called the **Conformation Dependent Immunoassay (CDI)**. According to Aventis Behring, the CDI detected small amounts of prions that were intentionally introduced ("spiked") into normal individual and pooled plasma donations. Aventis is using the new technology to evaluate the ability of its manufacturing processes to remove spiked prions. The resulting data will be part of Aventis's assessment and management of the theoretical risk of vCJD prions in blood or plasma.

There is no accurate test for CJD. Over the past five years, many companies have announced tests for CJD prions, but an accurate and sensitive blood or urine test for CJD prions remains elusive. Aventis has invested more than $20 million toward understanding prion science. If the CDI test proves sensitive enough to detect minute levels of prions in blood, it will be a major breakthrough in CJD research. *For more information:* www.aventisbehring.com/AventisBehring/NewsAndEvents/AdvPrionTest2001121801.asp

Factor VIII Supply Improves

The U.S. supply of recombinant factor VIII continues to improve. According to the **Plasma Protein Therapeutics Association** (PPTA), 102.48 million IU of rFVIII were distributed in the U.S. in November 2001. This is the largest distribution since the factor shortage began, and more than four times the amount of factor VIII distributed in July at the height of the shortage, when only 24.164 million IU were distributed. *For more information:* www.plasmatherapeutics.org/ppta_worldwide/1215_factor8_midmonth.pdf

Factor supply update

In December, **Bayer Biological Products (BP)** announced that effective January 2002, Bayer BP will resume releases of the 1,000 IU vial size of Kogenate® FS and KOGENATE® Bayer. Current efforts now focus on the manufacture and release of 500 and 250 IU vials, expected to be available by March 2002. Bayer BP hopes to achieve normal supply of Kogenate® FS in mid-2002. *For more information:* www.bayerbiologicals.com/html/global_utilities/newscenter/news_events/20011201.html

To the Editor

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nant product is Bayer's Kogenate® FS. If the U.S. had stopped export, New Zealand would have faced an extreme situation.

2. The world organizational model for hemophilia is unique, and the global hemophilia community derives its strength from this model. All people with hemophilia have a concern for those with hemophilia in other countries—we are all in this together.

3. If the U.S. is going to be a world leader, it must lead in good times and bad. The U.S. does not "own" the technology, nor the material produced; it just happens to be a site of production. The Global Supply Summit promoted by Bayer [in June] was a grand example, resulting in world distribution of product on the basis of need—not parochialism, politics or belief. What better model could one use? *—Mike Carnahan, President, Haemophilia Foundation of New Zealand*

THANK YOU FOR THE ARTICLE ON THE FACTOR SHORTAGE. It obviously took tremendous effort to assemble and summarize all the opinions on the perceived or real shortage of factor. The article offered readers an opportunity to extract the truth from the comprehensive facts presented. It was eye-opening to read so many differing points of view on the same critical subject. I applaud you for taking the first major step in alleviating situations like this shortage by simply communicating the opinions of the entire community. *—Joe Cannon, Director, Corporate Accounts, Aventis Behring*

Reaching a Star

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been born. Possibly I am one of those affiliated with the IMSS, and will suffer from its limitations, although it is the best we have. Yet I do not regret being born in Mexico. I am proud to be Mexican, and have defined my mission in life already. The future is not yet written. We cannot change the past. What is important is the here and now, because only by accepting my present will I be able to create my future.

Gene therapy, for me, is something like reaching a star. We all want to follow a dream; we all want to live with hope. The hope for a certain and permanent cure is like a dream. But allow me to dream—to shelter the hope that some day, for my children or the children of my children, the word hemophilia will be just another vocabulary word, one that belongs to a past full of pain and unhappiness that should never be repeated.

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The hemophilia newsletter by the families...

ADDRESS SERVICE REQUESTED

and for the families.

Inside:
Setting the Standards for Gene Therapy

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Daytime Phone ( ) _____ E-mail Address _____

Name & Date of Birth of Child(ren) _____

_____

Child(ren) with Hemophilia _____

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Check any that apply...

☐ patient ☐ parent ☐ medical treater
☐ educator ☐ hemophilia organization
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PEN maintains a special network of parents of children with hemophilia to provide us with information for upcoming articles and projects. We want to get **your** ideas, opinions and experiences periodically through telephone surveys, interviews, or written questionnaires. If you'd like to be on our team, check the box below!

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