PEN

inside

CLEARING A PATH:
Women Need a New Diagnosis

Christy Bergeon Burns

"During the past twenty years, several workers have claimed that abnormal bleeding occurs, and significant prolongation of the coagulation-time can be demonstrated, in a proportion of the female carriers of haemophilia."

This quotation[1] may not strike some of our community advocates as particularly surprising, given the recent surge in advocacy efforts regarding the identification and treatment of "symptomatic carriers," that is, women who carry a mutation for hemophilia and have abnormal bleeding symptoms themselves. But what may surprise most advocates is that the quotation was drawn from a scientific article published about *sixty-five years ago* in an esteemed medical journal. The authors described a study in which they sought to identify a reliable method to measure this coagulation "defect" in known carriers (for example, women with more than one son with hemophilia). They reported bleeding symptoms in some of these carriers, such as prolonged bleeding after tooth extraction. Then, using various laboratory methods that were newly developed at that time, the authors observed abnormal clotting behavior in blood samples from 3 of the 21 known carriers.

The study's important finding that individual carriers vary in their bleeding and clotting patterns was wholly overlooked in 1951. The authors of the study deemed the results "too indefinite and inconsistent to be of diagnostic value" and "disappointing." The authors' hope had been that their laboratory tests would show some subtle difference in coagulation in the blood of all known carriers. Then, tests could be used to definitively identify carriers among woman of uncertain carrier status (for example, women with a brother or uncle who had hemophilia). This specific focus can be understood from a historical perspective: most males born with severe hemophilia in the 1940s did not live to adulthood. Prognosis was so poor that identifying carriers was seen as vital for only one reason: carriers would "probably elect to remain childless."[1]

Our generation of women is clearing the path for our daughters, granddaughters, women and girls down the line, to be safe to be the woman or girl they are.

—Tabby Biddle
Find Your Voice: A Woman's Call to Action

1. C. Merskey and R. G. MacFarlane, "The Female Carrier of Haemophilia: A Clinical and Laboratory Study," *Lancet* 1 no. 6653 (1951): 487–90, http://www.ncbi.nlm.nih.gov/pubmed/14805104.

» page 7

welcome

I'll admit it: I'm guilty. I've referred to women who transmitted hemophilia to their children as carriers, and women who have bleeding issues or even just technically low factor levels as symptomatic carriers. Why? Because that's what the medical establishment has always called them. That's what our national organizations have called them. So that's what I have called them.

But there's a quiet revolution going on. Women are starting to speak out. They aren't just carriers, and they're not the only carriers of the hemophilia gene. If you examine the hemophilia transmission charts, you'll see that men and women both transmit the gene that is defective for hemophilia. Men transmit it to their daughters. If being a carrier means "carrying" the hemophilia gene, then men with hemophilia and women with an affected X chromosome are all carriers.

And women who have bleeding symptoms? They are no longer just symptomatic carriers. *They have hemophilia.* And they need factor and medical care, just like anyone diagnosed with hemophilia. There are many reasons this concept is catching fire now, and we explore them in this issue of PEN, dedicated to women with bleeding problems and carrier status, and yes—with hemophilia.

Women with improperly diagnosed bleeding disorders have been asking for help for a long time—perhaps even since biblical times, if you read Richard's Review. Now is the time to put the subject of "women as bleeders" on the table, to draft new policies, and to change our treatment protocol. It's time to reclassify how we view women with the hemophilia gene. Carriers? Old school. Bleeders? Maybe too casual. Women with hemophilia? That sounds about right. And this is the right time.

Laurie

inbox

"Living with Hemophilia and Depression"
PEN, Aug. 2016

Depression is a seriously important topic that doesn't get talked about enough in the hemophilia community. I've had severe bouts of depression and been through therapy. I think that one of the basic problems is that not many therapists or psychiatrists know anything about hemophilia and the related issues. I have had to start at the beginning and essentially "teach" the person I'm seeing at the time. And with all the other health issues, it is a lot to take in for someone not in the know. Depression is overwhelming and can just ruin a person's life.

Michael Elhardt
California

It's as nice to hear as it is sad to hear that we are not alone with this struggle. Bipolar and depression runs on both sides of my family and has impacted us in a big way. I was depressed as a child and even more as a young adult. While my friends were making plans to further their education, I was blindly trying to join the military, due to my drive and dedication to my personal health and our

» page 18

PARENT EMPOWERMENT NEWSLETTER | NOVEMBER 2016

Editor-in-Chief Laureen A. Kelley
Senior Editor Sara P. Evangelos • Science Editor Paul Clement
Assistant Editor Tara L. Kelley
Contributing Writer Richard J. Atwood
Layout Designer Tracy Brody
Publications Manager Jessica O'Donnell
Director, Project SHARE Zoraida Rosado

PEN is a newsletter for families and patients affected by bleeding disorders. PEN is published by LA Kelley Communications, Inc., a worldwide provider of groundbreaking educational resources for the bleeding disorder community since 1990.

PEN respects the privacy of all subscribers and registered patients and families with bleeding disorders. Personal information (PI), including but not limited to names, addresses, phone numbers, and email addresses, is kept confidential and secure by the LA Kelley Communications editorial staff in accordance with our privacy policies, which can be viewed in entirety on our website. PEN publishes information with written consent only. Full names are used unless otherwise specified.

PEN is funded by corporate grants or advertisements. Sponsors and advertisers have no rights to production, content, or distribution, and no access to files. The views of our guest writers are their own and do not necessarily reflect the views of LA Kelley Communications, Inc., or its sponsors.

PEN is in no way a substitute for medical care or personal insurance responsibility. Parents or patients who question a particular symptom or treatment should contact a qualified medical specialist. Parents or patients with personal insurance questions should contact their employer's human resource department, Medicaid or Medicare caseworker, payer representative, or HTC social worker.

Articles may be reprinted from PEN only with express written permission from the editor, and with proper citation. PEN and/or its articles may not be published, copied, placed on websites, or in any way distributed without express written permission.

LA KELLEY communications, inc.

37–39 West Main Street #8
Georgetown MA 01833 USA
978-352-7657 • fax: 978-352-6254
info@kelleycom.com

My Journey from Carrier to Hemophilia A

Shellye Horowitz

I am a symptomatic carrier of hemophilia A. My father was a symptomatic carrier of hemophilia A. My grandmother was a symptomatic carrier of hemophilia A. My great-grandfather was also a symptomatic carrier of hemophilia A. With my nephew's diagnosis nine years ago, hemophilia A can be traced through five generations.

Yet, on paper, my male relatives are not acknowledged for their carrier status. By labeling them as having hemophilia A, by not acknowledging their carrier status, our medical community is discriminating against men. Yes, men are indeed carriers of hemophilia, as much as women are. But it's women who are seen as carriers or as symptomatic carriers, and they are often not acknowledged as actually having hemophilia.

It is my strong belief that the term *symptomatic carrier is* archaic, discriminatory, and unnecessary, and stands as an enormous barrier between women with hemophilia and the care they need.

When I was five years old, in the 1970s, I was tested by a top HTC and received a carrier label. I started off as a carrier because women were not normally diagnosed with hemophilia. The belief at the time was that because women have two X chromosomes, although hemophilia is linked to one, the other would always compensate...except when it does not. Research has evolved and proven those ideas wrong.

My life as a carrier meant that I was picked last for every elementary and middle school sports team, my ankles were always swollen, and I hated anything that required me to run. My parents took me to doctors to see what was wrong, and they were told that I just imagined the ankle pain and swelling, that this was a ploy to get out of PE. No one thought to explore a connection with hemophilia.

My life as a carrier meant that when I was rear-ended by a one-ton truck at 55 mph, it would take over five years to heal from a traumatic brain injury, and from back and neck injuries. No one explored a connection with hemophilia.

My life as a carrier meant that I went through two gynecological surgeries, and had wounds from incision sites that continually reopened and would not heal. Still no one explored a connection with hemophilia.

My life as a carrier meant that when I needed to have multiple moles removed, the surgeons had to add extra stitches because the removal site kept bleeding, but hemophilia was not acknowledged or explored.

Throughout my life, every time I was injured, I healed slowly and no one ever offered a reason or acknowledged that this was not okay. I needed stitches so many times as an infant that my parents thought they would be turned in for child abuse, yet not once did it occur to any medical professional that the continual need for stitches could be linked to a bleeding disorder.

When I was in my mid-twenties, I finally had my factor VIII level checked—it was 35% (my numbers were never again as high as that initial test). At that time, I was told I might be a *symptomatic carrier* of hemophilia, a term new to me. I was told it was similar to having mild hemophilia. No treatment or treatment plans were offered.

I was then given a fantastic opportunity to work at an international school in Israel. This changed my healthcare trajectory, and I am so grateful for the help I got—in a foreign country. My second year in Israel, I had a spontaneous bleed. Over a few days, I watched a bruise spread from quarter-sized to over half my calf. So I asked for a referral to a local hematologist. Coincidentally, I was referred to Professor Seligsohn, MD, who happened to be head of the hemophilia treatment center (HTC) in Israel. He asked about my history and became very animated when he learned that hemophilia A ran in my family. He pulled out a sheet of paper and mapped all the people in my family with hemophilia. He ran my factor VIII level, and found it was 20% (it has remained at that level ever since).

When my factor VIII level came back, Dr. Seligsohn asked what my treatment plan had been in the States. Treatment plan? What on earth was he talking about? He explained to me that I had mild hemophilia A and that I needed a plan for day-to-day injuries and surgeries. I questioned the need: "I'm a symptomatic carrier, so I have an X chromosome that compensates for the one my father passed to me. Do I really need a treatment plan?" The doctor put a fist on his desk and said, "Shellye, your factor VIII is 20%. When we have a person

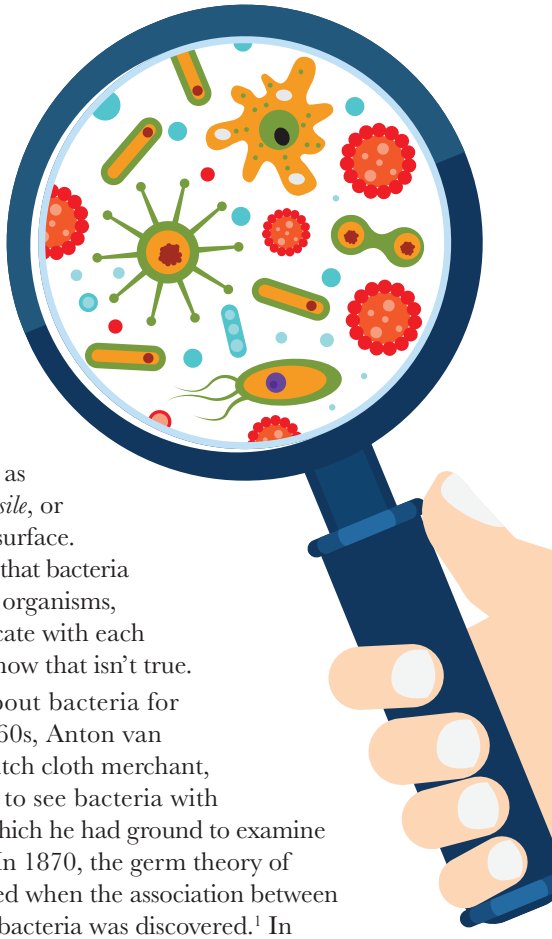
» page 11

Biofilms

or

Why can't we get rid of port infections?

Paul Clement



Bacteria! Does this single word cause a chain reaction of negative words—filthy, diseased, contagious? Or positive words—antibacterial, disinfectant, antiseptic? Few people think of bacteria as beneficial, yet we depend on bacteria. Without them, there would be almost no life on Earth, because bacteria are major players in decomposing organic matter and breaking down compounds into the basic elements necessary for life. Only some bacteria—less than 1%—cause disease. But implanted medical devices such as artificial joints, ports, and catheters are prone to bacterial infections. What can we do to help prevent these infections?

Bacteria are everywhere: inside clouds; in the boiling springs of Yellowstone National Park; even in the frigid depths of Antarctic lakes, under 2,500 feet of ice. They live on our skin and in our bodies. In fact, the bacteria we carry outnumber our own cells by 10 to 1. In other words, 90% of the cells in your body are not human! Our bodies are home to an estimated 100 trillion bacteria—that's a 1 followed by 15 zeros! Even when we're healthy, we disperse anywhere from 500,000 to more than 1 million bacteria a day by touching objects, breathing, or simply moving around. We have a cloud of bacteria around us.

Most of the bacteria we carry live in our gut, especially in the large intestine, where the body employs some as "subcontractors" to help digest food and perform other services. Without bacteria, babies cannot fully digest mother's milk. Bacteria help us digest plants. They also help us manufacture some enzymes and vitamins K and B, as well as other essential nutrients. They help train our immune system, and actively help keep disease-causing bacteria from gaining a foothold in our intestines. Bacteria are critically important to humans, but we're only just beginning to understand *how* important.

Biofilms: A new branch of microbiology is born

So what does all of this have to do with port and implant infections? First, our early assumptions about how bacteria live were wrong: we assumed that most bacteria lived as floating *planktonic* organisms, as opposed to being *sessile*, or living attached to a surface. Second, we assumed that bacteria were mostly solitary organisms, unable to communicate with each other, but we now know that isn't true.

We've known about bacteria for centuries: in the 1660s, Anton van Leeuwenhoek, a Dutch cloth merchant, was the first person to see bacteria with magnifying lenses, which he had ground to examine the weave of cloth. In 1870, the germ theory of disease was developed when the association between several diseases and bacteria was discovered.[1] In 1887, Julius Petri invented a simple pair of nesting glass dishes—now called Petri dishes—to help us study bacteria. When a gelling nutrient agent called *agar* was placed on a dish and covered, bacteria could be grown.

For more than a century, Petri dishes were considered the best way to grow bacteria to detect an infection, and they are still used today. First, a swab of the suspected material or a blood sample is rubbed on sterile agar in a Petri dish. Then the dish is incubated for a couple of days to allow bacterial colonies to grow. The colonies are then observed under a microscope and identified. But Petri dishes have a problem: they are only good at growing planktonic bacteria, so this skewed our perceptions of how bacteria live.

It wasn't until the late 1970s that we started to realize that perhaps most bacteria are not planktonic. When submerged rocks were observed, it was found they had thousands to tens of thousands more bacteria than the water surrounding them.

» page 12

1. The germ theory of disease holds that some diseases are caused by microorganisms such as bacteria. Previously, diseases were thought to be caused by "bad air."

richard's review

Linda Weaver's Studio

Richard J. Atwood

Being Whole: Women with Bleeding Disorders

Have you ever experienced one of those light-bulb moments? You know, when you look at something for a long time, and then inexplicably see it from a different perspective?

While researching references to women with bleeding disorders, I looked at the Bible, Matthew 9:20-21:

> *And, behold, a woman, which was diseased with an issue of blood twelve years, came behind him, and touched the hem of his garment; For she said within herself, If I may but touch his garment, I shall be whole.*

That was my light-bulb moment. Could this biblical passage be the earliest written record of a woman with a bleeding disorder? Maybe she had von Willebrand disease, or maybe even hemophilia?

The debate over whether women can have hemophilia is ongoing. In the first known article on bleeding disorders, printed in 1803 in the *Medical Repository*, America's first medical journal, Philadelphia physician John Conrad Otto stated that only males are affected with a "hemorrhagic disposition," while females are exempt but are still capable of transmitting the disposition to their male children. This is an early observation of what we now know to be the "sex-linked recessive" inheritance pattern of hemophilia—in which we believed only males, having only one copy of the X chromosome, show symptoms of the disorder.

Otto's article on "bleeders" prompted the publishing of additional cases of bleeding disorders worldwide. The opinion that only men suffered from a hemorrhagic tendency was substantiated by nine other American journal articles, plus additional European articles. Then, in 1841, Thomas Smethurst, an English surgeon, reported that women could also have bleeding disorders, and described two female cases subject to hemorrhagic tendency. After this article was published, more cases of women with bleeding disorders were reported.

A characteristic of some medical journal articles, textbooks, and monographs on bleeding disorders in the 1800s is that newly reported cases were added to the number of

» page 15

2007 Shannon Wirrenga, "Reach of Faith," shannonsartroom.com

We're More Than Carriers

Laurie Kelley

Not even 10 years ago, you might have been told that women could get hemophilia, but that it was very rare. And that probably, only about 10 women with hemophilia[1] existed in the US. Today, those statements are totally wrong. Why?

Why is the relatively small number of women as "bleeders" about to shift into the thousands and upend all our statistics? Because the belief that only males get hemophilia is no longer valid. Hemophilia has been described as mostly affecting males because the gene for hemophilia was found on the X chromosome. You probably know how it goes: men have only one X chromosome and can inherit the disorder from a mother who also has an affected X chromosome; women "carry" the disorder and pass it to their offspring. So traditionally, a woman who was dubbed a carrier might have low levels of factor, and if she showed some abnormal bleeding, she was delicately called a "symptomatic carrier." But she was most definitely not called a person with hemophilia. Not until now.

Where does that leave YOU, a symptomatic carrier—a woman with an affected X chromosome, who has low factor levels and who bleeds? You're pretty much a woman without a treatment plan, and that can be dangerous. Today, women with low factor levels who carry the hemophilia gene are calling themselves "women with hemophilia." And they're also calling for big changes: in our community's beliefs, and in how women are treated by hemophilia treatment centers (HTCs).

Silent Suffering

So many women who are labeled symptomatic carriers have suffered deeply, lacking a proper hemophilia diagnosis and appropriate treatment. "Do I consider myself a woman with a bleeding disorder?" asks Rita Epstein, mother of an adult with hemophilia. "You bet I do! During various surgical procedures over the years, I had major bleeding problems that actually caused doctors to stop the surgery. Once I was identified and pretreated as well as post-treated as a person with hemophilia, the surgical field was clear [of blood] and my procedures were easily handled."

Mary Boudreaux notes, "I've had more [bleeding] issues than my brother who has hemophilia! I've never been diagnosed with hemophilia—only as a carrier—and most doctors I see don't even want to hear about hemophilia because they say only males have that."

"I look back and think how different some of my experiences could have been, had I known I had a bleeding disorder," reflects Stormy Woods Johnson. "I could have avoided 45-day periods, a blood transfusion, and possibly four miscarriages. My ankle has given me trouble for over 15 years. It stayed swollen and painful for over three years before I finally found out I had tears in the tendon and large amounts of blood in it."

With a correct hemophilia diagnosis, so much suffering could have been avoided. But through the years, most of the US medical community grew comfortable assigning the label "symptomatic carrier" to women with signs and symptoms of bleeds who had children with hemophilia. The focus was almost always on the boys with hemophilia.

Treatment Jeopardized

Being labeled only a carrier can result in a more casual medical approach to treatment, whether for surgery, childbirth, menses, or just regular activities. Melissa Howell admits that most doctors say to her, "Oh, you're a carrier, so we don't need to do anything else."

By using the carrier label, physicians may even encourage women with bleeding issues to ignore their instinct that something is wrong. Brandi Worthington recalls, "I always thought I had anemia, and didn't know what was wrong because I bruised easily and had very heavy periods twice a month. When I got into a car accident while pregnant with my first child, I had unbearable pain. My doctor said it was just normal pregnancy pain."

Brandi ended up with internal bleeding and a huge blood clot that became infected. Her nephew had hemophilia, but no one realized she might be a carrier or have low factor levels. Five years after the accident and one month before the birth of her third child, who was diagnosed with hemophilia, Brandi tested positive as a carrier with mild hemophilia. "It was my nephew's nurse," she explains, "who said I should get my levels retested since I was pregnant again."

» page 14

1. Only women with severe hemophilia were considered to have hemophilia.

Of course, times have changed. Testing the blood of carriers is now seen as vital for a second reason: to meet the healthcare needs of carriers who may have reduced clotting ability themselves. In the age of recombinant factor and prophylaxis, severe hemophilia in the US is more manageable than ever. It is perhaps only against this modern backdrop that the priorities of both the medical field and the hemophilia community have expanded to allow greater attention to be given to less severe cases. We understand today that as many as one-half of hemophilia carriers may have a mild form of the disorder, yet most are not diagnosed as having hemophilia. In 2010, National Hemophilia Foundation's Medical and Scientific Advisory Council (NHF's MASAC) issued Recommendation 197 concerning girls and women with inherited bleeding disorders. This includes the recommendation that all females with a family history of bleeding disorders have their factor levels tested, and that females with factor levels lower than 50%—those with mild hemophilia—be given factor under certain circumstances, such as bleeding episodes.[2]

Why Are Some Women "Bleeders"?

The scenario just outlined describes women who are often called "symptomatic carriers," and who typically meet two separate criteria. First, these women show abnormal bleeding symptoms, frequently supported by lab results showing factor VIII or IX levels less than 50%. Second, they are known as carriers because one of the two copies of their factor-producing gene has a mutation, while the other is normal. This genetic carrier status is often determined by a family pedigree. So, why are some carriers symptomatic while others are not?

The most common explanation is *skewed X-inactivation* (see "Devil in the Details," page 8). Briefly, females have two X chromosomes (XX) and males have just one (XY), yet only one X chromosome can be active in a cell. Nature has a way of leveling the playing field by shutting off one of the two X chromosomes in each cell of a female's body. The process of X-inactivation ensures expression of just one copy of many genes on the X chromosome in females—which occurs by default in males, who have only one X. The decision of which X to shut off in each cell is usually *random*, so in some cases, female carriers by chance will end up with more cells expressing the X chromosome containing the factor VIII or factor IX mutation rather than their normal copy (a skewed ratio from the expected 50/50). They may have mild hemophilia as a result. Infrequently, X-inactivation is *non-random*, resulting in a much more extreme skewing, and potentially very low factor levels or severe hemophilia.

In other rare cases, a woman may also have a mutation on *both* of her X chromosomes, for example if her mother is a carrier for hemophilia A or B and her father has the same disorder. In this instance, the daughter could have hemophilia with a range of possible degrees of severity, like that seen in males.

There are several other causes of abnormal bleeding in women. Most women with bleeding issues have von Willebrand

2. https://www.hemophilia.org/sites/default/files/document/files/masac185.pdf.

disease (VWD), the most common bleeding disorder in both men and women, affecting 1% to 2% of the population. VWD is caused by a mutation in the gene responsible for the production of von Willebrand factor (VWF). Unlike factors VIII and IX, the gene for VWF is located on chromosome 12 and is inherited identically in males and females, so the disorder occurs equally in men and women and can be passed on from either (or both) parents. There are several different types of VWD, and they can vary in severity.

Several other factor deficiency or platelet disorders also affect both sexes, including factor VII deficiency and factor XI deficiency (hemophilia C). These bleeding disorders are generally inherited recessively, meaning that the mutated copy of the gene must be passed on by both parents, which is exceedingly rare. However, shared ancestry can increase the incidence of rare recessive genetic diseases in certain ethnic groups.

Identifying and Treating Bleeding Symptoms in Women

Many of the symptoms that women with bleeding disorders experience are similar to those of men with hemophilia. These may range from milder symptoms, such as prolonged bleeding

Devil in the Details: X Chromosome Inactivation

Human cells have 23 pairs of chromosomes, each pair containing a set of genes from the mother and a matching set from the father. *Gene expression* is the process by which a cell follows the instructions of the gene, like an architect reading a blueprint, to build a trait exactly as specified. The majority of human genes are located on chromosomes 1–22 (called *autosomes*), and both copies of each gene on these chromosomes are typically "expressed" simultaneously in the child, to produce traits that are often a blend of both parents'. In contrast, the 23rd pair of chromosomes is known as the *sex chromosomes*. Unlike genes on the autosomes, many of the genes on sex chromosomes require only one of the two copies to be expressed in each cell to produce the desired trait. A second key difference from autosomes is that the pair of sex chromosomes is not the same between males and females: although both sexes receive one X chromosome from the mother, females (XX) receive a second X chromosome from the father, while males (XY) receive a Y chromosome from the father. The Y chromosome is largely involved in development of male-specific traits, so only males need it. On the other hand, the X chromosome contains genes that are important for both sexes in equal measure, such as the factor VIII and IX genes containing the code for making clotting factors! In order to keep females from having double the desired amount of expression of the genes on the X chromosome, and to bring their expression level down to that of males, female cells undergo what's called *X-inactivation*—the turning off of genes on one of each cell's two X chromosomes.

Here's how x-inactivation works: When a female is still just a newly formed embryo made of a small number of cells, one of the two X chromosomes in each of her cells is randomly selected to be tightly bundled up, so that most of its genes will remain forever inactive. As the embryo grows, and each of those early embryonic cells is replicated, the same X chromosome will be inactivated in *all* the cells that come from each original embryonic cell. On average, about half of the cells in every female will have an active X chromosome from one parent, while the other half of the cells will have an active X chromosome from the other parent. So typically about half of the factor-producing cells of a hemophilia carrier will have an active X chromosome containing a factor VIII or factor IX mutation, and the other half will have an active X chromosome that is normal. Because most people make more factor VIII or IX than they need for clotting, having around half of cells with a functional factor VIII or factor IX gene is usually plenty for a carrier to produce factor levels within the normal range (50%–150%). But they will tend to be on the lower end of that range.

However, because the embryonic X-inactivation process is usually random, a small proportion of female carriers—just by chance—will end up with significantly more than half of the cells in factor-producing tissues expressing the X chromosome containing the mutated copy of the factor gene, leaving the intact copy inactive; these women may have mild hemophilia. Other carriers may by chance have the ratio skewed in the opposite direction, with more cells expressing the X chromosome with the intact copy of the factor gene, resulting in factor levels more comfortably within the normal range. Even more rarely, the X-inactivation process is non-random: in some cases, other mutations on X chromosomes can result in selection of just one particular X chromosome to be inactivated in embryonic cells, or in the survival and replication of only those embryonic cells in which one particular X chromosome was inactivated. In these cases, the skewing would be more extreme. If the X chromosome with the factor VIII or factor IX mutation ended up being expressed in most or all cells in pertinent tissues, this could mean severe hemophilia for the woman who is genetically a carrier.

following dental procedures or bruising, to more serious bleeds, including joint bleeding and intracranial hemorrhage.

Significantly, women with bleeding disorders experience some symptoms that are distinct from those experienced by men: prolonged or heavy bleeding during menstruation (*menorrhagia*), and bleeding complications related to pregnancy and childbirth. The stigma that most cultures place on discussing menstrual bleeding can present a particular challenge to identifying women with bleeding disorders, especially those with mild symptoms or who lack a family history. It's common for a woman to be unsure if the amount of bleeding she experiences is—or is not—normal, and the problem may be missed if she doesn't bring it up with her physician. On the other hand, some bleeding disorders, such as VWD, may actually be more often diagnosed in women than in men, even if they occur at a similar rate. This can be attributed to the challenges of excessive menstrual bleeding in affected females once they reach puberty, compared to affected males, who may not be diagnosed unless they have a serious injury or surgery. Increasingly, new resources, such as the website betteryouknow.org and the Victory for Women initiative developed by NHF, are available to help both men and women assess whether they are symptomatic and open dialogues with their physicians.

Diagnosis and treatment of bleeding symptoms in women should be comparable to what men receive when reporting similar symptoms or factor levels. Yet some women with bleeding disorders have been challenged when sharing their concerns with physicians and seeking treatment. This may be due in part to the rare incidence of many bleeding disorders. In the case of potential carriers of hemophilia A and B, there may be an additional hurdle: the common misconception among primary care providers that such X-linked recessive bleeding disorders affect only males. Additionally, because some physicians are more familiar with autosomal recessive disorders in which carriers usually do not have symptoms, they may wrongly assume that a female carrier of an X-linked recessive disorder must also be asymptomatic. Even experts at some hemophilia treatment centers (HTCs) may have work to do: some carriers of hemophilia A and B have reported being told by HTC personnel that they were hypersensitive to the possibility of bleeding symptoms because of their family history, or that "only males can be affected"…only to be later diagnosed.

Identifying carriers with low factor levels as *having hemophilia* is key to countering this persistent misconception.

Through NHF's program My Life, Our Future, potential carriers can now be genotyped (a process of identifying the specific gene mutation causing a person's bleeding disorder) for free or at low cost through one of the participating HTCs to find out whether they carry the gene for hemophilia. In fact, most HTCs are willing to test women and girls who want to know their carrier status, or find out whether they have a low factor level. The National Hemophilia Program Coordinating Center (NHPCC), funded through the American Thrombosis and Hemostasis Network (ATHN) by the Health Resources and Services Administration (HRSA), has also funded a project of national significance at Children's Hospital of Philadelphia to develop a "Genetic Education Toolkit for Female Relatives at Risk of Carrier Status" to support education on this issue. What's more, groups such as the Foundation for Women and Girls with Bleeding Disorders focus on advocacy for women

with all types of bleeding disorders by educating their healthcare providers. Similarly, Healthy People 2020, a 10-year agenda launched in 2010 to improve the nation's health, is helping to raise providers' awareness of the importance of diagnosing bleeding disorders in women. The group is tracking progress in identifying women with VWD and getting them into treatment by age 21, listing this among the indicators of quality healthcare in the US.

Stand Up and Be Counted!

How can we measure the success of these initiatives to ensure that women and girls with bleeding disorders are diagnosed and treated? In short—data! Diane Aschman, president and CEO of ATHN, and Barbara Konkle, MD, of Bloodworks Northwest and the University of Washington, point to several projects that ATHN is involved in to collect data about women who are carriers of hemophilia—those who have abnormal factor levels (less than 50%) as well as those whose factor levels fall within the normal range. For example, if a woman is confirmed as a carrier of hemophilia A or B through the My Life, Our Future project, HTCs will document her factor activity levels, and may also document her standardized bleed score, a survey used by physicians to help diagnose the type and severity of a bleeding disorder.[3] This project builds on the primary ATHN dataset, in which HTCs can enroll women with bleeding disorders, as well as carriers, to record baseline factor level and other demographic and clinical information. In addition, Community Counts is a Centers for Disease Control and Prevention Public Health Surveillance for Bleeding Disorders project. HTCs submit (through ATHN) an HTC Population Profile, which counts all patients with specified bleeding and

3. F. Rodeghiero, et al., "ISTH/SSC Bleeding Assessment Tool: A Standardized Questionnaire and a Proposal for a New Bleeding Score for Inherited Bleeding Disorders," *Journal of Thrombosis and Haemostasis* 8 (2010): 2063–65 (plus supplementary material), http://www.ncbi.nlm.nih.gov/pubmed/20626619.

Donna's Story

Although she knew from a young age that her biological father had died when she was a baby, Donna B. of Grand Rapids, Michigan, didn't find out until she was a teenager that he had died from complications related to hemophilia. Now 61, Donna recalls feeling shocked when she began learning about genetics in high school, and when her mother revealed that Donna and her sister carried this disorder. "We probably had questions," says Donna, "but nobody really talked much about our biological father back then." There were limited remaining ties to his side of the family, and no other affected relatives. Donna's mother's second husband adopted the girls soon after their biological father's death. Donna recalls that her mother didn't want to talk about hemophilia, except to say that "only boys get it, and [my sister and I] needed to know for when we had children of our own." Meanwhile, Donna had tremendous difficulty controlling her menstrual flow during puberty, but never made the connection to hemophilia…and, well, her mother didn't really want to talk about that topic, either.

When she eventually married, Donna and her husband simply hoped for girls—and "our prayers were answered." They had a daughter in 1982 and another in 1983. Despite Donna losing consciousness and requiring medical attention following a dangerous hemorrhage after the birth of her second child, she never even considered this could be related to her carrier status, nor did any doctors. "We forgot about it quickly as we focused on the gratitude we felt that our daughters would not be affected by hemophilia." Similarly, Donna didn't think about her carrier status when she bled excessively after wisdom teeth extractions—nor when she struggled again with menorrhagia as menopause approached, missing work and often feeling that she couldn't leave the bathroom. "It wasn't until my two grandsons were diagnosed with severe hemophilia B that it became something I would spend much more time thinking about." When Donna's daughter received a questionnaire from the HTC that cared for Donna's grandsons, about potential bleeding symptoms in carriers, she immediately thought of her mother and encouraged Donna to get tested.

Donna recently contacted her ob/gyn and asked to have her factor IX level tested. Her level came back at 54%. Although this is technically within the normal range, Donna explains that both she and her physician found the result enlightening. He offered to refer her to a hematologist, but she declined—for now. "If I had known years ago what I know now, I might have had cause to pursue treatment and could have been spared some difficulties." Yet, Donna also points out that in a sense, she was lucky: "Had I been treated for hemophilia at the time that my daughters were born, I might have received contaminated blood products."

Donna feels content to be classified as "just a carrier," but she's also grateful to have learned that her levels are considered borderline for mild hemophilia. "If I end up needing some kind of surgery down the road, I think I might ask to bring a hematologist onboard or have my level tested again. Certainly I'm glad to have learned that carriers can also have symptoms, and will consider sharing the results with my grandson's HTC."

clotting disorders, including women whose levels fall either within or outside the normal range. These numbers will be tracked over time.

Each of these data projects will shed light on the number of women with bleeding disorders, differentiating the number of women and girls from males with each disorder and categorizing each individual based on severity. Once published, the data on the number and severity of these disorders in women will provide evidence of need, often the first step in designing appropriate strategies to prevent complications. Such data will also help inform providers, payers, and patients about bleeding disorders in women.

Could This Apply to Me?

Whether you are a known carrier, a woman with a family history of bleeding disorders, or a woman who has experienced unusual bleeding—your first step is to have your symptoms assessed. You can contact your local HTC, but you may prefer to start with a self-assessment (betteryouknow.org) or reach out to your primary care physician. Either way, keep records of your symptoms. Don't hesitate to ask to have your factor levels tested, even if you encounter some skepticism. Keep in mind that it may take more than one discussion or appointment to be properly diagnosed. It's also important to remember that factor VIII in particular can be elevated during times of stress or pregnancy, so multiple blood draws at different times may be necessary to establish an accurate baseline.

Once your results are in, ask a hematologist to put a treatment plan in place based on your lab results, symptoms, and lifestyle. Remember—just as with hemophilia in males, bleeding tendency in females doesn't always perfectly correlate

with factor level, and members of the same family may have different bleeding patterns. You may want to encourage other women in your extended family to consider being assessed. Carefully consider enrolling in an ATHN study, where your data may contribute to a broader understanding of bleeding disorders in women. Above all, be your own advocate!

Christy Bergeon Burns lives in Bloomington, Indiana, with her husband Steve and their two sons, Charlie (5) and Kenny (2), who both have severe hemophilia B. Christy holds a BS in biopsychology from the University of Michigan and a PhD in biology from Indiana University, where she is currently director of a core animal behavior research laboratory. She plans to one day become a genetic counselor.

As I See It... from page 3

with severe hemophilia A who is hurt or needs surgery, we make sure his factor VIII is brought up to between 50% and 100%, depending on what the procedure is. If we are bringing a person with severe hemophilia up to at least 50% factor VIII, why would it be okay to leave you at 20%?"

A light bulb went off. For years I had been labeled a carrier, then a symptomatic carrier, and both of these terms had prevented my healthcare providers and me from making sure that I had the medical plan necessary to properly address bleeding issues. Even though I was a woman, *I needed factor VIII too!* I had a bleeding disorder as much as any man did.

My eyes were open. It took a move to Israel to understand how the US uses discriminatory labels that undermine women's ability to get proper hemophilia treatment and care. The discrimination was not orchestrated; it was an evolution of knowledge about what hemophilia is and how it is inherited. As our understanding evolved, the term assigned to women with hemophilia changed from carrier to symptomatic carrier—when it should have changed to mild hemophilia A.

Because I met Dr. Seligsohn and got the correct label of mild hemophilia A, I am now connected with an HTC. I have had mole and wisdom teeth removals safely with factor VIII concentrates. After these procedures I healed in days, not months. I even formed scabs!—something I'd never done in the past. I continue to unlearn the years of accepting incorrect understandings of women with hemophilia.

I have also learned that I must remain a vigilant self-advocate. Just last week I met a new local hematologist. She was very sweet, but did not understand why a woman with 20% factor VIII levels would need to use "expensive meds" because 20% should be enough for me to heal. She was taught that idea in medical school many, many years ago. Too many doctors are walking around with this misinformation. Even websites of some hemophilia organizations still refer to women as symptomatic carriers, which creates barriers to obtaining proper treatment.

It's critical that women receive accurate diagnostic labels that rid the medical establishment of false assumptions about women and hemophilia. Lives depend on it.

Shellye Horowitz has an MA in school counseling from Humboldt State University and a certificate in educational administration from Gonzaga University. She is a middle school principal in Eureka, California, and lives among the redwood trees of Northern California with her two teenaged daughters.

Inhibitor Insights... from page 4

And in the early 1980s, films of bacteria were first observed on implanted medical devices. But the significance of these observations wouldn't be known for almost a decade because of technological limitations: there was no easy way to observe and study the bacterial films. That is, not until the early 1990s, when a new type of microscope allowed scientists to observe wet surfaces in three dimensions.[2]

What the scientists found turned microbiology upside down! Instead of most bacteria living as free-floating planktonic forms, as we had thought, 99.9% of bacteria are sessile, living attached to a surface. And instead of bacteria being solitary organisms, bacteria are colonial and can communicate with each other. A new branch of microbiology was born: the study of biofilms.

Biofilms: Key to bacterial survival

Biofilms are elaborate colonies of bacteria. Sometimes they consist of a single species, and sometimes of several different bacteria species. The bacteria adhere (stick) to a surface and secrete a slimy glue-like layer, or *matrix*, around themselves. We're all familiar with biofilms: you can feel them forming on your teeth several hours after brushing; they are the slime in pipes, the soap scum on shower curtains. Biofilms can be found on almost any moist surface.

Biofilms start when planktonic bacteria attach to a surface and begin reproducing. Surprisingly, bacteria are not solitary little creatures, and they are not isolated: they communicate with each other chemically. Bacteria can sense how many of their companions are nearby through a poorly understood chemical signaling process called *quorum sensing*. Here's how it seems to work: Once a sufficient number of bacteria—a "quorum"—is reached, the bacteria release chemical signals that alert the group to change their behaviors. Instead of acting like solitary planktonic organisms, they now behave like sessile communal organisms. Then they work together to form a biofilm.

Biofilms increase the bacteria's odds of survival, especially if they are disease-causing pathogenic bacteria trying to evade a host's—a human's—immune system. The slimy matrix makes it hard for the immune system to identify and attack the bacteria. The matrix also helps protect the bacteria from antibiotics; compared to their planktonic relatives, biofilms are up to 1,000 times more resistant to antibiotics! To make matters worse, antibiotic treatment—especially a low-dose short treatment, or one that the patient doesn't complete—may allow some cells to develop resistance to the antibiotic and survive. The survivors can then transfer this antibiotic resistance to their offspring as they grow a new biofilm, which now consists of bacteria resistant to one or more antibiotics. The protection against antibiotics offered by the biofilm matrix, plus the ability to rapidly develop antibiotic resistance, makes biofilm infections very hard to destroy.

We have learned that almost all human infectious diseases are caused by biofilms.

Biofilms: Immune system evaders

The human body's immune system is skilled at preventing the formation of most pathogenic biofilms. But if you're immune compromised, on chemotherapy, or taking anti-rejection drugs; or if you have poor blood flow (as in diabetes), have a medical implant, or are in generally poor health, then your immune system may not be up to par. Biofilm bacteria can then gain a toehold, resulting in a chronic infection.

Medical implants that concern people with bleeding disorders usually include ports and artificial joints. Implants give bacteria an artificial surface to colonize—the immune system is not as effective in preventing bacteria from colonizing foreign bodies as compared to the body's own tissues. Three biofilm-forming bacteria, which normally live harmlessly on your skin and nasal passages, are responsible for most implanted medical device infections: (1) *Staphylococcus aureus*, the most common biofilm bacteria, which may cause almost half of infections; (2) *Staphylococcus epidermis*; and (3) *Pseudomonas aeruginosa*. These three make up about 75% of all the biofilms found on implanted medical devices.[3]

Port infections in children with hemophilia are not uncommon: about one-third will experience a port infection, and possibly up to two-thirds of those with hemophilia and inhibitors will develop one.

Joint replacements have a much lower infection rate as compared to ports, but people with hemophilia have a higher risk of infection than the general population: the infection rate of knee replacements due to osteoarthritis is about 1%, but for people with hemophilia, the rate is between 6% and 7%.

2. Images from standard light microscopes are essentially two-dimensional, like a photograph, and do not show biofilm structures. A new type of microscope, called a confocal laser scanning microscope, shows the three-dimensional structure of biofilms by assembling many 2D images to make a 3D image, similar to how a CAT scan takes many 2D images and assembles them to make a 3D image. 3. S. J. McConoughey, R. Howlin, J. F. Granger, et al., "Biofilms in Periprosthetic Orthopedic Infections," *Future Microbiology* 9 no. 8 (2014): 988–1007.

Infections of implants can be serious. Port infections can cause a bloodstream infection called *bacteremia*, resulting in an immune response called *sepsis*, which can be fatal. Infections of joint implants result in inflammation, pain, bone loss, and loosening of the implant. Because implant infections are usually caused by biofilms, they are hard to eradicate. Clearing the infection often requires removal of the port or implant.

What's being done to reduce implant or port infections?

Researchers are looking at the materials used for implants to lower the ability of bacteria to stick to their surfaces. For example, stainless steel is more prone to biofilm infections than titanium. Various coatings on the implants may also discourage bacterial adhesion. To reduce implant infections for artificial joints, researchers are considering different types of cement, and additives to the cement such as antibiotics. And a prototype "smart venous access port" is now being perfected: it uses biosensors and a radio signal to send an alert when the interior of the port develops a biofilm.

Researchers are also exploring ways to attack biofilms directly. They have identified some of the chemical signals used by bacteria in quorum sensing, and have developed specific molecules that can be used to target the chemical signal generator, the signal itself, or the signal receptor to prevent formation of the biofilm. This leaves the bacteria in a planktonic state, making them susceptible to antibiotic therapy. Researchers have also designed compounds such as Dispersin B, which break down the slimy matrix of the biofilm, allowing antibiotics to be effective. Use of biofilm-disrupting drugs may become standard treatment for implant infections in the future.

What can you do to help prevent implant or port infections?

A lot!

- Postpone port surgery if your child is ill or has an infection; illness increases the risk of a port infection.
- After port surgery, maintain high factor levels for at least a week to ensure that the implant site does not bleed. Bleeds around the port or implant increase the infection risk.
- Use antibiotic therapy before port surgery and lasting until the site has healed.
- If the infusion site is bruised (indicating blood around the port), do not use the port.
- Transdermal anesthetic creams, such as EMLA, can trap bacteria over the infusion site, where they can be forced through the skin into the port during the infusion. Don't just wipe the cream away before infusing; thoroughly clean the infusion site with an antiseptic, place the cream, and then scrub the area with soap and water to remove the cream before performing your final antiseptic routine.[4]
- Maintain good oral hygiene, and take your child to the dentist regularly for good oral health. Gum disease gives bacteria access to the blood, increasing the risk of a port infection.
- National Hemophilia Foundation's Medical and Scientific Advisory Council (NHF's MASAC) advises the use of antibiotic prophylaxis for invasive procedures, including dental work, to help prevent port infections.[5]
- Maintain aseptic technique when accessing the port: aseptic handwashing with liquid antibacterial soap and a hand brush; sterile gloves and face masks for both patient and caregiver; and strictly following correct skin preparation protocol as instructed by your HTC team.[6]
- Don't assume that all medical personnel know how to properly access a port! Speak up if someone isn't following protocol.

Ports are a lifesaver for many parents of young children, especially when they have an inhibitor. Ports make infusions easier while eliminating the stress of finding a vein. Even so, ports are not without side effects—mainly port infections and blood clots. But with proper care and attention to aseptic technique, you can reduce the risk of a biofilm infection, possibly allowing your child's port to last for several years!

4. Riten Kumar, Rajiv K. Pruthi, and Vilmarie Rodriguez, "Central Venous Access Devices (CVAD) for Pediatric Patients with Hemophilia: A Review," *Journal of Coagulation Disorders*, Sept. 17, 2009: 85–91, www.researchgate.net/publication/43529484 (accessed Aug. 22, 2016). 5. MASAC Recommendation 115 Regarding Central Venous Access Devices Including Ports and Passports: June 9, 2001. 6. "Practice Guidelines for Central Venous Access: A Report by the American Society of Anesthesiologists Task Force on Central Venous Access," *Anesthesiology* 116 (2012): 539–73, http://anesthesiology.pubs.asahq.org/article.aspx?articleid=2443415 (accessed Sept. 6, 2016).

YOU... from page 6

Audrey La Bolle shares, "When I was tested, I had less factor VIII than my son with hemophilia, but I was told by the hematologist at the HTC that a diagnosis of hemophilia could only be applied to males. I was 'just' a symptomatic carrier, even though I almost bled to death several times after surgeries and giving birth."

"I am a woman. I am a hemophilia carrier. I have bleeding issues," writes Michelle Thompson in her blog.[2] "They are not severe, usually, but I still have them. When I go to the dentist, when I strenuously exercise, when I bump something pretty hard, and when I clumsily fall. The bruises and bleeds come and I can feel them. But that isn't good enough for my HTC. I guess they want me to look like [I have severe hemophilia], swelling like a balloon to acknowledge that I am a woman and I bleed too. But my son is moderate/mild…When he has a bleed we treat it."

Sometimes it's difficult for the HTC to accurately diagnose; stress and hormones can affect factor levels. "You know what frustrates me the most?" seethes Tela Kirk-Aguilar. "It's when you are a 'symptomatic carrier,' and get tested to see if you might have hemophilia, but your levels are too high! The HTC thinks you're fine, but you get bruising and heavy periods; or you throw your knee out while your eight-year-old tells you, 'It sounds like a bleed, Mommy.' You can't do anything about it because you can't get factor!"

Even When You Are Diagnosed

It's an uphill battle to get correctly diagnosed and treated, because it's hard to change widespread beliefs in the medical community. Even women who *are* diagnosed sometimes aren't believed by the general medical community, or by payers.

Stormy was diagnosed with hemophilia just 18 months ago. Though she received the correct diagnosis, "I still feel I am treated differently than a male with hemophilia."

Mary Haugen insists, "The diagnosis of being a female with hemophilia is essential to our treatment. It opens doors for our insurance to cover treatment, better treatment by medical professionals, and a better life."

Genny Moore, mother of a child with hemophilia, says, "The HTC should understand the importance of properly identifying hemophilia. If the factor levels show mild, moderate, or severe range, it is important that we are identified as indeed *having* a bleeding disorder in order to ensure proper treatment especially in an accident or surgery."

But Stormy warns, "It will take time for the HTCs to really embrace the fact that we have hemophilia. I think some have accepted it openly, some have accepted it with caution, and some will never truly accept it. It will take a bit of time for them to treat us by symptoms and not gender or numbers."

Appropriate treatment can change women's lives. "The two weeks of factor replacement after my last delivery made my recovery amazing," recalls Michelle. "I'm not only talking about the amount of bleeding (that was so much less too!) but also the time it took to heal from the episiotomy and to just heal in general. Wow. If I'd known before that it could be like that, maybe we wouldn't have waited 10 years before having our last child."

Women with Hemophilia–Unite!

Mentioning the subject of women having hemophilia—or "women as bleeders," as Facebook friends often call themselves—creates a flood of opinions, from men and women. Women are frustrated. Men are supportive.

"Hemophilia symptomatic carriers—are you out there?" posts Michelle. "Let's start talking among ourselves and compare stories. If research studies could be done, then there would be information out there for the doctors to finally realize that their textbook answers will not cut it when it comes to women [with hemophilia]."

What are next steps? What can you do?

1. Get your factor levels correctly diagnosed at your HTC, and discuss your bleeding history.[3] Don't do this at your son's annual clinic visit, where the focus is on him. Make your own appointment. Remember, this is about YOU.
2. If your levels are 50% or lower, ask to be diagnosed as a person with hemophilia, not as a carrier or symptomatic carrier. Even women with factor levels of 60% can have bleeding problems.
3. Develop a treatment plan before dental procedures, childbirth, injuries, and surgeries. You might need a prescription for factor.
4. Invest in medical identification jewelry, just as you did for your child with hemophilia.
5. Get support from the community. Start with your local hemophilia organization—what are its opinions and policies about women being diagnosed with hemophilia? Make this a topic at your annual meeting.

We must also advocate for widespread changes in how we think about carriers and hemophilia. A carrier should never automatically be thought of as someone who has the gene for hemophilia but does not have the disorder. Women who are carriers and have low factor levels often have bleeding issues: bruising, bleeding into joints and muscles, and menstrual periods with abnormally heavy or prolonged bleeding. The moment a woman is diagnosed as a carrier, HTCs need to start investigating a hemophilia diagnosis and have a treatment plan in place.

Women who are defined as symptomatic carriers want the label removed permanently. They want to be known simply as "women with hemophilia" if their levels are lower than 50% and if they experience abnormal bleeding. If this change happens, women will have their own personalized treatment plans and access to factor concentrate.

This is what personalized healthcare is all about: identifying your unique medical and treatment needs, and addressing them, without limiting labels. If you're classified as a symptomatic carrier and believe you're not getting the personalized healthcare you need, call your HTC today and get the ball rolling.

2. Michelle Thompson, "Hemophilia Symptomatic Carriers…Are You Out There?" chellebellebooks.blogspot.com, Feb. 29, 2012 (Accessed Sept. 1, 2016). 3. Labs at HTCs have more expertise in accurately measuring factor levels. Also, several tests should be performed at different visits because factor VIII levels can vary widely in response to stress and hormones. For example, stress causes an increase in factor VIII levels.

Richard's Review... from page 5

existing cases in running tallies, so that an international prevalence (number of people living with a disease) was continually being updated. In Germany in 1851, Lange reported on 260 cases of "hemophilia," including 31 females. (The term *hemophilia*, or *haemophilia*, was coined in 1823, and at that time referred to any bleeding tendency.) Also in Germany in 1872, Grandidier reported on 631 cases of hemophilia, including 48 females. Then in 1883, Thomas Dunn from Pennsylvania reported on 780 cases of hemophilia, including 63 females. These summaries reflect the total medical literature of known cases of hemophilia in the 1800s. Yet many members of the medical community still questioned the validity of a medical diagnosis for hemophilia in women.

The first description of a female with a bleeding disorder, later to be identified as true female hemophilia, was in a medical journal article written in 1886 by Sir Frederick Treves, a London surgeon. Florence Parker, a six-year-old girl from a well-known "bleeder" family originating in Essex, presented with obstinate bleeding after a molar extraction. Her family included 11 male "bleeders." The extended family underwent numerous diagnostic investigations by medical experts as the number of identified cases grew to 22 family members, including 5 females. Although Florence died at age 21, shortly after the birth of her first child, her bleeding disorder was diagnosed as hemophilia A based on blood tests of one of her sisters and a nephew. Peter Kernoff and Charles Rizza of England reported this diagnosis in a 1973 medical journal article.

I believe the medical community took a stronger stance against the possibility of female hemophilia once British physicians William Bulloch and Paul Fildes published their extensive worldwide study of the entire Western medical literature on hemophilia in 1911. Bulloch and Fildes stated that the occurrence of hemophilia in women was unsupported by firm evidence. Their study put a damper on tallying women with bleeding disorders because the authors' professional stature was too great to be disputed. And their position that only men could have hemophilia fit in neatly with the simple concepts of inheritance popular in the 1910s—that only men could have a sex-linked disorder.

So, as a result of Bulloch and Fildes's opinions, the realization that women could have bleeding disorders took much longer to be accepted, even as additional cases were documented. Sadly, this simple concept of Mendelian inheritance, and the idea that only men can have a sex-linked recessive disorder, is still held by many physicians. This has prevented or delayed proper diagnosis and treatment of many women's bleeding disorders.

Decide for yourself: Does the biblical story of a suffering woman—who, according to some accounts, spent her money over 12 years in a desperate search to effectively treat her bleeding condition—truly represent the first written report of a woman with a bleeding disorder? Read Matthew 9:20-21. Or listen to 1950s legend Sam Cooke and the Soul Stirrers singing "Touch the Hem of His Garment." This emotionally stirring gospel song, based on the biblical verse, could easily be a motivational theme for women with bleeding disorders.

For a list of sources used for this article, see PEN at www.kelleycom.com.

headlines

manufacturer

Getting Under Our Skin

Genentech presented encouraging phase 1/2 clinical trial results for its new hemophilia A medicine emicizumab (ACE910) at the 2016 WFH World Congress in Orlando, Florida. ACE910 mimics the function of factor VIII by bringing together factors IXa and X to initiate clotting without the need for factor VIII. Patients were treated with an under-the-skin injection once a week, and the drug has a half-life of four to five weeks. ACE910 is on the FDA "fast track": a phase 3 global study in hemophilia A patients with factor VIII inhibitors is currently underway. Phase 3 global studies in patients without factor VIII inhibitors and pediatric patients are planned for later this year. Why this matters: This treatment could revolutionize management of hemophilia A with inhibitors and allow prophylaxis in hemophilia A patients, with and without inhibitors, without the need for venipuncture.

For info: hemophilia newstoday.com/

Factor Recalls

Bayer is recalling 10 lots of Kogenate FS, due to loss of potency. CSL Behring is recalling 42 lots of Helixate FS, due to loss of potency. Kogenate FS and Helixate FS are the same product. CSL is licensed to sell Kogenate under its brand name, Helixate. Why this matters: Loss of potency means factor may not be as effective as it should be.

For info: www.hemophilia.org/

nonprofit

Boatload of Trouble

Jacob (left) and Chris (right)

University of Georgia students Jacob Pope (who has hemophilia B) and Chris Lee competed in the 2,400-mile Great Pacific Race from California to Hawaii starting June 12. A week into the journey, they encountered heavy seas with 14-foot waves bashing the boat every few seconds. Their boat severely damaged, Jacob and Chris requested rescue by the Coast Guard. Why this matters: Jacob is the first person with hemophilia known to attempt an ocean row, and even though the men didn't reach Hawaii, they raised funds for Hemophilia of Georgia's Camp Wannaklot.

For info: www.facebook.com/rowforhemophilia

Getting High for a Cause

A team of nine, including LA Kelley Communications president Laurie Kelley and three other executive leaders in the hemophilia community, summited Mt. Kilimanjaro in August. The team raised awareness and funding for patients with bleeding disorders in developing countries through Save One Life, Inc. Kilimanjaro is the highest free-standing mountain in the world, and the highest in Africa. Why this matters: Personally involving community leaders in such a huge, unusual fundraising event helps raise awareness and may lead to greater long-term commitment of funding.

For info: saveonelife.net

soundbites

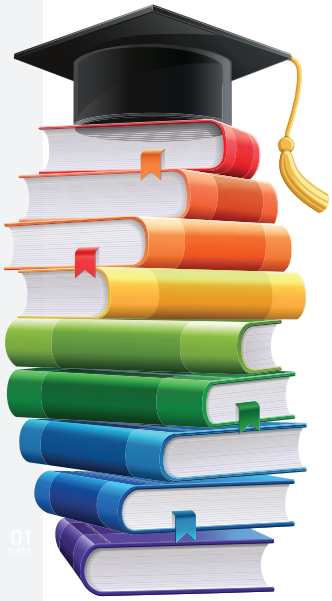
- Emergent BioSolutions, manufacturer of Ixinity (recombinant factor IX), has spun off its biosciences business to **Aptevo Therapeutics Inc.**
- NHF's MASAC has issued **Recommendation 243** on the **SIPPET** (Survey of Inhibitors in Plasma-Product-Exposed Toddlers) study, called "Results and Recommendations for Treatment Products for Previously Untreated Patients with Hemophilia A."
- Shire ended Baxalta's hemophilia B **gene therapy** program (BAX-335), which had inconsistent results. Instead, Shire is emphasizing its hemophilia A gene therapy drug BAX 888, which the company expects will start trials by the end of 2016 or early 2017.
- Believe Limited's **BloodStream podcast** is a free monthly podcast hosted by community member Patrick James Lynch. In episode 1, Patrick interviews Glenn Pierce about inhibitors and SIPPET.
- **Hemophilia Federation of America's (HFA) Symposium** April 6–9, 2017, in Providence, RI.
- **Spark Therapeutics** and **Pfizer** received FDA Breakthrough Therapy designation for hemophilia B treatment SPK-9001, an adeno-associated virus (AAV) vector expressing a high-activity human factor IX variant, being investigated in an ongoing phase 1/2 trial as a potential one-time therapy.
- Biogen has sold off its hemophilia division. A new company, **Bioverativ**, will continue to manufacture Alprolix and Eloctate.
- **Bayer Hemophilia Awards Program** supports basic clinical research and education in hemophilia, and has awarded more than 255 grants totaling over $31 million to researchers and caregivers from 32 countries.
- BioRx released the newest version of its iOS and Android app **MyFactor**, which allows hemophilia patients to record bleeding episodes and treatment while sharing with caregivers, physicians, pharmacists, nurses.

payer

Access to Marketplace Insurance Act (HR 3742)

Because of a poorly worded FAQ (Nov. 4, 2013) from the Centers for Medicare and Medicaid Services, insurance companies in 38 states with Marketplace health exchanges are refusing third-party premium assistance payments from entities including Patient Services Inc. (PSI), religious organizations, and service clubs such as Rotary or Shriners. HR 3742 is commonsense, bipartisan legislation that would allow nonprofit charities to continue to provide premium assistance. Why this matters: Without third-party assistance, families who purchase health insurance through a state Marketplace may not be able to maintain coverage. Contact your Congress member to request co-sponsorship of this bill.

For info: search "Co-Sponsor HR 3742" on www.hemophilia.org



Education Advantage

Baxalta, now part of Shire, has awarded educational scholarships to 63 students with bleeding disorders from 13 US states, for the seventh consecutive year. Baxalta has already awarded more than $1.7 million in 139 merit- and financial-need-based scholarships. During the 2016–17 school year alone, Baxalta is providing more than $375,000 to 21 new recipients, and to 42 students who received renewals to their previous scholarships. Why this matters: Although the Education Advantage scholarship program has been open to people with hemophilia A or B, including those with inhibitors, this was the first year that students with von Willebrand disease were also eligible to apply.

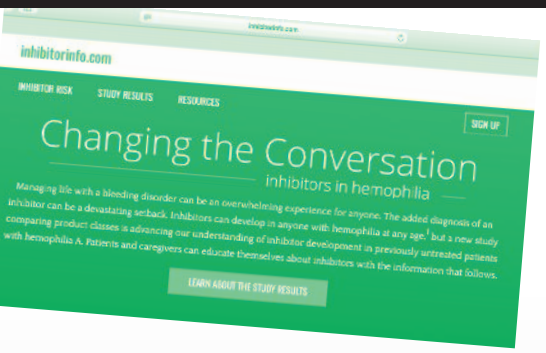
For info: www.baxaltahematology.com/

Most Expensive Drugs

A report shows that factor concentrate is among the most costly prescription drugs, although it isn't widely used by Medicaid patients and doesn't represent a significant portion of the Medicaid drug budget. Antivirals, including drugs to treat HIV and hepatitis C, are among the most widely used of these expensive drugs. Of the most expensive drugs, 45 fall into the high-cost category, mainly because they are frequently prescribed. Why this matters: The increasing number of specialty drugs like factor drives the increase in healthcare costs, and this has already caught the eye of legislators, whose efforts to control prices may lead to inappropriate regulation of these drugs.

For info: kff.org/medicaid/issue-brief/

patient resources



Updated Website for Inhibitor Patients

Grifols has relaunched its inhibitorinfo.com website, with info about inhibitors for people with hemophilia A and their families. Check out short videos from some of the world's leading hematologists, download resources to help you speak with your doctor, and stay up-to-date on breaking news about inhibitors. Why this matters: The SIPPET study (Survey of Inhibitors in Plasma-Products Exposed Toddlers) found that plasma-derived factor VIII concentrates containing von Willebrand factor (VWF) have a significantly lower risk of inhibitors in previously untreated patients (PUPs), as compared to some recombinant factor VIII products. This has renewed interest in plasma-derived concentrates containing VWF.

For info: inhibitorinfo.com

Patient Notification System

Did you receive an email about recent product recalls? If not, sign up for the free Patient Notification System (PNS), a confidential 24-hour communication system providing info on plasma-derived and recombinant factor withdrawals and recalls. Currently, only about 8,000 patients with bleeding disorders—about 40% of the bleeding disorder community—are enrolled in PNS. Why this matters: It's important to receive immediate notice of any safety concerns about factor.

For info: www.patientnotificationsystem.org

VWD: Get Informed

Beyondthebleed.com, an unbranded website sponsored by Shire, offers educational resources for people with von Willebrand disease. The site explores VWD diagnosis and treatment, and how to live with the disorder. Why this matters: People with VWD need easy-to-understand online educational resources.

For info: beyondthebleed.com

Inspiring Change Videos

Novo Nordisk has a new video series, "Inspiring Change in Hemophilia." Each video profiles one person who lives with hemophilia and finds ways to excel and create positive life changes. Available on Facebook, Twitter, LinkedIn. Why this matters: Some patients learn best through video media.

December: Inspiring Change in Hemophilia through nutrition features hemophilia nutritionist Brigitte Dilkrath and her patient Jonah Völker.

February: Inspiring Change in Hemophilia through outdoor life features hemophilia B patient and outdoor enthusiast Chris Bombardier.

For info: video.novonordisk.com

Inbox... from page 2

country. When I found out I couldn't join the military, it tore me apart. I felt like America, land of dreams, had turned its back on me. Everything I wanted to do in life was shot down because of my hemophilia. I feel America still discriminates against us regarding certain career paths. My mind is what keeps me strong. Through my own research and thought experiments, I have discovered that our mental state plays a huge role on our personal physiology. When we are in a good mental state, our minds and bodies are in homeostasis. Our hormones release properly, and we get sick less, because our immune system is on top of its game due to our good mental state. Depression can kill you, literally. Depression is a part of my life, and I battle it daily. My role in this world is to motivate others to accomplish things they once thought were impossible. I don't want depression to hinder other hemophiliacs, and I want to help in any way I can.

Jay Garman
California

I can't say I've had actual depression as it relates to my disorder, but this past year, I struggled with anxiety. It started with my ongoing job-related insurance issues that forced regular treatment to be on hold for months. This led to phobia of the emergency room. That was followed by the strong recommendation to treat my HCV infection, which was diagnosed in 1998 (high school). That has contributed to everything from "not sure I want to deal with this now" to nervous anticipation over seeing the results. I agree with what PEN said about community support. I've come across at least half a dozen individuals in the hemophilia world who can fully relate to my journey these last few months, and many more are always willing to listen. We older ones in particular have faced depression and anxiety as a result of challenges we had to deal with when we were younger. However, we also can be examples of the resiliency to overcome anything.

Angel Parrett
Kentucky

I LOVE GETTING your email newsletters and PEN. You recently sent some information on a product that we are switching my son to. Thank you for passing along any and all information. You are a great resource for the hemophilia community. I appreciate all that you do.

MEGAN SPENCE

inbox

Project SHARE

ON BEHALF OF Hemophilia Advocates, we would like to share that the two boys with inhibitors—Yanni (John Merck) Salazar, who had hematuria [blood in the urine], and Jom Gordola, who had a brain bleed—have now fully recovered and have both been discharged. Thank you so much for the prompt response to our request. We cannot overemphasize how much Project SHARE has helped the Philippines.

ANDREA H. TRINDAD ECHAVEZ
The Philippines

MR. MOHAN'S SURGERY to remove a pseudotumor was done in the Grande Hospital by Dr. Bhaskar. Nepal Hemophilia Society provided the FEIBA and NovoSeven, which was in our stock as the doctor advised for Mr. Mohan's emergency surgery. We are always indebted to your support in every situation.

LAXMI KARKI
Nepal Hemophilia Society

MY NEPHEW RAYYAN is doing great with the help of the factor that you sent to him. Thanks a lot from my sister and her husband, and for always being so nice and helpful.

AFRIN AKTHER
Bangladesh

THANK YOU FOR the donation, which helped me. I am recovering now and in good health. Thanking you from the deep of my heart.

S. V. BRAHMESWARA RAO
India

THANKS FOR YOUR support! Without it, my life would be worse. Your program is a tremendous support for people with hemophilia.

SITAN KONG
Cambodia

LA KELLEY
communications, inc.
37–39 West Main Street #8
Georgetown, MA 01833 USA
www.kelleycom.com

Visit Your HTC Annually!

BAYER
access solutions

Don't let insurance or financial challenges get between you and your treatment

- **Free Trial Program*:** Talk to your healthcare provider about requesting a free trial
- **Access to Therapy:** You may be able to receive the prescription treatment at no cost if you experience challenges getting insurance coverage for a Bayer product†
- **$0 Co-pay Program‡:** You may be able to receive up to $12,000 in assistance per year
- **Live Helpline Support:** Our experts are waiting to help you with any insurance coverage questions you may have†

*The Free Trial Program is available to newly diagnosed patients and patients who are currently using other therapy. Participation in the Free Trial Program is limited to 1 time only. This program is complimentary and is not an obligation to purchase or use a Bayer product in the future. Reselling or billing any third party for the free product is prohibited by law.

†The program does not guarantee that patients will be successful in obtaining reimbursement. Support medication provided through Bayer's assistance programs is complimentary and is not contingent on future product purchases. Reselling or billing any third party for free product provided by Bayer's patient assistance programs is prohibited by law. Bayer reserves the right to determine eligibility, monitor participation, determine equitable distribution of product, and modify or discontinue the program at any time.

‡People with private, commercial health insurance may receive co-pay or co-insurance assistance based on eligibility requirements. The program is on a first-come, first-served basis. Financial support is available for up to 12 months. Eligible patients can re-enroll for additional 12-month courses. The program is not for patients receiving prescription reimbursement under any federal-, state-, or government-funded insurance programs, or where prohibited by law. All people who meet these criteria are encouraged to apply. Bayer reserves the right to discontinue the program at any time.

CALL **1-800-288-8374**

8:00 AM–8:00 PM (ET) Monday-Friday. Spanish-speaking Case Specialists are also available.

Printed in USA 03/16 PP-775-US-0085