



The Doctor, the Patient and the Vector — A Day in the Life of a Gene Therapy Trial

The Doctor

A man wakes early on a nondescript morning, prepared to embark on a potentially historic endeavor. While other people are preparing to go to work and perform essentially the same tasks they did the day before, this man will spend the day doing something he will remember for the rest of his life. He has a lot at stake, especially since he is working with science, which can be at once cold and calculated, while at the same time unpredictable.

He has spent most of the previous night going over details in his head to make sure he has not overlooked anything. According to the man, "There was a lot of anxiety and caution the night before, thinking things over and making sure all the 'i's were dotted and 't's were crossed." In fact, the drive to the hospital consists of a con-



Dr. Glader



PICTUREQUEST/BRAND X

stant stream of details running through the man's head.

He arrives at the hospital at 7AM for a meeting with other members of the staff. Chances are, they spent the better part of the previous evening with the same kind of electric anticipation as the man did.

The man's name is Doctor Bertil Glader from California. He is a hematologist and has been for half of his life. In his 30 years of practice he has seen the progression of treatment for bleeding disorders and he views the task he is to take on today as an awesome responsibility, but one that is a necessary step in the road to a cure. He will be present when a vector carrying the gene for factor IX production is placed, via catheter, into a patient's liver, the site of normal factor production.

The Patient

Another man awakens in a strange bed. He is in a hotel, but he isn't on vacation. Jim Johnson is also a doctor in his home state of Oklahoma, but his role on this particular Monday will be as a patient in a gene therapy trial at Children's Hospital of Philadelphia. Dr. Glader and Dr. Johnson may never meet. In fact, their trials took place many miles and many months apart, but they both share roles as pioneers. They also share the belief that gene therapy is the way hemophilia will be cured.

Dr. Johnson makes his way to the hospital, which is directly across the street from the hotel, with a slow gait and a pronounced limp. Hemophilia has taken its toll on his body, and the limp is more of a pronouncement that he is a survivor rather than a sign of weakness.

Dr. Johnson's friendly and confident demeanor serves him well as he embarks on his long day ahead. He refers to himself jokingly as a human guinea pig. To be more precise, he calls himself "lab rat number 6," as he is the sixth participant in the phase one trial.

Call it a premonition, but Johnson always knew that gene therapy would be on the forefront of a cure. Twenty years ago, when Johnson was in his 20s, the prospect of gene therapy sounded like science fiction. "In college I had written a research paper about hemophilia, and one of my conclusions was that in the foreseeable future there would be the possibility of gene therapy to correct the problem." Little did he know that he ►



Jim Johnson



FACT > Treatments Less Often

What will a cure mean? It won't mean that a patient receives a shot and exits the doctor's office cured. It will still mean a dosing regimen for those with chronic illness, but regimens are likely to be every few weeks or months.

► would put his body on the line to prove it.

Johnson is a hands-on type of guy. He wasn't courted by researchers looking for volunteers; he took it upon himself to search out a trial. The idea came to him while he was surfing the Internet and happened upon NHF's Web site (www.hemophilia.org). While reading an article about gene therapy trials, Johnson decided he wanted to become involved and made the appropriate contacts. The extraordinary chain of events that led Johnson to the hospital on this Monday morning are not lost on the doctor/patient. He claims, "I feel like the first guy stepping on the moon being involved in these trials."

There was another feeling that occupied the seat next to pride for Johnson this Monday morning, and that was hunger. For the procedure, Johnson had to fast because of the anesthesia that he would be given at the trials. Most patients don't require anesthetics for injections into the thigh muscle; but then again, most patients will not be given 49 shots into their leg. Johnson is a

heavy-set man, thus he will receive a greater amount of injections. The site of each shot is tattooed on his leg so that a section of muscle can be removed at a later date and a biopsy can be performed.



Amy Chew

Nurse Amy Chew hugs Johnson when they meet that morning. They are meeting after corresponding for more than a year prior to Johnson's arrival. Chew feels as if she knows him already. The nurse spent the previous night realizing the gravity of what will go on at the hospital this day. She has arrived early to prepare for the litany of tests that Johnson will have to partake in before he receives his first injec-



tion. He is wheeled to each different department by Chew, his wife and his daughter. After the lengthy admissions process there is the chest X-ray and bloodwork. Because Johnson's veins are so difficult to find, he draws his own blood. It's unconventional, but so is the science that underlies what occurs when the 49 shots are administered.

The Vector

To complete the cast, another character in the gene therapy equation must be introduced. It is the vector, which has a job to do as well. Because the therapeutic gene that may help the patient produce factor can't be directly inserted into the patient's cell, there needed to be some crafty thinking on the part of the genetic researchers. The story of the vector is one of science taking the best man for the job and reforming him a little. The vector used is a virus that is an expert at entering into cells. To be of use, the virus is stripped of all its DNA and replaced with a therapeutic ►



PHOTO TAKE

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FACT > The Road to Phase I

Before a patient even is considered for a clinical study, pre-clinical studies are performed on animal models and tissue culture systems. Toxicity and side effects are what are studied, along with the amount of time the gene therapy product stays in the body and the product's therapeutic effect. Once these conclusions are made, an Investigational New Drug application is submitted to a division of the Food and Drug Administration (FDA). Once approval is granted, the hospital or clinic at which the phase I clinical trial is to take place must have its Institutional Review Board (IRB) give consent.

► gene. It all works in theory, but there are risks.

For the patient to understand the risks involved in this nascent medical technique, there is a very thorough informed consent procedure adhered to in case theory turns into danger. Before Johnson enters the minor surgery room, he is led to a consultation room where he is briefed extensively by the principal investigator and asked to sign an informed consent form. The potential dangers range from an immune risk to genetic changes to cancer. Johnson understands, yet he is unwavering in his desire to participate.

Johnson is wheeled down the hallway to the minor surgery room with the knowledge that this trial will not benefit him directly, though it is thoughts of future generations that spur him on. Perhaps, most notably, any children his daughter Ashley may one day have.

The minor surgery room is not as sterile-looking as one might expect. There is a colorful trim painted around the walls and there is a framed poster of a polar bear family looking down on the proceedings. According to Chew, "Once Dr. Johnson was taken to the procedure area, he was prepped for the injections so we had to shave that portion of his leg,

administer factor and have a cardiac anesthesiologist come in and interview him. The surgeon came in after this to meet with him. There was an hour-and-a-half wait while all this went on."

The procedure itself is a relatively long one. It isn't simply giving the patient his 49 shots and sending him on his way; these shots have to be administered with ultrasound guidance. This is a way for the surgeon to avoid hitting any blood vessels on the way to the muscle. Ultrasound pictures serve as a map for this endeavor.

There is a great deal of anticipation and lead-up to the shots, and it is actually the aftermath that causes the most concern. Johnson spent the night after the procedure in a private room at the hospital so he could be watched for any untoward events, though the thought of something going wrong didn't consume him. "I'm an eternal optimist," Johnson says. "I knew enough about gene therapy to know that there was always a chance that something unexpected might happen. I wasn't alarmed about the prospect, though." He does joke, however that he hoped the therapy wasn't going to turn him into the human fly.

Dr. Glader, Later

Dr. Glader, on the other hand, was a

bit more nervous following the administration of the vector at his patient's gene therapy procedure. "I called the hospital that night several times to make sure there was no bleeding from the site and that the patient was okay." In both Glader's and Johnson's cases, everything was fine. They had set out to prove the safety of the therapy and both were successful.

Surely this would be the time for celebration, but both men seemed as if they'd rather wait before popping champagne bottles as there is still a long road ahead. Johnson has used his status as a trial participant to advocate for further studies. In fact, he has presented just such a plea at a hearing held by the Food and Drug Administration.

There is a mutual respect between clinicians and patients taking part in these trials as it is only through collaborations such as these that discoveries can be made. Glader calls the participants "some of the most terrific people I've ever met." Johnson claims that his interaction with the hospital staff enhanced his experience. For Johnson, life has returned to the way it was before his involvement in these trials. His participation is key to the science that will one day affect generations and he will always have the tattoos to prove it. 🔄