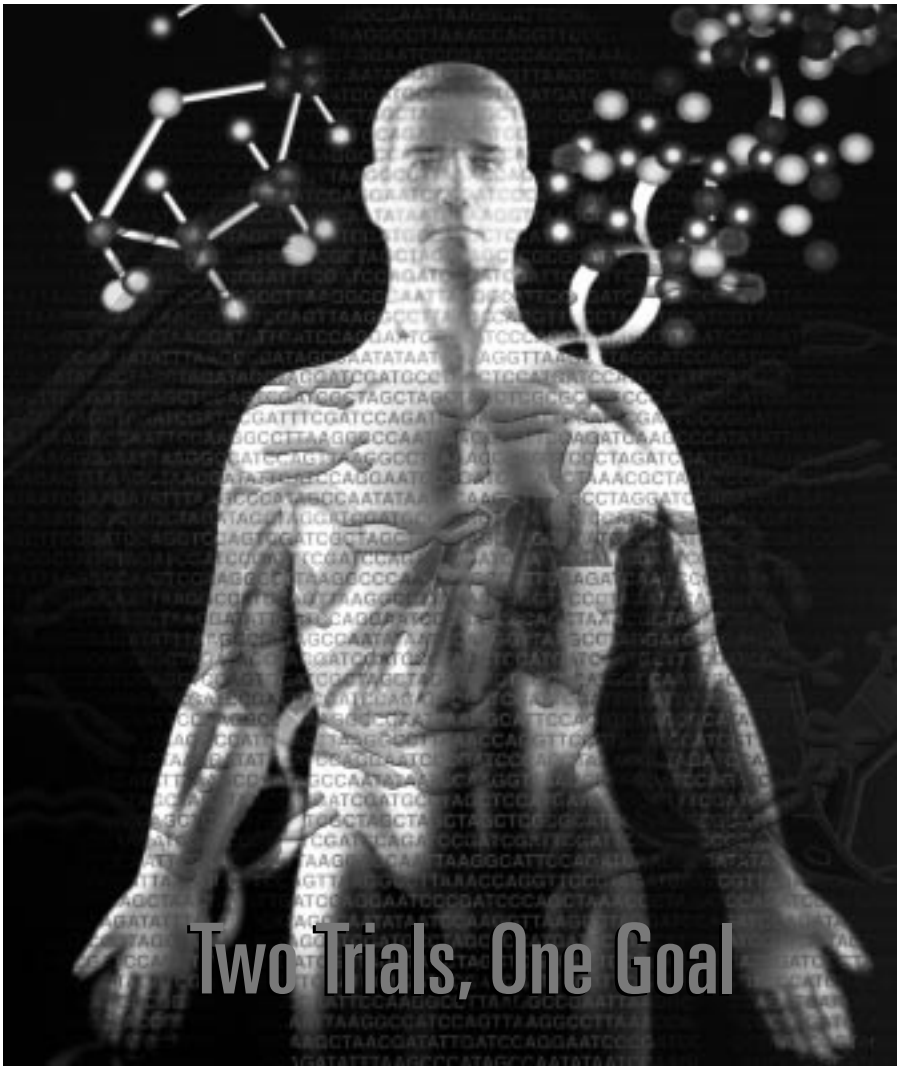

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Two Trials, One Goal

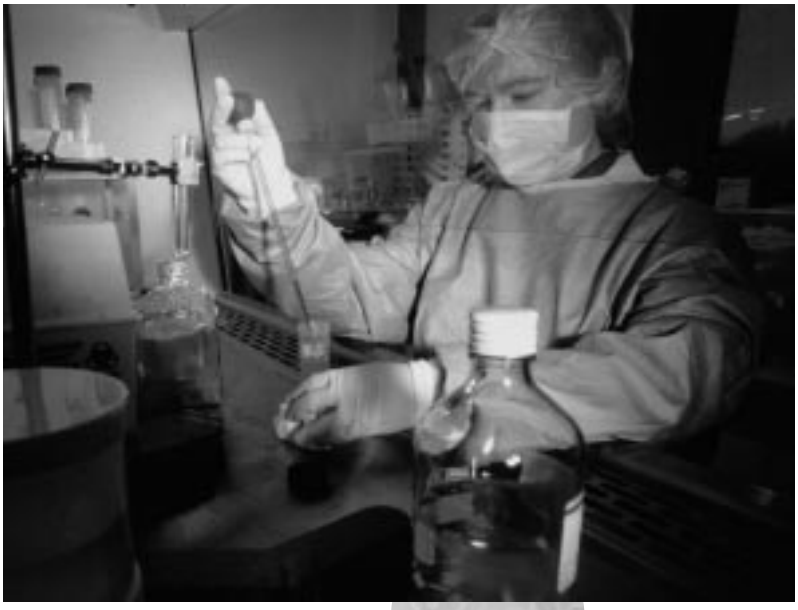
To date, three clinical trials have been completed while two, sponsored by GenStar Therapeutics and Avigen, Inc., are ongoing. All five of these studies are phase I clinical trials; they are small trials focusing primarily on safety, designed to determine if these novel treatments can be given without triggering adverse effects. While everyone is anxious to know if gene transfer actually works, the required steps of evaluation must be followed. That means: prove its safety first, then demonstrate its effectiveness.

The two current studies share some features but differ in other areas. Both use a virus to transport their cargo into the cells and both aim to deliver the genes specifically to the liver—the organ normally responsible for producing factor. The studies, however, vary from each other in that they use two different viruses, loaded with two different genes to treat two different kinds of hemophilia (hemophilia A and hemophilia B). Patients in both studies are required to have healthy livers, limiting potential candidates, as many adults with hemophilia have liver damage from hepatitis C.

Genstar Therapeutics' Study

In the first study, undertaken by GenStar Therapeutics, Dr. Gilbert White of the University of North ▶

BY JUDY BERLFEIN



Genetic therapy: recombinant viral manipulation.

PHOTOAKE

▶ Carolina at Chapel Hill reported on gene transfer in a single patient with hemophilia A. The transport vehicle was a common cold virus, known as adenovirus (AV). AV is appealing because it works its way easily into cells and is fairly manageable to produce. However, AV in its native form poses concerns. When an individual is infected with adenovirus, the immune system responds so vigorously that serious damage can occur throughout the body. Scientists have spent years manipulating this native form of AV, also known as first generation adenovirus. The goal is to develop a stealth vehicle—one that efficiently delivers desired genes without eliciting an immune reaction. GenStar is one of many research groups hoping to convert a toxic transport vehicle into an innocuous carrier. The company stripped away those genes believed to be most harmful, the genes responsible for producing viral proteins. The outer shell, a "vessel" for factor genes, remained intact. It appears, though, that the shell, once believed to be harmless, may serve as an alert to the immune system, according to the conclusion drawn by those at GenStar following the treatment of its first patient, the patient's reactions proved greater than anticipated. The trial was put on temporary hold following these events. After extensive discussions with the Food and Drug Administration (FDA) and NHF's Gene Therapy Working Group, White stated GenStar has been given a green light to proceed, although additional patients will receive a reduced dose.

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Simultaneously, scientists at GenStar are exploring new approaches to circumvent these immune reactions by either preventing AV from eliciting a response in the first place or stopping the body from responding to the virus. Addressing the first goal, GenStar is using a "Trojan horse" model to prevent an immune response to the foreign injection—they aim to fool the body by encasing the outer wrapping of the virus in a lipid bubble. To achieve the second goal, researchers will use a biologic agent to try and block the immune response while treatment is being administered, hopefully circumventing reactions observed in the first patient.

Avigen's Study

In the Avigen study, two patients with hemophilia B have received infusions of adeno-associated virus (AAV). The virus shuttled DNA programmed to synthesize factor IX. The subjects have fared well following treatment, Dr. Bertil Glader of Stanford University Medical Center reported. One of the many tests performed to verify safety raised a red flag, though, as the DNA intended specifically for the liver has also appeared in semen. Due to these concerns, the study was temporarily halted. However, it appears the genetic material is only present in semen for a short period following treatment. "It's very unlikely that the genetic material is actually infecting the sperm cells," stated researcher Mark Kay of Stanford University, one of the scientists behind the study. If this were indeed to transpire, it is even less plausible that the genetic material would work its way into the sperm's chromosome. Even when scientists try to force genetic material from AAV into a cell's chromosome, it rarely happens. "We can't say definitively that sperm is not being infected," Kay commented. "However, the risk is extremely small." An advisory board to FDA has recommended that the study proceed. Kay is confident FDA will abide by its recommendation, and the trial will begin enrolling patients again. "The approaches that work best in 2002 may not be the ones that work 10 years later," Kay added. "I think it's really important that people continue to look at multiple approaches, because we don't know in the end which one is going to be the winner." People with hemophilia, their families, healthcare professionals, scientists and the world wait in anticipation as the three phase I trials and the ongoing trials (discussed in this article) provide new insight into gene therapy.