PERSPECTIVE


HEATHER VAN UXEM LEWIS

The fix is in

History explains why people with haemophilia, and their physicians, are cautious to believe that a cure is in sight, says **Stephen Pemberton**.

In 2011, a remarkable study[1] in the *New England Journal of Medicine* detailed the successful treatment of six adults with haemophilia B, which is caused by a deficiency in the coagulation protein known as factor IX. All of the participants were able to eliminate or reduce the frequency of clotting-factor-replacement injections — the current standard treatment for the disease — after their livers began producing functional levels of factor IX. The experimental therapy came in the form of an adeno-associated virus (AAV) carrying a gene that encodes instructions for production of normal levels of human factor IX. Three trials of AAV-mediated gene transfer in patients with haemophilia B are ongoing, with high expectations.

After more than 20 years of research on gene transfer, it is a promising time for haemophilia therapies. It now seems likely that a single-dose treatment for haemophilia B using an AAV or another gene-transfer technique will be a viable option for many people in the next decade or two.

Yet haemophilia researchers are not inclined to speak enthusiastically of a cure. Part of that caution comes from recognition that there are still problems to solve. For example, some 40% of people with haemophilia B would find no refuge in an AAV treatment because they produce antibodies that attack and neutralize this virus[2].

And even if that problem were solved, the treatment would apply only to those with haemophilia B. The more common form of the condition, haemophilia A, stems from a deficit in another protein — factor VIII — and the gene for that protein is a more difficult target. Regardless of the type of haemophilia, researchers remain hesitant about gene therapy owing to the unresolved ethical issues that arose decades ago.

RESEARCHERS ARE HESITANT ABOUT GENE THERAPY OWING TO THE UNRESOLVED ETHICAL ISSUES.

The unfettered optimism that characterized the early years of gene-therapy research came to a screeching halt in 1999, when 18-year-old Jesse Gelsinger died in a phase I clinical trial at the University of Pennsylvania in Philadelphia. Gelsinger had undergone an experimental gene transfer for his otherwise treatable metabolic disorder. His death, along with a series of other harmful events in early gene-therapy trials for a variety of diseases, threatened the whole field.

Haemophilia specialists who were engaged in gene-transfer studies were more guarded than most of that era's self-proclaimed gene doctors[3]. The source of their reserve goes beyond the cautious optimism that characterized such research after 1999; it is grounded instead in the long and troubled experience that the haemophilia community has had with technological fixes.

By the late 1970s, a therapeutic revolution had transformed haemophilia from an obscure hereditary malady into a manageable disease[4]. But the glory of this achievement was tragically short-lived. The same clotting-factor-replacement therapies that delivered a degree of normality to the lives of people with haemophilia brought unexpected and fatal results: tens of thousands of people with haemophilia were diagnosed with transfusion-related HIV/AIDS in the 1980s and with hepatitis C virus (HCV) in the 1990s.

The memory of tainted transfusions still haunts those who have, or work with, haemophilia. Add Gelsinger's death into the mix and it is clear why specialists are debating thorny ethical problems, such as when to try out AAV-mediated gene transfer on children. Gene therapy is not even the most promising treatment for haemophilia on the immediate horizon. The biotechnology industry is producing recombinant-clotting-factor products for both haemophilia A and B that can limit bleeding episodes with less-frequent injections (see page S162).

But the lure of a less-intrusive form of treatment raises a historical spectre of its own. It was this same desire for convenience that led many haemophilia physicians and patients in the United States in the 1980s to continue using clotting-factor concentrates that had a high risk of HIV contamination rather than switch back to older, more cumbersome but less risky forms of plasma-replacement therapy. Thousands of people with haemophilia contracted HIV and HCV because of this acculturated preference[4].

Finally, there is the difficulty of making costly treatments available to the vast majority of the world's haemophilia patients who live in low income countries. About 75% of people with haemophilia still receive inadequate treatment, particularly in less-developed nations where clotting-factor therapy is limited[5]. An effective gene therapy could well offer these underserved patients their first chance at effective intervention[6].

History suggests that the fix will not lie in just one solution, but will be contextual and messy. The wants and needs of people with haemophilia in the developed world might not be the same as for those in low income countries. Yet social justice demands that there be equity in access to treatment. The transfusion scandals of the past remind us of the importance of bringing together patients and treatment professionals with stakeholders from industry and public health to weigh the various technological fixes. If such discussions had taken place in the 1970s and 1980s about the known problem of transfusion-related hepatitis B, the haemophilia community would not have been blind-sided by the emergence of HIV and HCV. ■

Stephen Pemberton *is a medical historian at the New Jersey Institute of Technology in Newark, and author of* The Bleeding Disease: Hemophilia and the Unintended Consequences of Medical Progress.
e-mail: stephen.pemberton@njit.edu

1. Nathwani, A. C. *et al. N. Engl. J. Med.* **365,** 2357–2365 (2011).
2. High, K. H., Nathwani, A., Spencer, T. & Lillicrap, D. *Haemophilia* **20** (Suppl. 4), 43–49 (2014).
3. Wailoo, K. & Pemberton, S. *The Troubled Dream of Genetic Medicine: Ethnicity and Innovation in Tay-Sachs, Cystic Fibrosis, and Sickle Cell Disease* (Johns Hopkins Univ. Press, 2006).
4. Pemberton, S. *The Bleeding Disease: Hemophilia and the Unintended Consequences of Medical Progress* (Johns Hopkins Univ. Press, 2011).
5. Mannucci, P. M. *Haemophilia* **17** (Suppl. 3), 1–24 (2011).
6. High, K. A. & Skinner, M. W. *Mol. Ther.* **19,** 1749–1750 (2011).