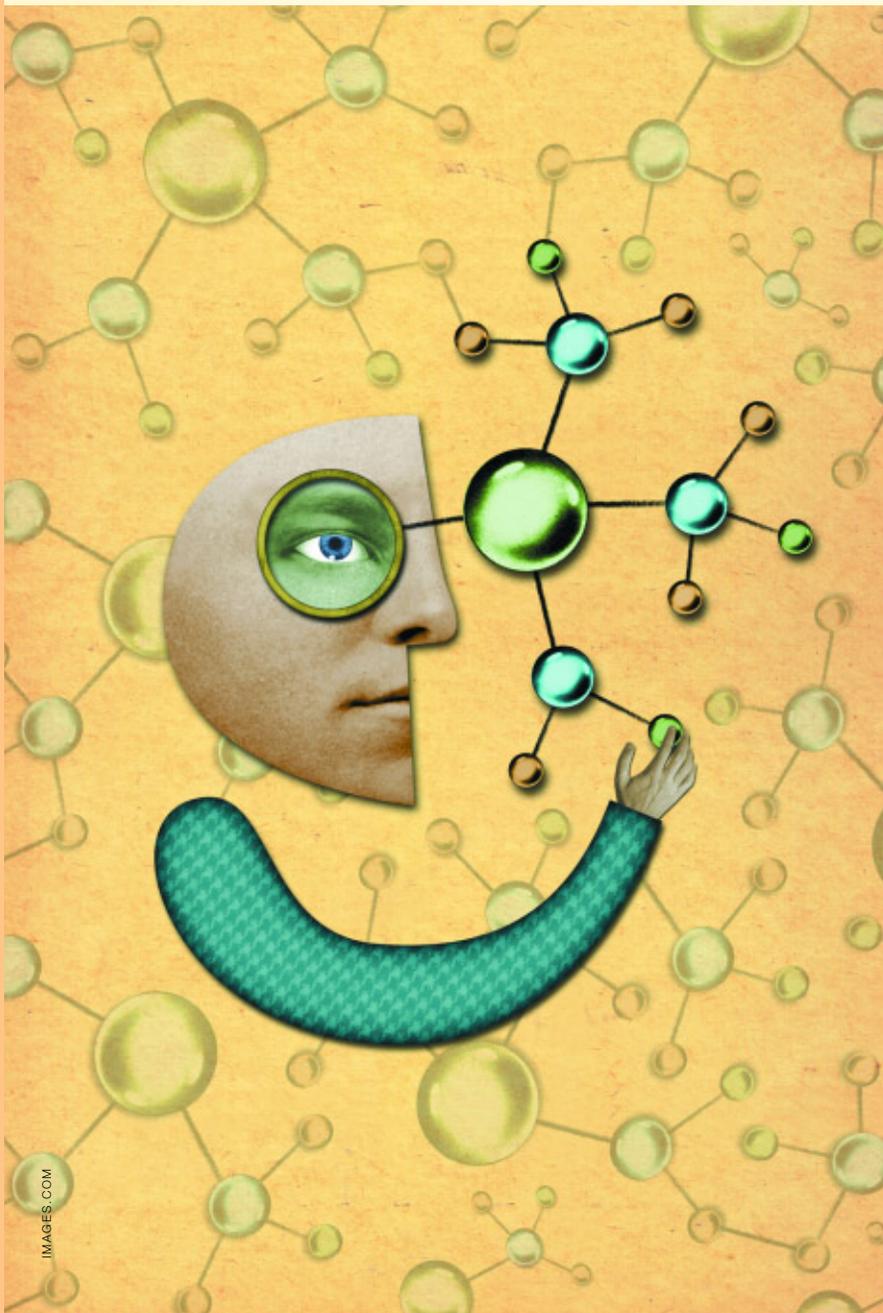


# GENE THERAPY

## WHAT IS BEING TREATED?

**It has been fifty years**

since Watson and Crick proposed a model for the structure of DNA.<sup>1</sup> That proposal allowed an explanation for the faithful transfer of genetic information to both daughter cells when a cell divides. The same mechanism explained the transfer of genetic information from parents to offspring. In the following half-century a veritable explosion of knowledge in genetics occurred. Scientists offered not only explanations of transcription of genetic information, but also the mechanisms of translation of that information into individual human beings. Researchers have deciphered an example of the structure of the human genome in detail and they can identify the structural change in a genome that results in a hereditary “disease,” such as hemophilia. There has always been an ongoing debate about the contributions of *nature* versus *nurture*. Is the way we live our lives the consequence of our physical body and our genes? Or is it the consequence of the environment within which we live and of the way we are reared by our parents and our community? The discovery that one’s genetic makeup was stored in a defined molecule made the argument of nature versus nurture swing strongly toward nature. We are who we are because of our genetic makeup. We think that this destiny can neither be avoided nor denied. A change in our destiny would require a change in our chemical basis of heredity. If our chemical basis of heredity predestined us to a disease, like hemophilia,



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then we need to manipulate our genes to avoid that fate; in other words, we call for gene therapy.

There is a danger in that reasoning in that we might ignore the considerable influence of nurture.<sup>3</sup> Some obvious examples may be cited:

Humans cannot make vitamin C. Thus they are dependent on a source of that vitamin in their food. We share that need with guinea pigs, dalmatian dogs and elephants. Most other animals need no vitamin C in their diets. Because we live in organized societies, we can ignore that defect in our nature because we create an environment in which the intake of vitamin C is assured. Sailors in the sixteenth century, however, developed scurvy on long voyages until the British Navy introduced rations of lime juice to the crew. That is the origin of their nickname, "Limeys."

Another example is color blindness. This is very widespread among males. Normally green-red color blindness is not a problem; however, in Texas many small towns have flip-flop traffic lights: red is on top in one direction and green is on top in the other. Color blindness can be a lethal disease in rural Texas.

Examples of the environment determining the consequence of a genetic variant abound. Even in mild hemophilia the need for intervention is dependent on the nature of the activities of the person. In addition, the use of aspirin may change the consequences of the genetic mutation.

We reserve the possibility for gene therapy for those individuals in whom the genetic variation results in an unacceptable quality of life. Gene therapy has not been perfected and for various reasons, hemophilia has turned out to be a good

area in which to test the modalities that might be expected to work. Therefore, ethical and philosophical questions about gene therapy will first have to be answered for persons with hemophilia.

In an earlier letter I addressed the idea of *cure*.<sup>3</sup> That is an important issue, but I will not address it here. What I want us to think about is the term *therapy*, as in gene therapy. Usually, we use the term therapy in the sense of treatment. However, when we have a disease and ask for treatment, there are several responses possible. The physician might treat symptoms, such as pain and this is an extremely important component of any medical intervention. Further, the physician may try to treat the cause, such as prescribing an antibiotic to kill a bacterium when the patient has pneumonia. But when a patient has a chronic disease, the treatment also involves recommendations for a change in lifestyle. Changing one's diet and exercising regularly are common prescriptions for people with heart disease.

**W**hen we use the term gene therapy, however, do we mean a treatment of a defective gene by replacing that gene, or do we mean the treatment of a person with a specific gene? This makes a profound difference.

If we focus on only replacing a defective gene, we are adherents to the notion that only nature determines our destiny. It is a passive approach to life and it is also bound to disappoint because treatment may never be so cut and dry. Furthermore, unless the treatment is done *in utero*, before birth, all the consequences of nurture will still be with the recipi-

ent. The boy will be a person who used to have hemophilia, which is still very different from a person who never had that genetic makeup.

If we treat a person with a gene, we know there are other ancillary problems with which to contend. An analogy could be made between this and a person with a heart attack. If we just unblock the coronary arteries with by-pass surgery or with a stent, the immediate problem is solved, but the problem is bound to recur. The patient has to change his lifestyle to avoid a recurrence. By the same token, the person with hemophilia who underwent fully successful gene therapy must still unlearn all the behaviors and thinking of the pre-therapy days. Furthermore, his environmental influences must change as well. Finally, whatever ravages hemophilia caused in the body must still be addressed, even when the tendency to bleed has been removed.

It is the fervent hope that gene therapy will become a routinely available tool without unexpected consequences, though the use of gene therapy will still require ancillary interventions. Psychosocial support and treatment must remain a high priority of NHF for the far foreseeable future, and physical therapy and orthopedic surgery must remain readily available options to the bleeding disorders community. In the time required to perfect gene therapy, we must work diligently to improve our current approaches to replacement therapy options. 

## REFERENCES

- 1 Watson JD: *The Double Helix*. New York, Atheneum, 1968.
- 2 van Eys J: Who then is normal? *Church and Society* 1982;73(1):81-86.
- 3 van Eys J: It's time for clarifying a cure. *HemAware* 2001; February:34-35.