Silencing Bad Genes

(This article was first printed in the Summer 2005 Special Edition of Newsweek*, Vol. 145, Issue 26A.)*

Scientists are trying to harness a form of RNA that interferes with the disease process. The purple-petunia payoff.

A 6-year-old boy is suddenly engulfed by pain. It is his first attack; he will suffer repeated agony, along with breathlessness and debilitating fatigue, for the rest of his short life. Over the course of a few days, a 35-year-old lawyer loses her appetite and energy, then the whites of her eyes turn yellow. Trying to open a stuck window, a 55-year-old nurse feels a sudden sharp pain just above her wrist. The bone has broken, weakened by cancer cells that have silently spread there from her breast, and are multiplying uncontrollably.

In each case, wayward genes are the culprit. The boy inherited a defective gene that makes a misshapen version of the hemoglobin protein inside his red blood cells, causing sickle cell anemia. The lawyer has been infected by a hepatitis virus that has commandeered her liver cells, instructing them to make proteins from viral genes instead of from human genes. The nurse inherited a breast-cancer gene from her Ashkenazi Jewish parents, and the gene is ordering the cells to multiply.

Doctors have long dreamed of a magic bullet that could travel harmlessly through the body to diseased cells, enter those cells and switch off the wayward genes that cause the suffering. Now, new research holds out hope for just such a treatment, through a technique called RNA interference. Since the 1960s it has been the central tenet of biology that a specific sequence of DNA (a gene) makes a specific sequence of messenger RNA, which in turn makes a specific protein. This profoundly important insight led to an important question, however. What controls that process? All our genes are contained in each of our cells. But in each cell, certain genes are expressed while others remain dormant, which is why the trillions of cells in the human body look and function differently from one another.

Over the past 30 years, scientists have identified various proteins that activate or silence genes. However, those proteins are large and complex molecules that are difficult to harness in order to control disease. The surprise breakthrough came in 1990. A team of plant scientists at the University of California, Davis, and a company called DNA Plant Technology were trying to make a purple petunia even more purple by inserting into it a gene for purple pigment. Instead of turning a deeper purple, however, some of the flowers were pale white and others were mottled. The researchers discovered that the inserted gene had stimulated the production of very small RNAs, and that these microRNAs shut down the gene activity that led to the production of purple pigment. Other scientists then found microRNAs in primitive animals and in humans. The microRNA attaches to the messenger RNA and destroys it before it can produce its designated protein, thus "interfering with" or "silencing" the instructions of the gene.

Considered just a curiosity at first, RNA interference has since revolutionized biological research. It allows scientists to silence specific genes very precisely in cell cultures and even in animals, like mice. Since science has now identified every gene in humans, in several animals and in many microorganisms that cause human disease, researchers can systematically silence one gene after another, and observe what happens to the cells or the animals—a direct test of a gene's function, including its role in causing a particular disease. If a gene plays such a role, it becomes a target for developing a conventional or novel drug treatment.

Could microRNA technology lead to the magic bullet—drugs that silence wayward genes? It's easy enough to produce microRNAs that silence a particular gene. Such synthetically made RNAs are called small interfering RNAs, or siRNAs. The hard part is delivering the siRNA to the cells deep inside the body, where the wayward genes are causing mayhem. But progress is being made. Scientists are figuring out ways to protect the siRNAs from destruction as they circulate through the body, and to allow them entry into the target cells. In animal studies, siRNAs have stifled autoimmune hepatitis, a neurological disease called spinocerebellar ataxia, several viral diseases and several types of cancer, and have dramatically lowered cholesterol levels. And, in human studies, siRNAs have recently shown promise in the treatment of macular degeneration, the leading cause of blindness in the elderly.

It's true that we already have conventional drugs that inhibit the reproduction of some viruses, slow the growth of cancer and lower cholesterol. But RNA-interference technology offers a number of advantages. For one thing, there are many pathological genes for which no counteracting drugs have yet been developed. And while the process of looking for conventional drugs that counteract the effects of wayward genes is getting faster and more efficient, it's still ponderous and expensive. Once scientists know the identity and structure of a wayward gene, they can easily make siRNAs to silence it. And, compared with most conventional drugs, siRNAs are simple molecules that should be very inexpensive to produce. Also, since the immune system does not recognize siRNAs as foreign, they would likely produce fewer side effects

than conventional drugs.

Though there are reasons to be optimistic that this new technology will lead to powerful and nontoxic new treatments, there are many obstacles to overcome. It remains to be seen whether siRNAs will be able to reach all their potential targets deep in the body. And there is the possibility of collateral damage; some siRNAs may silence not only a wayward gene but several healthy genes with similar structures as well. It is also uncertain how durable the effect of this new form of therapy will be. It's possible that in chronic diseases, siRNAs, like conventional treatments, will need to be given repeatedly in order to sustain a beneficial effect. Eventually, gene therapy may be used to express microRNAs throughout a patient's life, but gene therapy has been plagued by difficulties.

While the value of RNA-interference therapy in humans remains to be proved, the story of its discovery is just the latest example of how an investment in basic research can lead to completely unexpected, and enormously beneficial, results. Who could have imagined that trying to make a petunia more purple would reveal a potential new approach for shutting down the growth of cancer? No one. That's why it's wise for a society to invest in curious people who try to understand how living things work.

By Anthony Komaroff, M.D. and Judy Lieberman, M.D., Ph.D.

Dr. Komaroff is a professor at Harvard Medical School. Dr. Lieberman is a professor at Harvard Medical School.

(This article was first printed in the Summer 2005 Special Edition of Newsweek*, Vol. 145, Issue 26A.)*