brain
JANUARY 2006 BRIEFINGS

OUR GENES GUIDE THE PRODUCTION OF PROTEINS THAT PLAY IMPORTANT ROLES IN OUR LIVES, BOTH GOOD AND BAD. UNFORTUNATELY, ON THE DOWNSIDE, GENES CAN TAKE PART IN CAUSING MANY DISORDERS OF THE BRAIN AND NERVOUS SYSTEM. RESEARCHERS, HOWEVER, MAY SOON BE ABLE TO COUNTER THIS NEGATIVE ASPECT WITH A NEWLY DEVELOPED TECHNIQUE, GENE SILENCING, WHICH CAN DRAMATICALLY REDUCE PROBLEM GENE ACTIVITY AND IMPEDE THE DISEASE PROCESS. FOLLOWING POSITIVE RESEARCH IN ANIMALS, THE TECHNIQUE IS NOW BEING TESTED IN PEOPLE.

GENE SILENCING

Thick hair? Thank you, genes. Chiseled chin? Thank you, genes. Killer green eyes? Thank you, genes.

Genes, however, also can have an unattractive side.

In our cells, genes produce proteins that play a key role in how we look, develop, and function. While sometimes this translates into movie star tresses, other times it can mean disease. Many disorders of the brain and nervous system are caused, at least in part, by genes that create detrimental proteins, detrimental protein accumulation, or detrimental protein activity.

Researchers have long imagined that they might be able to counter this ugly dimension of genes and treat disease by finding a way to straightjacket or "silence" select genes and reduce their problematic protein production. Now, following recent studies, scientists are getting closer to making this goal a reality. The research is leading to:

- The development of gene-silencing techniques that offer a new way to treat an array of human diseases that harm abilities, such as thinking, moving, or seeing.
- A better understanding of how genes influence various disease processes.

The idea of gene silencing gained momentum following a 1998 study in worms that found that a particular technique termed RNA interference or RNAi (see illustration) was especially effective at obstructing select gene activity. Soon after, scientists determined that the technique also could efficiently reduce activity in mammalian cells.

Since then, researchers have examined the ability of RNAi to battle disease. Following encouraging animal studies, scientists have begun plans to test the technique in people with age-related macular degeneration, a leading cause of blindness in elderly Americans. This eye disease can occur when blood vessels abnormally grow and leak inside the fragile eye. The RNAi strategy obstructs specific genetic activity and protein production in order to

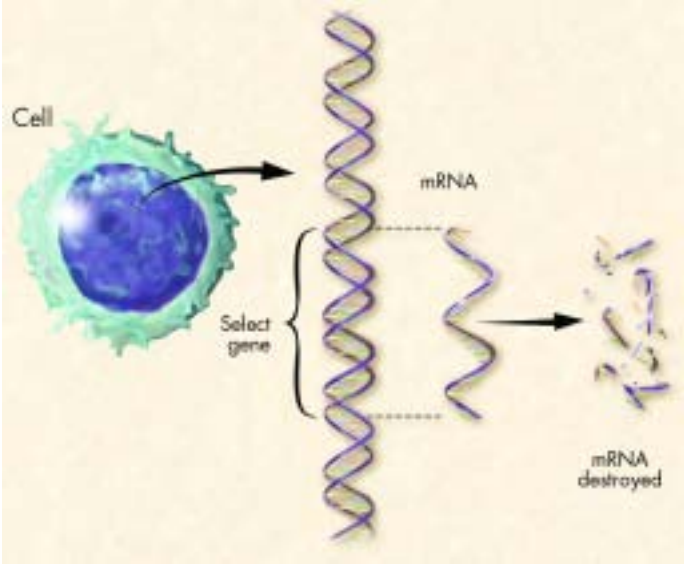

ILLUSTRATION BY LYDIA KIBIUK.

▲ **MANY DISORDERS OF THE BRAIN AND NERVOUS SYSTEM ARE CAUSED, AT LEAST IN PART, BY GENES THAT CREATE DETRIMENTAL PROTEINS, DETRIMENTAL PROTEIN ACCUMULATION, OR DETRIMENTAL PROTEIN ACTIVITY. TO COUNTER THIS NEGATIVE SIDE OF GENES, RESEARCHERS RECENTLY DEVELOPED A METHOD, KNOWN AS RNA INTERFERENCE, THAT STRAIGHTJACKETS OR "SILENCES" SELECT GENES AND SIGNIFICANTLY REDUCES PRODUCTION OF PROBLEMATIC PROTEINS. DURING THE PROTEIN PRODUCTION PROCESS, A GENE USES A MOLECULE TERMED mRNA TO SEND A MESSAGE THAT DESCRIBES THE INSTRUCTIONS TO MAKE A CERTAIN PROTEIN. BUT BEFORE THE PROTEIN HAS A CHANCE TO BE MADE, THE RNA INTERFERENCE STRATEGY SENDS IN A MOLECULE THAT BINDS TO THE mRNA. THIS CAUSES THE CELL TO DESTROY THE mRNA AND HAMPERS THE GENE'S ABILITY TO MAKE THE PROTEIN.**

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sideline a substance, termed VEGF, thought to aid the abnormal vessel growth.

Recent animal research suggests that RNAi strategies also hold promise in treating ALS, a disorder that impairs movement and is ultimately fatal. In the work, scientists used RNAi to straightjacket a problem gene that causes ALS-like symptoms in mice and found that it slowed the progression of the disease.

RNAi also may aid the movement disorder Huntington's disease, according to animal research. Recently researchers tested an RNAi technique in mice that model the disorder. They found that the technique prevents some of the physical symptoms and brain damage caused by Huntington's disease. Earlier work also shows that RNAi benefits mice with spinocerebellar ataxia, a condition similar to Huntington's disease.

Despite the progress, scientists note that gene silencing is in an early stage and that some uncertainties still exist. For one, researchers need to ensure that the technique won't accidentally obstruct other beneficial genes.

But even with the current reservations, many scientists think that with more work gene silencing could potentially aid numerous diseases. In addition to age-related macular degeneration, ALS, and Huntington's disease, researchers also believe it may benefit many other common and devastating ailments like the memory-robbing brain disorder Alzheimer's disease and paralyzing traumas, such as spinal cord injury. For example, research indicates that those with Alzheimer's disease can have abnormal accumulations of certain proteins in their brains. Blocking the production of disease-causing proteins with gene-silencing techniques could possibly treat the disease. Researchers also know that a protein termed Nogo inhibits the repair of nerve fibers damaged from a spinal cord injury. They think that perhaps blocking Nogo activity with gene silencing could allow repair to occur.

The technique could also aid diseases indirectly. Animal studies that involve the systematic silencing of genes could allow scientists to gain insights into the molecular processes that lead to various diseases. This could help them design traditional types of medicines that target involved molecules.

Thank you, gene silencing.

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