Medical milestones in gene therapy

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ON THE wedding night of her fourth marriage, a woman confided to her groom that she was a virgin.

"A virgin," her husband exclaimed, "how is that possible if you've been married three times before?"

"Well," she answered, "my first husband was 93 and nothing happened, my second husband was gay and wasn't interested, and my third husband was a genetic engineer.

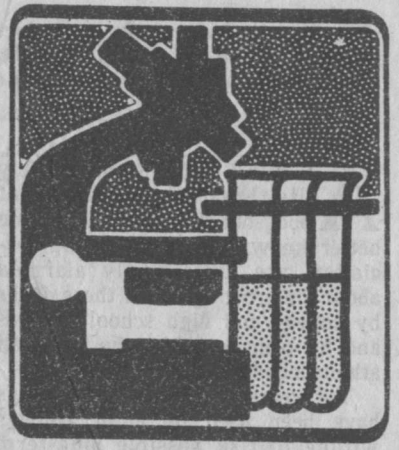
"You know genetic engineers — promises, promises, nothing but promises."

Biochemist Robert Williamson told this joke as part of his remarks at a recent conference on gene therapy held at the Medical College of Wisconsin. He was pointing out, in a lighthearted way, how for more than a decade genetic engineers have probed human DNA for the basis of disease in the hope of improving therapy for a host of disorders, but so far few hopes have come true.

Gene therapy hopes range from advances in sickle-cell anemia and muscular dystrophy to cancer and heart disease. Gene probes also are being used to pinpoint the causes of such mental disorders as manic depression and alzheimer's disease.

By unraveling the faulty genes involved in disease, researchers can uncover key proteins in the body that lead to disease when missing, defective, or present in excess.

Scientists hope to use this information to design drugs that fill the protein gap or remove protein excess. And once a gene is linked to a particular disorder, it is hoped that



Genetic engineers probe DNA as the basis of disease

tests can be devised to predict prenatally who will develop the disease or who will be a disease carrier.

Although many promises made by genetic engineers are just that, some progress is being made on the gene front of disease. The milestones include:

■ **Prenatal diagnosis.** There are more than 500 inherited diseases whose culprit genes have been cloned — a first step in creating a gene probe for prenatal diagnosis and carrier determination, said Williamson. Gene probes are used to test for only 15 to 20 genetic diseases prenatally, however, said Renata Laxova, a professor of medical genetics and pediatrics at the University of Wisconsin — Madison.

These diseases include sickle-cell anemia, hemophilia, cystic fibrosis, Huntington's disease and a type of eye cancer called retinoblastoma. Although the use of gene probes has not yet dramatically expanded the range of prenatal diagnosis, "the field will burst someday," Laxova predicted in a separate interview.

Williamson recounted one case in which a woman pregnant with twins underwent prenatal testing for cystic fibrosis, a fatal disease characterized by chronic respiratory malfunctions. The tests showed that one of the twins had the disorder. The woman's doctor was able to terminate her pregnancy with the cystic-fibrosis twin while allowing the normal twin to go to term.

■ **Discovery of proteins** crucial to disease. Scientists have pinpointed proteins that play a critical role in several different types of cancers and other disorders, the most recent one added to the list being Duchenne's muscular dystrophy. No new therapies have sprung from these findings although several laboratories are busily pursuing this vein.

■ **Animal models** that allow researchers to test the effectiveness of drugs for inherited diseases. Geneticist Oliver Smithies of the University of Wisconsin — Madison has developed methods to genetically manipulate mice so that they have the same genetic flaws as those found in a variety of inherited human disorders.

Smithies created a mouse model of Lesch-Nyhan disease, a rare inherited disorder marked by the disturbing symptom of compulsive self-mutilation, such as biting off one's fingers and lips. A mouse model of sickle-cell anemia, which afflicts one out of every 400 or 500 blacks, and for atherosclerosis is around the corner, he said. Progress in effective therapies for diseases like sickle-cell anemia has been hampered, said Smithies, by not having an animal model of the disorder in which to test drugs.

Although some may consider these minor milestones in light of some of the grandiose promises being made by genetic engineers, Williamson advised "give it a bit of time. Nowadays there's a feeling that if something's discovered in January, it ought to be out there doing things for people by February. That's unrealistic."

The pace of things may speed up now that the National Academy of Sciences recently recommended Congress set aside $200 million a year for the next 15 years to finance researchers attempting to tease apart human DNA into all its constituent genes. This is a daunting task since the winding strands of DNA found in each human cell contain more than 100,000 genes. But once a gene "map" is done, the roadways leading to understanding of particular diseases will be more obvious.