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Retrofit for genetic diseases

The unique properties of retroviruses, discovered in research on AIDS, point toward a cure for once untreatable maladies.

Retroviruses, a unique set of viruses which lack the usual genetic material DNA, have been much in the news since one of them, known as HTLV-III or LAV, has been identified as the cause of Acquired Immune Deficiency Syndrome (AIDS). Another of these organisms, HTLV-I, causes a rare form of leukemia and, according to a recent report, may be carried by up to 1 million Americans.

Now, an article in the May 1985 issue of *Science Digest* reports that retroviruses may soon be used to replace missing or defective genes responsible for a number of genetic disorders. Of the more than 3,000 known genetic diseases, approximately 1,600 result from absence or defect of a single gene. At present, medical science is capable of treating only a few of these diseases, and the treatments do not remedy the underlying problem.

Now, a number of teams of scientists are working to develop a practical technique to utilize the unique properties of retroviruses to insert missing genes into the cells of patients who lack these genes.

The approach used is to take advantage of the ability of these viruses to reprogram the genetic machinery of the cells they infect. When a retrovirus, which contains RNA instead of DNA, enters a cell, it uses the cell's genetic machinery to synthesize a complementary DNA, which then produces multiple copies of the virus. The complementary DNA is actually inserted into the DNA of the host cell and becomes part of the cell's genetic material, thus permanently altering the cell. In the case of HTLV-III, this results in the death of the target cell, and in the case of HTLV-I, the target cell is transformed to a cancer cell.

The technique now being developed consists of splicing a missing human gene into a retrovirus and using the virus as a messenger to ferry the gene into a cell and insert it into the cell's genetic material. Experiments by Richard Mulligan of MIT and Inder Vermer of the Salk Institute proved that retroviruses will insert foreign genes into host cells.

While the viruses used in the initial experiments do not cause human disease, viruses used to insert material into human cells would have to be at least infectious enough to enter the cells in question. Mulligan and his MIT co-workers got around this problem by using two incomplete viruses, each of which is incapable of breeding new virus particles. In one virus the desired gene is inserted and the genes necessary to enter the cell are removed. From the second virus, called the helper, the genes which are necessary to form a new virus are deleted. When the two viruses are placed in a cell culture, the helper virus inserts the engineered virus into the cell. Since the helper virus lacks the genes to form new virus particles, it cannot reproduce itself, and since the engineered virus lacks the ability to enter other cells, it is trapped in the host cell.

At present, two diseases are prime candidates for treatment by gene therapy. These are adenosine deaminase deficiency (ADA) and Lesch-Nyhan syndrome. ADA produces severe immune system deficiency and was the disease which affected the "bubble boy" David, who spent his 12 years in a plastic germ-free bubble to avoid exposure to infection. Lesch-Nyhan syndrome is a rare disease characterized by seizures, gout, kidney failure, arthritis, mental retardation, and self-mutilation. Each of these diseases results from deficiency of a single, well defined enzyme, and potentially would respond to replacement of that enzyme.

ADA is especially susceptible to this type of treatment, since the enzyme defect occurs in white blood cells. These cells can be obtained from the patient's bone marrow, cultured with the virus, and then reinserted into the marrow. In Lesch-Nyhan syndrome, the seizures and retardation result from lack of the specific enzyme in the brain. The problem is to find a method of delivering the gene to the brain cells.

The ultimate potential of this sort of therapy is immense, just in terms of the approximately 1,600 single-gene deficiency diseases, and illustrates how diverse areas of basic research have the potential to interact in unexpected ways. A great deal of the retrovirus work was stimulated by the effort to define the cause of AIDS and the ability to isolate and characterize individual human genes is a result of laser research at Los Alamos and Lawrence Livermore National Laboratories, which are using the technique of flow cytometry to compile a complete library of the human genome.

The supreme irony of the situation is that, just as we stand on the verge of conquering previously untreatable diseases, starvation and its attendant diseases, such as tuberculosis, are staging a comeback in many areas of the United States—a testament to the strength of our economic "recovery."