# Scientists Repair Genetic Flaw Involved in Blood Disease

Scientists have succeeded in creating a gene capable of correcting a genetic mutation responsible for a common form of blood disorder. But even while the research community is applauding the conceptual advance, scientists are warning against raising false hopes for a cure through genetic manipulation.

The so-called "suppressor" gene effectively countermands instructions from a defective gene that causes victims' red blood cells to produce insufficient chains of the protein beta-globin, resulting in an extreme form of anemia — called beta-thalassemia — that is often fatal. Because the researchers have so far corrected the defect only in frog eggs, it remains unclear whether the manipulation will work in human red blood cells without producing deleterious side effects. The preliminary results were reported in the April 8 NATURE by hematologists Gary F. Temple of Bethesda Research Laboratories in Maryland, Andree M. Dozy and Yuet Wai Kan of the University of California in San Francisco, and Kenneth L. Roy of the University of Alberta in Canada.

The thalassemias, a group of hereditary blood disorders particularly common in Mediterranean countries, are caused by a variety of genetic defects, all of which interfere with the natural production of hemoglobin. Victims — who typically suffer from growth retardation, sexual retardation, bone deformation, frequent fractures and fevers — rarely survive beyond their early thirties. Two of the more severe forms of beta-thalassemia are known to be caused by the presence of what are called "nonsense mutations" in the coding region of the gene, which signal the body's protein synthesis machinery to stop production prematurely. Where the gene should instruct the cell to manufacture a specific amino acid, it calls a halt to production, and the resulting globin chains are too short.

The manner in which the researchers have corrected the genetic defect is generating considerable excitement.

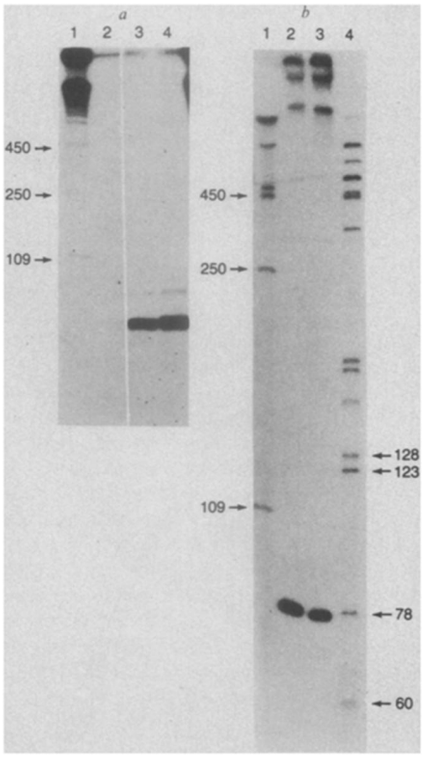
Scientists have had little success in altering the gene that codes for globin itself. What Temple and his colleagues have done instead is to work with the gene that codes for transfer ribonucleic acid (tRNA), the substance that reads the genetic code and arranges the amino acids in correct sequence. They have altered the human tRNA so that, in effect, it will overlook a stop signal in the middle of a protein and produce an amino acid instead. It "suppresses" the nonsense mutation by reading it as a meaningful genetic instruction, in this case as an instruction to produce the amino acid lysine needed to complete the protein. In the experiment with frog eggs, the altered tRNA did ignore the stop signal and instruct the cell to manufacture complete protein.

Although thalassemia researchers are very interested in the experiment, and concede that it does demonstrate the ability to increase beta-globin production through genetic manipulation, most are reluctant to discuss the potential for gene therapy. The dominant sentiment expressed by Temple and others is that the work represents a very preliminary step toward correcting such genetic defects in humans. At least three major obstacles remain to be overcome. First, it is not yet known how to insert altered genetic material into human cells, which are not as simple as the frog eggs; there has been speculation that genetic material might be somehow implanted in human bone marrow, which produces red blood cells, but the idea has not been tested.

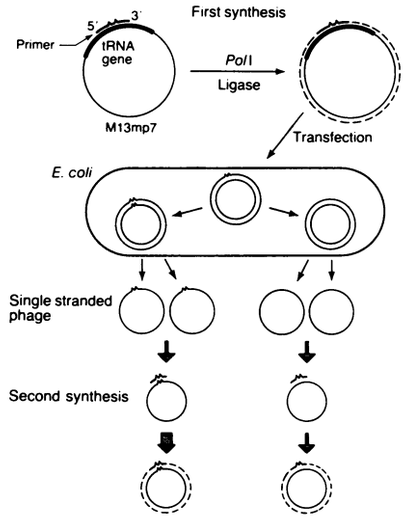
Second, it is uncertain how "efficient" the corrective gene would be if it were in the cell — that is, how much genetic information would be successfully translated into the production of complete proteins. Thalassemia actually results from an imbalance of two kinds of globin chains (known as alpha- and beta-globin), so that too much beta-globin is as harmful as too little, and scientists currently do not know how to regulate the production of beta-globin.

Finally, and perhaps most important, researchers emphasize it is impossible to know what harmful side-effects such a genetic rearrangement might have. Every protein in the body is affected by the same three chemical stop signals, and the same signal that is a disastrous nonsense mutation in hemoglobin production might play an important role in the normal and necessary production of another protein — the protein that makes up the cell wall, for example. If tRNA is so altered that it always ignores a stop signal and produces an amino acid instead, it might interfere with normal cell function or, in the extreme, act as a lethal poison. "Evidence from bacterial studies suggests that generally suppression is not lethal and, in fact, is tolerated quite well," Temple says, "but we don't know at present if that is true in higher cells."

Temple is at least as cautious as others in the field when it comes to the question of genetic therapy for thalassemic patients. He says that he and Kan (in whose laboratory the work was done) debated whether or not to mention the therapeutic potential of their work, but decided that it offered a conceptual if not very practical approach to gene therapy. The results are most useful because they provide a method for further studies of suppression in cells, he says; with any clinical application still far off, he emphasizes, thalassemic patients would be mistaken to hope now for a genetic cure. —*W. Herbert*






*Using recombinant DNA methods, researchers changed the gene for normal transfer RNA into a gene for tRNA that ignores nonsense mutations in the genetic code (above). Autoradiography shows that genes for both the normal and altered tRNA were successfully transcribed into tRNA in frog eggs (left).*