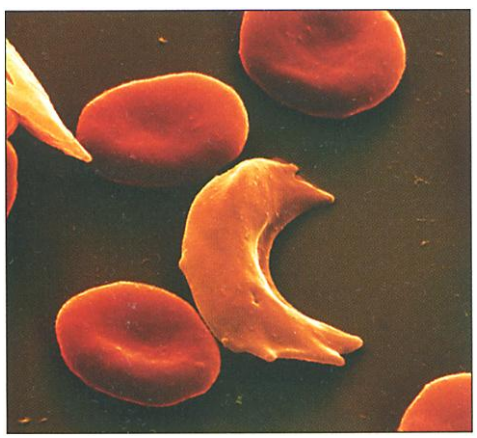
the other hand, what they write about the timing of [mammalian] divergences seems completely unreasonable." Like many others, Gingerich thinks the fossil evidence strongly suggests that mammals diversified most after dinosaurs went extinct, only about 65 million years ago. Molecular studies by other researchers had already indicated an earlier date, which this new extensive analysis supports. The two camps are far from reaching a truce. However, O'Brien and others hope that with the help of the long-deceased Reverend Thomas Bayes, the two views will one day be reconciled. –ELIZABETH PENNISI

GENE THERAPY

Gene *Gemisch* Cures Sickle Cell in Mice

Twenty years ago, sickle cell disease looked like one of the few inherited disorders that might be an easy target for gene therapy. All one had to do, it seemed, was correct a simple mutation that causes red blood cells to become distorted and "sickled." As researchers dug deeper, however, they found a "nightmare" of complexity, says gene therapy researcher Philippe Leboulch of the Harvard Medical School and the Massachusetts Institute of Technology in Cambridge, Massachusetts. After a long struggle, researchers believe they've now overcome a major barrier to gene therapy: On page 2368, a team led by Leboulch reports having used an HIV-based vector to cure sickle cell disease in mice.



Sickling. Normal disc-shaped cells become elongated and block circulation.

"This is a very important advance," says Arthur Nienhuis, a leading researcher in blood disorders at St. Jude Children's Research Hospital in Memphis, Tennessee. He thinks this is one of several signs that gene therapy could become a reality for this disease, but, he adds, "there's still a lot of work to be done."

The mutation that causes sickle cell disease is a single-base defect in the human β^A-globin gene. People who inherit the mutation from both parents produce an abnormal hemoglobin that forms a polymeric fiber, making red blood cells rigid and sticky. Because having a single copy can help protect against malaria, the gene occurs widely in tropical regions. But having two copies causes red blood cells to form clumps and block circulation, damaging organs. Roughly one in 13 African Americans carries the gene, and about 72,000 people in the United States have the disease, which can be fatal.

The first attempts to cure sickle cell disease using gene therapy focused on replacing the defective β^A-globin gene in stem cells in the bone marrow, where new blood cells are produced, by using a vector made from a mouse retrovirus. The results were disappointing. But during the 1990s, the National Heart, Lung, and Blood Institute upped its funding for gene therapy in this field to roughly $13 million per year, stimulating the development of new approaches.

To boost expression of the β^A-globin gene, various researchers added a key control region to the gene package they transferred to stem cells. They tried new retroviral vectors as well. But the turning point, researchers say, came as two teams began using HIV-based vectors—one group led by Michel Sadelain of Memorial Sloan-Kettering Cancer Center in New York City and the other by Leboulch, who has ties to a Cambridge, Massachusetts, biotech company named Genetix Pharmaceuticals.

Last year, Sadelain's group used an HIV vector to insert a healthy β^A-globin gene into transgenic mice, curing them of β thalassemia, a related but milder blood disorder. Leboulch has now used an HIV vector to insert a different gene—a synthetic construct that includes parts of the β^A- and γ-globin genes—into two strains of mice with a form of sickle cell disease. Leboulch says his group decided to create this new therapeutic gene because γ-globin produces a stronger antisickling effect than β^A-globin does.

Leboulch's team focused on a critical part of the γ gene (codon 87) and added it to the sequence for the β^A-globin gene, creating a *gemisch* that they call $\beta^{A\text{-}T87Q}$-globin. They also tinkered with a control region to improve gene expression. The team then inserted the sequence into stem cells from two strains of mice with sickle cell disorders. It was a success: 99% of the red blood cells in the mice expressed the protective gene for up to 10 months, with no signs of sickling.

Before researchers try these techniques in the clinic, they must solve a couple of difficult problems, say Leboulch and Nienhuis. They must prove that HIV-based vectors are truly safe. And they must find a good way to remove unhealthy stem cells from patients' bone marrow so that new, genetically engineered cells can take over. Currently, the unhealthy stem cells would have to be removed by exposing them to destructive radiation or chemotherapy—which are life endangering.

Leboulch's group is looking into ways of giving a competitive edge to treated stem cells, such as enabling them to resist chemotherapy. If such approaches prove safe, he believes, it might be possible to begin clinical trials within a few years.

–ELIOT MARSHALL

GENE THERAPY

Panel Reviews Risks of Germ Line Changes

A high-profile experiment using gene therapy to treat hemophilia B has been on hold for 3 months because of concerns that it might alter the inheritable, or "germ line," DNA of patients in the trial. Last week, those concerns got their first public airing at a meeting of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health. The session did not yield a clear decision, but several panel members indicated that they thought the research should be allowed to resume.

The study, led by molecular biologist Mark Kay of Stanford University, came under scrutiny in September after traces of DNA from the vector, based on adeno-associated virus, appeared in the semen of a volunteer (*Science*, 23 November, p. 1640). He is the first of nine to be enrolled. Kay and Elliott Grossbard, vice president for clinical research at Avigen Inc. of Alameda, California, which is sponsoring the clinical trial, told RAC that traces of vector were detected for 10 weeks in seminal fluid of the first volunteer. This had prompted concern that the vector could insert genes into the sperm during that time.

But one RAC member, neurobiologist Jon Gordon of Mount Sinai School of Medicine in New York City, said he believed the risks of germ line alteration are "extremely low."

On hold. Kay hopes his study will resume soon.

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