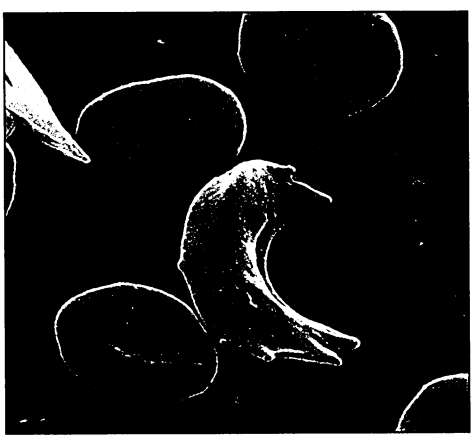
the other hand, what they write about the timing of [mammalian] divergences seems completely unreasonable." Like many others, Gingerich thinks the fossil evidence strongly suggests that mammals diversified most after dinosaurs went extinct, only about 65 million years ago. Molecular studies by other 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

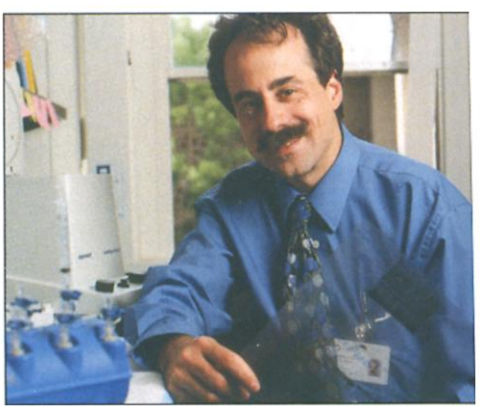
GENE THERAPY

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.

CREDITS: (TOP TO BOTTOM) MECKES/OTTAWA/PHOTO RESEARCHERS; BILL NATION

He and others pointed out that it is difficult for viral particles in blood to penetrate the nuclei of sperm, although they may more easily enter seminal fluid. And he noted that risks can be reduced easily by requiring subjects to use barrier contraception methods until all traces of the vector have disappeared. Other officials commented privately after the meeting that the Food and Drug Administration (FDA), which ordered the experiment to be put on hold, seems ready now to let it resume. But FDA almost certainly will ask the investigators to run more tests of germ line effects.

Kay interpreted the review as "reasonably favorable." So did Grossbard. But Grossbard noted a potentially big logistical problem. The first volunteer was given a low dose of the vector, and future volunteers who receive higher doses may take longer to clear the vector. If so, and if the FDA continues to insist that each patient be free of vector DNA for 3 months before the next is treated, Grossbard estimated that the time to complete a basic safety trial "may approach or exceed 5 years." He suggested that this was a heavy price to pay for "a very small theoretical risk."

Presenting FDA's concerns, agency scientist Stephanie Simek agreed that the risk was low but insisted that it is real. She also pointed out that the risk had not been flagged by preclinical animal studies and warned that there's a possibility that "all treated subjects" may test positive, at least initially. She then asked a provocative question: "Does the potential benefit of a [gene therapy] product outweigh the potential risk of developing a transgenic human?"

The most likely compromise, according to one observer who did not want to speak for attribution, may be to have the hemophilia B trial go forward as planned, but with a requirement that investigators collect additional sperm samples and analyze them "in a more timely fashion" than in the past.

–ELIOT MARSHALL

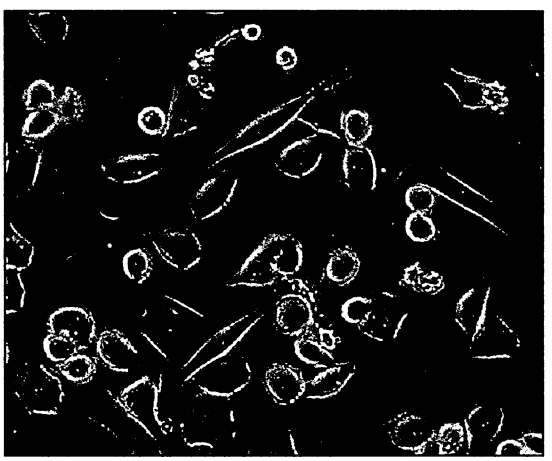
CARCINOGENIC BACTERIA

Cracking Gut Bugs' Cell-Skewing Strategy

Most of the bacteria that cause disease were tracked down long ago, but for decades one microbe got away with murder. Discovered in 1982, *Helicobacter pylori* infects two-thirds of the world's population; it causes ulcers and cancer that kill 7 million people each year (*Science*, 21 May 1999, p. 1328). Researchers have learned a lot about how the microbe digs into the wall of the stomach to cause ulcers, but they knew little about how the bug makes cells malignant—until now.

In a study published online by *Science* this week (www.sciencexpress.org), molecular oncologist Masanori Hatakeyama of Hokkaido University in Sapporo, Japan, and his colleagues have shown exactly how one of the bacterium's proteins hijacks a signaling pathway in stomach cells, pushing them to change shape and allowing them to move—an early step toward turning cells cancerous. "It's a major step forward," says cellular microbiologist Brett Finlay of the University of British Columbia in Vancouver.

H. pylori infections are about half as carcinogenic as smoking cigarettes: People infected with the bacterium are two to six times as likely as uninfected people to develop either gastric cancer, which is derived from cells in the lining of the stomach, or mucosal-associated lymphoid tissue (MALT) lymphoma, which is derived from immune cells that move to the stomach to battle the *H. pylori* infection. Researchers knew that when virulent strains of *H. pylori* infect the stomach lining, they cause stomach cells to elongate until they resemble hummingbird beaks. And virulent, but not benign, strains of the microbe inject a protein called CagA into the stomach cells, which then tag CagA with phosphate groups. Because tumor-causing viruses trigger cancer in part by spurring cells to add or remove phosphates from proteins, "I was wondering if such things also happen in bacterial infection," Hatakeyama says.



CREDIT: M. HATAKEYAMA

Haywire. By commandeering a signaling pathway, *H. pylori* causes cells to malform.

To find out, the researchers first made an educated guess about which human protein CagA interacts with once inside stomach cells. Others had shown that human cells treated with hepatocyte growth factor (HGF) also resemble a hummingbird beak and that HGF-treated cells tag a receptor protein with phosphates, much as occurs with CagA. The HGF receptor alters a signaling protein called SHP-2. Suspecting that this might be one more similarity between HGF and CagA, "we decided to examine if SHP-2 was involved with *Helicobacter*-induced morphological change," Hatakeyama says.

It was. Antibodies to CagA fished out SHP-2 and vice versa, suggesting that the two proteins team up inside the cell. What's more, cells infected with a mutated version of CagA that didn't bind SHP-2 no longer elongated into their characteristic shape.

Next, Hatakeyama's team asked whether CagA boosts SHP-2's ability to pass on signals. Ordinarily, cells send messages using a molecular bucket brigade. In HGF-induced signaling, SHP-2 is one of the recruits; it joins the HGF receptor and clips phosphates off other proteins. SHP-2 and CagA appear to form a similar complex: They team up only when CagA is phosphorylated, and SHP-2 clips phosphates from other proteins only when joined to CagA. That means CagA plugs into the normal cellular signaling system, Hatakeyama says, leading the cell astray and making it vulnerable to becoming cancerous.

Bacteriologist Stanley Falkow of Stanford University says the work "speaks to what must be an important event that predisposes [cells] to malignancy." But cell biologist Michael Naumann of the Max Planck Institute for Infection Biology in Berlin cautions that other signaling molecules probably help pass along the signal to elongate. Indeed, in work in press in *Molecular Microbiology*, microbiologists Rino Rappuoli, Antonello Covacci, and their colleagues at Chiron Corp. in Siena, Italy, identified two enzymes, c-Src and Lyn, that tag CagA with phosphates inside stomach cells. Many of the molecular links between *H. pylori* and cancer still remain to be discovered, Falkow emphasizes—but *H. pylori* investigators are closing in on their quarry.

–DAN FERBER

INDIA

New Report Tackles Wealth of Problems

NEW DELHI—The Indian government last week produced a harsh assessment of the state of science as part of a new draft statement on what's needed to help the country compete in a global economy.

"There is an urgent need to revitalize the scientific enterprise," declares the government's long-awaited draft of the Millennium Science and Technology Policy,* the first document of its kind since the country's independence in 1947. But its analysis should

* www.insa-india.org/newsdesk/sc-tc-pl.htm