without killing any of the mice. These results, Jacobs says, show that the mutated enzyme is not only critical to the ability of *M. tuberculosis* to cause disease but also to its ability to persist. "This is the first persistence mutant ever isolated," claims Jacobs.

Others question whether the gene is involved in persistence, partly because the mutant strains did not rapidly disappear in the mice after the initial stage of infection; thus, knocking out this gene did not dramatically cripple the bacterium's ability to persist. "It's an interesting gene, but I wouldn't consider it the crux of persistence," says Bishai.

But nobody is questioning the impact of the new technology for creating TB mutants, which Harvard's Rubin hails as "a huge advance." Indeed, Jacobs says that in the past 6 months his team has created about four times as many TB mutants (32) than have been published to date.

Both groups have more work to do in figuring out what role the genes they have identified might play in TB virulence and persistence. But in any new knowledge, there is hope. Says microbiologist Michael Mahan of the University of California, Santa Barbara: "The payoff is huge when you really understand a disease." —INGRID WICKELGREN

BIOMEDICAL ETHICS

HHS Plans to Overhaul Clinical Research Rules

Health and Human Services (HHS) Secretary Donna Shalala announced last week that the government intends to issue new guidelines and regulations designed to protect human subjects who participate in clinical trials. Curiously missing from the announcement, however, was the final word on a long-anticipated reorganization of HHS's framework for monitoring patient safety in clinical research.

The department is planning to appoint a "czar" who will run a new office in HHS that will coordinate efforts by 17 agencies to protect human research subjects. According to several sources, the job is being offered to Greg Koski, an anesthesiologist and director of human research affairs at Massachusetts General Hospital in Boston. But a deal had apparently not been consummated in time for last week's announcement, which came on the eve of congressional hearings on the topic, and the department was left proclaiming a new policy but not the person who will implement it.

> HHS needs "a world-class leader" ... from "outside the bureaucracy."
>
> —Donna Shalala

The announcement said HHS plans to ask Congress for civil penalties for lapses in obtaining informed consent from research subjects—up to $250,000 per clinical investigator and $1 million per institution. Both the National Institutes of Health (NIH) and the Food and Drug Administration are drawing up new guidelines on obtaining consent. HHS also plans an "aggressive effort" to train clinical investigators and members of Institutional Review Boards (IRBs) on the use of human subjects. And NIH intends to clarify its guidelines on conflict of interest to ensure that "any researcher's financial interest in a clinical trial [is] disclosed to potential participants."

As for the new czar, Shalala said earlier this month that the job will go to "someone who is experienced and is a world-class leader" but is from "outside the bureaucracy." That formula clearly ruled out one top candidate: Gary Ellis, the current director of the Office for Protection from Research Risks (OPRR), a small office at NIH that watches over institutions receiving federal money for clinical research. Ellis confirms that he will not go to HHS when the office moves but instead will be offered other employment at NIH. Under Ellis, OPRR experienced a sudden change of style. After being criticized in Congress in 1998 for not taking the initiative, OPRR came out with guns blazing over the past year and a half, shutting down half a dozen prestigious clinical research programs for noncompliance. Ellis's high-impact style may have cost him some support among university chiefs, observers say. But it also won praise. One leader in the field says Ellis "raised the public consciousness." He also got an endorsement from Representative Dennis Kucinch (D–OH), who said this month that Ellis's record was "the only bright spot" in a "dismal area" of federal oversight of human research subjects.

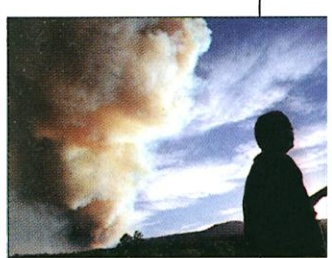
Koski—if he is the appointee—will clearly be wading into a contentious political job. An assistant professor who has spent the past 30 years at Harvard and Harvard Medical School conducting basic research, clinical medicine, and teaching, Koski declined comment.

One of the czar's first tasks will be to answer questions about federal monitoring of experiments such as the gene therapy trial in which an 18-year-old died last September (*Science*, 12 May, p. 951). The Senate public health subcommittee has scheduled a hearing on this case for 25 May. Meanwhile, a House Government Reform subcommittee, chaired by Representative

ScienceScope

Hot Air? When Congress ordered the federal government 4 years ago to sell off its massive helium gas stockpile by 2005, some scientists got a sinking feeling. They worried that the result could be shortages which would hamper a host of research-related technology efforts, from the development of fiber-optic cable to magnetic-resonance imaging systems. But a National Research Council report released this week says the end of the federal monopoly on the element is unlikely to affect users—in science or industry. Even so, the report calls for the government to explore new ways to locate supplies of the gas, improve storage systems, and search for substitutes.

Cash to Burn The wildfire that scorched the Los Alamos National Laboratory in New Mexico disrupted research and reduced some offices to rubble—but it may yield a hefty consolation prize from Congress. The Senate last week added $85 million to a defense spending bill to help the lab rise from the ashes that followed a controlled park-land burn that ran amok (above). The House is expected to follow suit.



CREDIT: AP PHOTO/THE NEW MEXICAN, S. POYNTER

The lab's 7000-person workforce is "almost completely" back on the job after 2 weeks off, says associate lab director Tom Meyer. And despite the destruction of dozens of employee's homes and about 30 chemistry offices in temporary trailers, officials say fears of harmful releases from stored waste have so far proven unfounded. Spectrometers and other equipment are still being checked for smoke damage.

Meanwhile, lab officials are making recovery plans, including how to spend $26 million for environmental restoration that is part of the defense bill. First on the agenda are measures to handle excess runoff from denuded watersheds, which could be hard hit by approaching "monsoons." Still, fire damage may pale in comparison to the wounds—in morale and hiring—inflicted by recent allegations of Chinese spying at the lab. Says physicist David Campbell of the University of Illinois, Urbana-Champaign, former head of the lab's Center for Nonlinear Studies: "The spy stuff was much more devastating."

John Mica (R–FL), is asking HHS to respond to criticisms from its own Office of Inspector General. Testifying before Mica's subcommittee on 3 May, HHS Deputy Inspector General George Grob called for "a greater sense of urgency" in improving the oversight of clinical research. He said that IRBs, in particular, need more resources.

"There's going to have to be a much greater investment in IRBs," agrees LeRoy Walters, director of the Kennedy Institute of Ethics at Georgetown University in Washington, D.C. "We have not modernized the research oversight system in the same way that we have modernized the research itself." Creating the new office at HHS and establishing an outside advisory panel is "a step in the right direction," says Walters. But he cautions that even this may not be enough: Ultimately, he says, an independent clinical research monitoring agency may be necessary.

Ralph Snyderman, president and CEO of the Duke University Health System, agrees that reform is needed, even if it costs more initially to beef up the IRBs, because "protecting human subjects may be the most important thing we do." He hopes the federal government will help pay for the cost. But he's "not passionate" about the idea of creating a new independent agency. His advice to the new czar: Begin by taking stock of OPRR's existing regulations and methods and consider "whether they are doing what they're supposed to do." **–ELIOT MARSHALL**

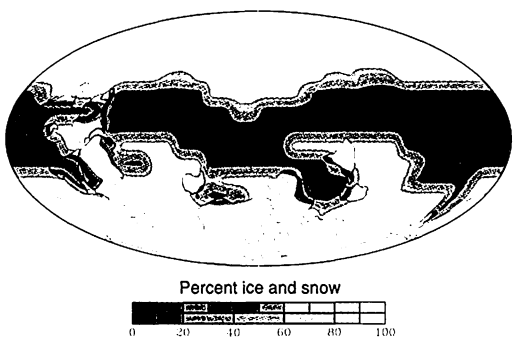
CLIMATOLOGY

A Refuge for Life on Snowball Earth

When a small group of geoscientists recently revived the snowball Earth hypothesis—the idea that the planet froze from pole to pole 600 million years ago—some scientists raised serious doubts. Although geologists have found evidence of extreme glaciation at that time, the paleontological record shows that complex life passed through unscathed. How could early life have weathered such a horrendous environmental catastrophe without suffering a mass extinction (*Science*, 10 March, p. 1734)? How could algae and perhaps even early animals have survived 10 million years sealed off by globe-girdling ice? Now climate modelers say that their most realistic models offer a possible resolution of the conundrum: In the tropics, climatic amplifiers built into clouds, winds, and currents may have counteracted the chilling effect of ice and snow.

Modelers trying to simulate the world of the Neoproterozoic era 600 million years ago are finding that the more realistic the climate model, "the harder it is to create climate change," says Mark Chandler of NASA's Goddard Institute for Space Studies (GISS) in New York City. "We've used the most realistic [model] boundary conditions to date, and we have not been able to freeze over the planet."

Work by Chandler and other modelers contradicts the so-called "White Earth solution" that climate modeler Mikhail Budyko of the Leningrad Geophysical Observatory came across in the 1960s. Working with the simplest possible climate model—a one-dimensional rendition of incoming solar radiation and Earth's outgoing radiation—Budyko found that if the planet's ability to retain heat through its carbon dioxide greenhouse were to weaken for any reason, then white, highly reflective snow and ice would creep toward the equator. The farther it got, the more solar radiation it would reflect back into space, further cooling the planet. If the sun were dimmer than today (it was about 6% dimmer in the Neoproterozoic), this albedo feedback effect would eventually take over, the ice and snow would rush across ocean and continent to the equator, and Earth would be locked in a snowball.



Not quite a snowball. A climate simulation of Earth 600 million years ago ices over low-latitude continents but not the tropical ocean.

In a paper appearing this week in *Nature*, paleoclimate modeler William Hyde of Texas A&M University in College Station and his colleagues report results for the Neoproterozoic from a more complex, two-dimensional version of Budyko's energy balance model. The model is coupled to a second one that can grow ice sheets on land, which in turn can affect climate. When greenhouse carbon dioxide is cut to half its concentration today—say, because unusually severe weathering of continental rocks sucked carbon dioxide out of the atmosphere—Hyde's model planet ices over, just as Budyko's did.

Albedo, however, is not the only feedback in the real world. Some loops work the other way, resisting cooling rather than reinforcing it. So Hyde and his colleagues had their model mimic one negative loop previously missing: the tendency for cooler temperatures to reduce the cloud cover and let in more warming sunlight. Even with the negative feedback, some tropical continents still iced over—consistent with geologic evidence of continental glaciation at low latitudes in the Neoproterozoic. But open water remained in the tropical oceans—a potential haven for life. "You could have open water," says modeler Thomas Crowley, Hyde's A&M colleague, "but we want to do more simulations" to tease out just which feedbacks are most important.

Simulations by other scientists confirm that the more realistic the model, the harder it is to freeze over the planet. Chandler and geologist Linda Sohl of Columbia University's Lamont-Doherty Earth Observatory in Palisades, New York, will soon report in the *Journal of Geophysical Research* that a GISS general circulation model (GCM) also leaves tropical waters open while icing over tropical continents. Unlike the A&M energy balance model, a GCM has an atmosphere as realistic as those used in weather forecasting as well as a simplistic ocean. "We kicked the model very hard" with a faint sun and greatly weakened greenhouse, says Chandler, "and it doesn't even come close to freezing over. The geologic record is doable with reasonable conditions for this time period."

Using an even more complex model, Raymond Pierrehumbert and Christopher Poulsen of the University of Chicago found that the model's ocean can also be crucial. "We can get Earth to freeze easily with a slab ocean," he says, referring to a model ocean devoid of currents. "But when we have a real ocean model, it transports enough heat [in currents] to the ice margin to hold the ice off."

Although these early modeling results are far too preliminary to prove that life would have had a refuge in any Neoproterozoic ice age, they offer some comfort to paleontologists. They're only models, says Guy Narbonne of Queen's University in Kingston, Ontario, "but what I find exciting is that [the A&M model] explains the geological relationships [such as low-latitude glaciation] and permits some of the things we see in the paleontological record." On the other hand, snowball proponents remind modelers that open ocean waters shouldn't be carried too far. "You can't have the whole tropical ocean open," says geochemist Daniel Schrag of Harvard University. "There's good evidence in the geological record that the ocean was sealed off or close to it." Even guessing how close will take more runs of more sophisticated models with more accurate Neoproterozoic conditions. **–RICHARD A. KERR**

SOURCE: M. CHANDLER AND L. SOHL/NASA GISS AND LAMONT-DOHERTY EARTH OBSERVATORY