150th Bash Draws a Crowd

From 12 to 17 February, some 5400 people descended on Philadelphia for the annual meeting of the American Association for the Advancement of Science (AAAS, which publishes *Science*), celebrating its 150th anniversary this year. President Bill Clinton addressed a packed hall, unveiling Neil Lane as his next science adviser and Rita Colwell as the next NSF director (*Science*, 20 February, p. 1122). But there were more reasons to celebrate: symposia on everything from the earliest Americans to martian life-forms, two of the topics featured in this special news section.

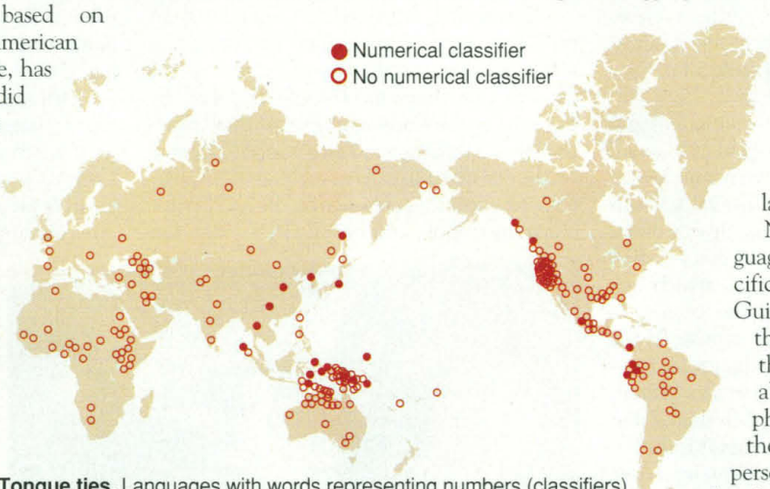
Mother Tongues Trace Steps of Earliest Americans

When several prominent archaeologists reached a consensus last year that humans lived in South America at least 12,500 years ago, their announcement struck a lethal blow to what had been a neat picture of the peopling of the Americas—that the first settlers were big-game hunters who had swept over the Bering land bridge connecting Asia and North America about 11,000 years ago. But this revised view of prehistory, based on 2 decades of study of the South American site called Monte Verde in Chile, has spawned a new mystery: When did the ancestors of Monte Verde's inhabitants first set foot in North America? Archaeologists trying to address that question have come up empty-handed, as there are few reliably dated digs in America older than the Chilean site.

At the AAAS meeting, however, a possible answer emerged from another field—linguistics. Using known rates of the spread of languages and people, Johanna Nichols, a linguist at the University of California, Berkeley, estimates that it would have taken about 7000 years for a population to travel from Alaska to Chile. Because that would put the first Americans' arrival squarely in the middle of the last major glacial advance, Nichols proposes that "the first settlers began to enter the New World well before the height of glaciation"—earlier than 22,000 years ago.

That date is early but is in accord with recent genetic studies suggesting that the diversity of DNA across American Indian populations must have taken at least 30,000 years to develop (*Science*, 4 October 1996, p. 31). In addition, Nichols's extensive analysis of Northern Hemisphere languages also suggests that several groups of Asians entered the New World, where they adapted rapidly to a range of habitats and adopted diverse ways of hunting and gathering.

This picture is winning favor with linguists. "I believe that her general analysis of the linguistic situation in the Americas is essentially right," says linguist Victor Golla of Humboldt State University in Arcata, California. "We need a much longer period of diversification among American linguistic stocks than the 11,500 years" allowed by the old view, he says. And although not totally embracing the linguistic findings, archaeologists acknowledge that, combined with other recent findings, Nichols's results indicate that the old, simple view of the peopling of the Americas is dead. "The bottom line," says University of Kentucky, Lexington, archaeologist Tom Dillehay, who excavated Monte Verde, is that "the picture is a lot more complex than it was."



SOURCE: J. NICHOLS

Tongue ties. Languages with words representing numbers (classifiers) circle the Pacific Rim, suggesting they arose from the same ancestors.

To try to get a better fix on how long it would have taken people entering the New World to get to Monte Verde, Nichols surveyed 24 language families that had spread over vast distances, such as Eskimoan languages that traveled from Alaska to Greenland and Turkic tongues that migrated from Siberia to central Europe. She found that the fast-moving languages that spread on foot—the only way the first American settlers could travel—moved 200 kilometers per century on average.

With this yardstick, Nichols calculated that even if early Americans made a beeline, taking the shortest routes over the 16,000 kilometers of varied terrain from Alaska to southern Chile, the trek would have taken at least 7000 years. This would have put the Monte Verdeans' ancestors in Alaska when glaciers made it "probably impossible" to enter the continent, she says. Instead, Nichols argues, the evidence "strongly suggests" a migration before a major glacial advance began 22,000 years ago.

Nichols checked her result against those obtained by other methods. For example, the New World has 140 language families—almost half of the world's total—and she estimated how long it would have taken this rich diversity of tongues to develop. Nichols began by surveying nearly all the language families of the Northern Hemisphere, from Basque to Indo-European, to see how often new language families have split off from an ancestral stock. She found that, on average, 1.5 new language families arose in each ancestral stock over the last 6000 years. Plugging that rate into computer models—which included an allowance for new migrations that carried in new languages after the glaciers retreated—yielded 40,000 years as the minimum time required to produce so many language families.

Nichols also found that languages along the coasts of the Pacific Rim, from Papua New Guinea north to Alaska and then down the west coast of the Americas, share a remarkable set of grammatical and phonological features, such as the sound "m" in the second-person pronoun (the singular "you" in English), verb order, and numerical classifiers—words used in some languages when a number modifies a noun (see map). These features set apart the coastal language families from those farther inland, indicating that coastal tongues were probably imported by later settlers.

These kinds of features prompted Nichols to propose the following scenario: The first immigrants from Asia crossed the Bering land bridge "well before" 22,000 years ago and made it to South America. After the glaciers retreated, some people spread north, where they gave rise to the Southwest's Clovis culture, perhaps, and to other peoples. Meanwhile, human beings were again on the move along the Pacific Coast in Asia, with some language families heading south to Papua New Guinea and others north over the land bridge into Alaska—where they could have crossed once

the ice sheets melted 12,000 years ago. Yet another group arrived at least 5000 years ago, she argues, giving rise to the Eskimo-Aleut family of languages.

These early dates from linguistics and genetics are prompting archaeologists to reexamine and take more seriously their earliest sites of human occupation, including possible signs of a human presence at Monte Verde as early as 33,000 years ago, says Dillehay. "These findings of great antiquity from linguistics and genetics help us out, but in the end, we have to get the actual time dimension from the archaeological record." To linguists, however, a thousand words are worth a fossil.

–Ann Gibbons

Gene Diversity Muddles Heart Disease Story

The genetics of heart disease is about as simple as a bureaucrat's flow chart: At least 50 genes are thought to play some role in the disease, and the significance of known mutations appears to depend in part on an individual's ethnic background. But now the picture is more muddled—and for clinicians, perhaps more depressing—than ever. Findings reported at the meeting suggest that healthy people have such widespread variation in one candidate heart disease gene that it is virtually impossible, for now, to tease out mutations that increase risk of the disease.

Pennsylvania State University population geneticists Kenneth Weiss and Andrew Clark and their colleagues examined one region of a gene coding for a protein called lipoprotein lipase. LPL is an enzyme that can reduce blood levels of certain fats linked to heart disease, so researchers have speculated that some variants of LPL could raise the risk of heart disease. But the Penn State team also found a high degree of variation in the gene among healthy people from three different ethnic groups. Such variability "makes it more difficult to figure out which [mutations] are causal and which are just evolutionary noise," says Trudy Mackay, a population geneticist at North Carolina State University in Raleigh. If similar variability turns up in other candidate genes now being studied, Weiss adds, geneticists may have a hard time designing simple genetic screens for the disease.

The finding emerged from a project to sequence 15 candidate heart disease genes, among them LPL, from thousands of healthy people. The project leaders—who also include Charles Sing at the University of Michigan, Ann Arbor, and Debbie Nickerson at the University of Washington (UW), Seattle—hope to decipher the widespread public health impact of the presence of different variations in these genes in the general population. The DNA came from healthy individuals of three disparate backgrounds: Finns from North Karelia, Finland, mixed Europeans from Rochester, Minnesota, and African Americans from Jackson, Mississippi.

In the first stage of the project, Nickerson and her UW colleagues sequenced a 10,000-base-pair region of LPL from 72 people, 24 members from each group. The researchers found variation at 88 sites along the sequence. Compared to a reference gene sequenced earlier, each individual varied at an average of 17 sites. Each group had some unique variable sites.

But in spite of the individual and ethnic variations, each sequence seemed to fall into one of two families of related variants, present in a 3-to-2 ratio in all three groups. The families, said Weiss, must have arisen "deep in human history and have been maintained in a diversity of human populations." Multiple forms of a gene usually persist because individuals who inherit two variants gain some type of adaptive advantage. That's the case, for example, with the sickle cell anemia gene, which confers protection against malaria. But "we have no idea" what the corresponding advantage of LPL variability might be, Weiss says. Random mutations might account for a misperception that there are two gene families, he points out. Hoping to settle the question, his team is now sequencing LPL genes from another ethnic group, Native Americans, to see if the two gene families show up in this population as well.

SUPERSTOCK

Genetically too diverse? High background variation in genes may make it hard to screen for heart disease risk.

Whatever the cause of this variation, says Weiss, "the bottom line is that there is a lot of variation in human genes." This, he says, will undoubtedly slow efforts to sort out the key genetic mutations that cause heart disease in individuals or specific ethnic groups.

–Robert F. Service

10-Gallon Molecule Stomps Tumors

Fourteen years ago, Jonathan Sessler set out to make a bigger version of porphyrin, a four-leaf clover–shaped pigment that ferries iron and other metals in the blood. Tinkering with the molecule could have a big payoff, because porphyrin mysteriously tends to pack inside tumor cells. Sessler thought that supersizing porphyrin might enable the molecule to lug larger cargo, such as a cancer drug, into a tumor cell. And there was another, lighter reason for pumping up porphyrin: "Everything is bigger in Texas," says Sessler, a chemist at the University of Texas, Austin. State pride was at stake.

At the AAAS meeting, Sessler unveiled the fruits of his effort: a porky porphyrin, suitably named texaphyrin, able to deliver heavy metals to tumors. In pilot trials, the new molecule has shown promise in enhancing the effects of radiation on inoperable brain tumors, and it is winning raves from cancer experts. "They're fascinating compounds," says Percy Ivy, a pediatrician at the National Cancer Institute (NCI), whose "unique properties are intriguing to us." NCI has chosen texaphyrins as part of its Decision Network—a group of what it considers to be the most promising therapies.

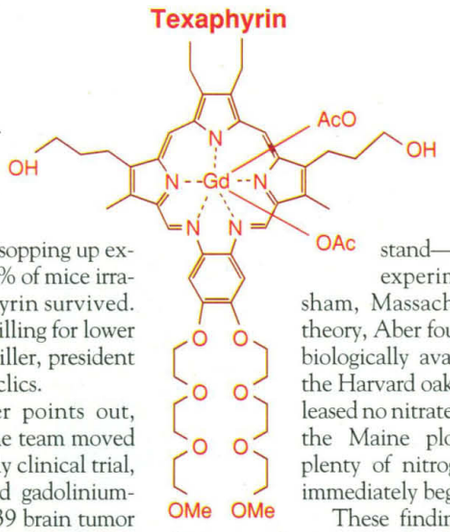
The road to texaphyrin wasn't easy. After months of fruitlessly trying to make the molecule, Sessler says, "everybody urged us to give it up." Then one day a postdoc picked up a forgotten test tube in which the element cadmium had been used to try to stabilize the molecule's lobes. "In retrospect, we should have known that cadmium would work," Sessler says. Analyzing the residue, he found that he and his coworkers had in fact synthesized a new five-lobed porphyrin shaped like the star on the Texas flag. Celebrating that evening, Sessler penned a whimsical note announcing the discovery of the molecule to the state legislature. Last year, he says, he received a Texas-sized thanks: "They sent me a $150,000 check to continue research."

This new, larger molecule had an increased appetite for electrons, which Sessler hoped would make it useful in radiation therapy. Radiation breaks down water inside cells into electrons, protons, and uncharged hydroxyls—an electron-hungry version of the free radical that kills cells by stripping electrons from DNA. If texaphyrins could sop up excess electrons, Sessler hoped, the hydroxyls would have a free hand at killing tumor cells. Because texaphyrin has a 20% larger carrying capacity than porphyrin does, Sessler was able to attach to it an atom of the heavy metal gadolinium, which is visible by magnetic resonance imaging (MRI).

To test whether the gadolinium-laden texaphyrins find their way into tumor cells as porphyrins do, Sessler and colleagues at Pharmacyclics in Sunnyvale, California, used MRI to scan cancerous mice before and after a texaphyrin injection. The scans indicated that texaphyrin found its target: The mouse tumors

SOURCE: J. SESSLER

glowed bright white for several days after an injection. After irradiation, the tumors decreased or disappeared altogether. About half the mice survived the 140-day study, Sessler says, suggesting that texaphyrin was indeed sopping up excess electrons. Only 10% of mice irradiated without texaphyrin survived. "We should get more killing for lower doses," says Richard Miller, president and CEO of Pharmacyclics.



Because, as Sessler points out, "mice are not men," the team moved on to people. In an early clinical trial, Sessler's group injected gadolinium-laced texaphyrin into 39 brain tumor patients 2 hours before radiation therapy for a period of 10 days. The patients, who were expected to live only 2 to 4 months, survived on average 188 days. Those in the highest dose group survived almost a year, on average. "There are people alive who would ordinarily be dead," Sessler says.

–Amy Adams

Amy Adams is a science writer in Santa Cruz, California.

Holding a Nitrogen Grudge

Philosophers may still debate whether people are prisoners of their pasts, but many ecologists are now convinced that forests are captives of a biochemical memory in the soil that nourishes them. At the meeting, researchers presented provocative new evidence suggesting that land use decades ago dictates how forests today absorb and release nutrients.

John Aber, a biogeochemist at the University of New Hampshire, Durham, described how unexpected results from a study of New England forests prompted him to brush up on local history. In 1989, Aber began to probe why some forests stockpile nitrogen compounds, absorbing these crucial nutrients and storing them up in leaves and stems, while others discharge them into ground water. Aber hoped his work might help researchers predict which forests will leak nitrate—a potentially toxic drinking water pollutant. The work could also help identify which forests might be harmed by storing too much nitrogen, now being pumped into the environment in unprecedented amounts by fossil-fuel burning and fertilizer use.

When Aber began his study, the conventional wisdom was that forests near cities, where nitrogen deposition is high, were like saturated sponges: Adding more nitrogen would produce more nitrate leaks. Unpolluted forests, however, were considered less saturated and able to soak up more nitrogen. To test the idea, Aber added nitrogen to a relatively pristine deciduous forest plot near Orono, Maine, and to two "saturated" plots—a pine grove and an oak stand—in Harvard University's experimental forest in Petersham, Massachusetts. Contradicting theory, Aber found that even when the biologically available nitrogen load of the Harvard oak stand was tripled, it released no nitrate for 8 years. Meanwhile, the Maine plot—predicted to have plenty of nitrogen storage capacity—immediately began leaking.

These findings also defied another prediction: that deciduous forests should take up and use more nitrogen than evergreen groves, because deciduous trees need the element to grow a fresh crop of leaves each spring. The Harvard forest's oak stand, however, used less nitrogen than did its pine grove. "The results were a really big surprise," Aber says.

Aber then sought an explanation in the history books. He realized that the Harvard evergreens grew on a century-old crop field that had been regularly plowed and fertilized with manure, which enriched the soil with nitrogen. But the nearby oak stand had been cut periodically and burned by wildfires. "Land use explains the results," he says. "The pine forest is like a saturated sponge, so it produced more nitrate. But the oak plot was squeezed hard, the nitrogen depleted by harvest and fire." That explains why the oak stand stored more nitrogen than did the pine grove or the similar deciduous plot in Maine, which had not suffered such a disturbance.

The findings suggest that land-use history deserves the increased attention it is starting to get in ecology, says Scott Bailey, a biogeochemist with the U.S. Forest Service's Northeast Research Station in Durham, New Hampshire. Adds Aber: "We have too long underestimated the fact that the landscape has a very long memory."

–David Malakoff

David Malakoff is a writer in Bar Harbor, Maine.

Prodding Cells to Make Proteins

Like polite passengers on a jammed airplane, cells in tissue culture avoid taking up more space when they brush up against nearby cells: They stop growing. How cells translate a neighbor's touch—and other mechanical forces—into biochemical signals has long mystified scientists, however.

At the AAAS meeting, Donald Ingber of Children's Hospital and Harvard Medical School in Boston offered new insight into this puzzling process. He and his colleagues have observed cells hastily setting up protein factories after their internal skeletons are pulled or twisted by forces applied to their surfaces. The findings, in press at *Nature*, could lead to a better understanding of how cells grow differently under microgravity and may also aid researchers trying to create better artificial tissues such as blood vessels and, eventually, entire organs.

Ingber has long championed the idea that the cell's internal skeleton is an intricate tension-bearing system that translates forces through the cell. His team had shown in previous work that tugging on particular parts of the cell's surface can rearrange the nucleus, causing structures called nucleoli to line up (*Science*, 2 May 1997, p. 678). The latest experiments "take that a step further," says cell biologist Michael Sheetz of Duke University Medical Center, showing that mechanical forces on the cell's internal skeleton directly influence protein assembly.

To probe a cell's response to mechanical forces, the scientists coated magnetic beads with fibronectin, a protein that specifically attaches to integrin receptors—cell surface proteins that reach through the cell membrane to the cell's internal skeleton. They allowed the beads to attach to receptors on human endothelial cells, which line blood vessels. As soon as the cells bound to the beads, they set up what Ingber calls "microcompartments" for protein synthesis—regions near the integrin receptor in which ribosomes and other protein-synthesis molecules were observed to gather. Applying a magnetic field that twists the beads recruited more protein machinery, whereas chemicals that disrupt cytoskeletal tension inhibited the recruitment. In another set of experiments about to be submitted for publication, Ingber and his colleagues found that twisting the integrin receptor also revs up the production of proteins in the cell nucleus that help to regulate gene expression, while tugging at other receptors had no such effect.

The work demonstrates one way that cells might sort through multiple competing signals, Ingber says. For example, although groups of cells or tissues may be exposed to the same set of growth factors, only those cells under a certain amount of tension might respond, he says. The work could have practical implications as well. For instance, understanding how a lack of gravity affects internal cell tension will be crucial for studying cell growth in space, says Peter F. Davies of the Institute for Medicine and Engineering at the University of Pennsylvania. In addition, he says, the work could help bioengineers design better scaffolding to support artificial tissues.

–Gretchen Vogel

Preventing a Mars Attack

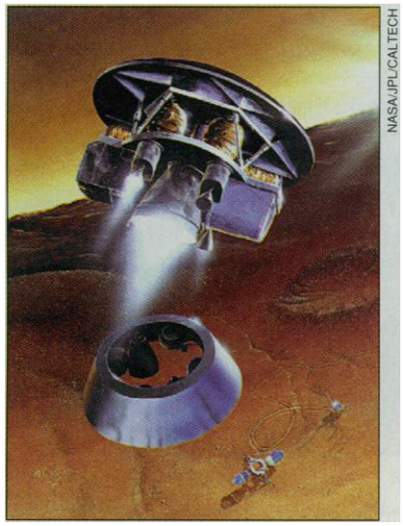
The supposed nanofossils riddling the famed meteorite from Mars may seem harmless enough, but consider this nightmare scenario: What if the next rock to arrive from Mars carries live martian microbes able to infect and decimate plants, animals, or people? Such fears, however remote, are high on the agenda at NASA, which is preparing a $500 million mission that would bring about 0.5 kilogram of martian soil and rocks back to Earth in 2008. At the meeting, scientists and NASA officials outlined their plans for containing any unwelcome visitors lurking in martian samples.

Nobody disputes the scientific benefits of bringing a chunk of Mars to Earth. Remote robots can't perform all the analyses scientists are eager to do, and it's unlikely they could settle the big question: Did Mars ever harbor life? "We'll never be satisfied until we bring a rock back, crack it open, and say 'Aha!'—or not," says Wesley Huntress, NASA's associate administrator for space science.

But when that rock arrives 10 years from now, it will get a reception worthy of the Ebola virus. No stranger to biosafety, NASA in the 1960s set up a quarantine lab for the astronauts on the Apollo 11 to 14 moon-landing missions and the roughly 100 kilograms of lunar material they brought back. Many scientists deemed these precautions superfluous—the moon seemed as dead as a celestial body could get—so they were dropped on later moon missions.

Now, the stakes are higher. Tougher environmental regulations governing imported materials, and the meteorite nanofossils found last year, however controversial, are making NASA think hard about protecting earthlings from any martian bugs. There's also a strong scientific argument for a quarantine: Without it, earthly microbes could contaminate the sample, complicating the search for extraterrestrial life.

At the meeting, Jonathan Richmond sketched how NASA plans to handle such samples. Richmond is director of the Health and Safety Office at the Centers for Disease Control and Prevention (CDC) and a member of NASA's Mars Sample Containment Protocol Subgroup. At the landing site on Mars, he said, robots will scoop up a sample "about the size of a baked potato" and place it in a double-layered canister that will be hermetically sealed and sterilized on the outside before leaving Mars.



NASA-JPL/CALTECH

Red alert? Bringing martian sample home in 2008 could be perilous.

If the canister should break or leak on the flight home, its contents will be sterilized, or the ship may be redirected from Earth.

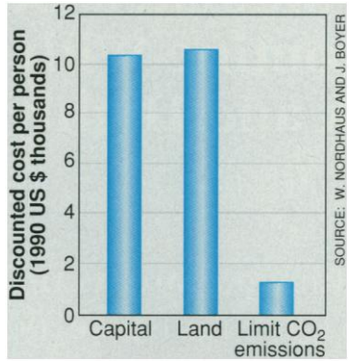
Upon arrival, the canister will be taken to a planned Mars Receiving Laboratory and placed in a low-pressure biological safety cabinet or "glove box." The outer shell, which by then would be considered contaminated by Earth, will be resterilized. Scientists will sample the Mars atmosphere between the shells, after which the outer shell will be stripped off and the inner one moved to a second glove box. There, the last barrier will be broken and the sample studied.

As elaborate as these precautions may seem, no one can guarantee they will suffice. For one thing, nobody knows what steps might be needed to contain an extraterrestrial bug. "One can read *The Andromeda Strain* and get ideas about totally different microbes that can dissolve rubber and glue," Richmond admits. "If that's the case, we'll have to have some pretty good disinfectants available." To most scientists, however, that scenario seems farfetched. The chances of finding anything living are remote, and the likelihood of martian critters posing a health threat is "very, very slim," contends microbiologist Rita Colwell, tapped earlier this month to head the National Science Foundation. The most important rationale for biocontainment, she says, is to protect the sample—not the planet—from contamination.

But society might see things differently, warns ecologist Margaret Race of the Search for Extra-Terrestrial Intelligence Institute in Mountain View, California. "Complete openness" about the risks and uncertainties of the mission will be essential, she noted—but even that will probably not prevent news stories warning of martian bugs on the rampage. "We can guarantee that the *National Enquirer* is going to love this one," she says.

–Martin Enserink

Martin Enserink is a science writer based in Amsterdam.



Per capita. Population growth may jack up societal costs by 2200.

Population Growing Pains

Does adding more people to the planet make society any worse off? Lately economists have tended to reject gloom-and-doom scenarios of impending environmental catastrophe, concluding that population growth should only slightly perturb living standards. At the meeting, however, two economists unveiled a new analysis suggesting that more people do impose a cost on society—one that could run thousands of dollars a head. If the analysis holds up in this hotly debated area of economics, the results could be "extremely important," says population biologist Joel Cohen of Rockefeller University in New York City. "It makes clear the interest of the present generation in slowing population growth."

Economists William Nordhaus and Joseph Boyer of Yale University took a fresh look at the old question of how population growth might affect a country's economic well-being. They used global data for 13 regions on gross domestic product, capital, and population from the 1960s to the 1990s to project the costs to society of each additional person, years into the future. The team went a step further than other economists have by estimating, for the first time, the economic costs of a slightly warmer planet as each person's activities spew out more greenhouse gases. Also unlike previous models, the researchers analyzed how parental decisions about family size might affect the economic well-being of not just the current generation but future generations, through the 22nd century.

That approach "makes all the difference in the world," Nordhaus says. When the duo counted only the cost to the current generation in their model, the net cost to society per extra person was close to zero. But when they included eight or so subsequent generations, the net cost per additional person soared to about $100,000 in the richest countries and $2500 in developing countries, for example in sub-Saharan Africa. Most of these costs arose from diminishing returns as land and capital were divvied up among descendants. The portion of the cost due to increased greenhouse gases was surprisingly small, Nordhaus says—only a few percent.

Because there are many uncertainties in the model, such as the economic toll of global warming, Nordhaus says he'd like to spend the next few years refining the model before he'll be ready to "make earth-shattering pronouncements." But if it holds up, experts say, it may add incentive for countries to adopt policies that encourage people to have smaller families.

–Jocelyn Kaiser