MEETING BRIEFS

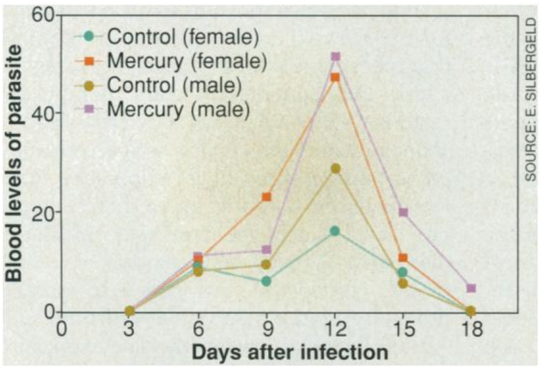
Toxicologists Shed New Light on Old Poisons

SEATTLE—Nearly 5000 scientists flocked here earlier this month for the Society of Toxicology's largest ever annual meeting. While the elements outside were cool and rainy, the elements indoors were hot: One presentation suggested that mercury exposure might increase malaria risk, and a symposium offered new insights into an old enigma of how arsenic causes cancer.

A Mercury-Malaria Link?

The gold rush now under way in developing countries from the Philippines to sub-Saharan Africa and Brazil has wreaked environmental havoc—and a toxicologist's nightmare. The often crude processes used to extract gold from sediments can expose workers to heavy doses of the element mercury, a neurotoxin. At the meeting, researchers discussed hints from animal studies that along with its known risks, mercury may also be lowering workers' immunity to malaria.

Millions of people are now employed in gold-mining operations in the tropics, and statistics from Brazil show that mining areas are malaria hot spots: Nearly 80% of cases occur in three Amazonian states with intensive mining. Prosaic factors such as standing water near mines—breeding grounds for mosquitoes that transmit the disease—may be contributing to the outbreaks. But another possible factor that has been overlooked until now, says Ellen Silbergeld of the University of Maryland School of Medicine in Baltimore, is the effect of mercury on the immune system.



As mercury rises, immunity falls. Exposed mice were hit hard by *Plasmodium yoelii* malaria strain.

One widespread mining process involves mixing sediments with mercury to extract clumps of gold-mercury amalgam, then evaporating the mercury, leaving the gold behind. In blood and urine samples from workers in the Brazilian state of Para, Silbergeld's group and collaborators in Brazil last summer detected mercury levels up to 100 micrograms per liter, five times the level at which adverse effects are seen in people, according to the World Health Organization. Mercury exposure is well-known as a trigger for the immune system to attack the body's own tissues, leading to kidney failure, and it has been shown to skew levels of the immune system's T helper cells, increasing the numbers of some kinds of T helper cells and decreasing others.

To probe for a link between mercury and malaria, Silbergeld's group turned to mice used in malaria studies by the University of Maryland's Abdu Azad. Silbergeld's team injected two strains of mice with mercury chloride or a saline control over 11 days, giving low enough doses so that the mercury-treated animals had no weight loss or other overt signs of toxicity. Next, the researchers injected the mice with a nonlethal strain of malaria. After 12 days, when parasite blood levels peaked, mice exposed to mercury harbored up to five times more parasites than controls did, they found. "We saw that [exposed mice] had a substantial reduction in their resistance to malaria," Silbergeld says.

The study is "suggestive but not decisive," says immunotoxicologist Allen Silverstone of the State University of New York, Syracuse. The researchers need to offer a cellular explanation of how mercury might lower an organism's defenses against malaria, he says. Silbergeld says her group plans to study the question and also investigate whether mercury lowers resistance to cholera and other pathogens as well.

Clues to Unsolved Arsenic Case

In Agatha Christie stories, a sip of an arsenic-laced cocktail means instant death. But arsenic also acts more insidiously. As far back as 1888, physicians noticed that some people who ingested an arsenic-based skin tonic later developed skin cancer. Arsenic has since gained a fearsome reputation as a carcinogen, which has led the Environmental Protection Agency (EPA) to propose drastically tightening the U.S. standard for arsenic in drinking water. Yet how chronic arsenic exposure causes cancer has remained a century-old mystery. And in a plot twist that has only deepened the puzzle, it seems that just people—not lab rats—get cancer from arsenic.

But now toxicologists finally have some solid leads as to how arsenic may do its dirty work. At the meeting, scientists reported that various mammal species—and possibly some human populations—differ sharply in how they metabolize arsenic. The finding suggests that certain individuals may be genetically predisposed to the element's toxic effects. Researchers also presented evidence that arsenic may turn cancer genes on or off by interfering with a key gene-regulatory process called DNA methylation.

Picture of health. These Chilean villagers drink arsenic-laced water, yet don't have elevated cancer rates.

While the lack of an animal model for arsenic toxicity has hindered research, lately it has turned up clues to the mystery. In general, humans and other mammals defang inorganic arsenic compounds—arsenate or arsenite, the forms usually found in ground water—by adding methyl groups to make two compounds thought to be less toxic, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). But researchers now realize that this methylation may be a double-edged sword. While tacking on methyl groups may protect against arsenic's immediate toxic effects, it could also explain why chronic arsenic exposure can lead to cancer.

Hints of a link between how people metabolize arsenic and cancer come in part from Vasken Aposhian's group at the University of Arizona, Tucson, which has found that the activity of a family of enzymes that catalyze these reactions, arsenite methyltranferases, varies widely across mammalian species. Aposhian says that unlike other mammals that convert arsenic to MMA and DMA, South American mammals like the marmoset and guinea pig convert little or none of the element to methylated forms. He suggests in an article in press at *Environmental Health Perspectives* that these species might have evolved an alternative way to tolerate inorganic arsenic in the blood—perhaps by binding it to proteins.

Intriguingly, people may have the same geographic split in their ability to detoxify arsenic. Aposhian's team has been studying a group of indigenous villagers in Chile, who for thousands of years apparently have been drinking water laced with dangerous levels of arsenic, but who have no signs of cancer. Aposhian hopes to isolate some of the group's arsenic-metabolizing enzymes from lymphocyte samples. It's "fascinating stuff," says the National Institute of Environmental Health Sciences' Michael Waalkes, who says some populations may have a genetic variant that causes them to metabolize arsenic differently. That could explain why people exposed to arsenic in Chile and other geographic regions, such as Mexico, seem to be less susceptible to arsenic-related cancers than are Taiwanese and Indians, Waalkes says.

A possible link between arsenic methylation and cancer fits squarely with a booming research area: the role of methylation in switching on or off cancer-related genes. When cells add methyl groups to arsenic, they deplete a compound called SAM that's needed to methylate DNA and tag genes that should be turned off. If the pool of SAM is depleted by arsenic, that might hinder the cell's ability to control gene expression, says Waalkes. His lab has done experiments showing that rat liver cells treated with arsenic are "hypomethylated"—that is, the genome doesn't have as many methyl groups as it normally would. He's also shown that an oncogene, *c-myc*, switches on in these cells.

But arsenic might also have a deleterious effect in some cells by boosting methylation, says Marc Mass, a toxicologist at EPA's research lab in Research Triangle Park. His group has found in experiments on human lung cells that arsenite spurs the activity of an enzyme that attaches methyl groups to the *p53* tumor suppressor gene. The methyl groups are added to a region of the gene where they would slow its transcription—and thus increase the risk of cancer, says Mass.

Clearly, the mystery is far from solved. And that leaves scientists in the uncomfortable position of assessing EPA's proposal to reduce maximum arsenic levels in drinking water without being able to point to a proven mechanism of arsenic's carcinogenicity. EPA wants to reduce those levels from 50 micrograms per liter to as few as 2 micrograms per liter in 2001—a plan that could cost utilities up to $1.5 billion a year.

–Jocelyn Kaiser

PALEONTOLOGY

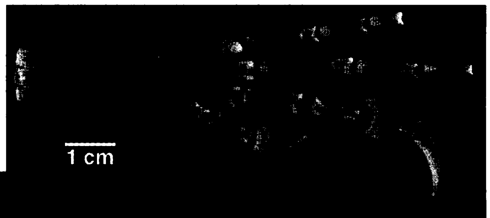
Missing Link Ties Birds, Dinosaurs

Paleontologist Catherine Forster and colleagues were working in their lab one weekend in 1995, chipping the skeleton of an ancient bird from a block of sandstone, when they noticed that the bird's half-buried second toe seemed unusually large. Forster joked that perhaps this specimen would help settle the long-running battle over whether dinosaurs gave rise to birds by having a long sickle claw like some dinosaurs. Half an hour later, the whole toe was exposed—and, amazingly, the raven-sized bird had a "wicked-looking" sickle claw, fit for a Velociraptor or other dromaeosaurid dinosaur. "We knew then that this was a really primitive bird, walking in the gray area between bird and dinosaur," says Forster, of the State University of New York, Stony Brook.

On page 1915, Forster and her colleagues describe this new species of primitive bird from Madagascar, called *Rahona ostromi* (*Rahona*, for menacing cloud in Malagasy, and *ostromi* in honor of Yale University paleontologist John Ostrom). *R. ostromi*, which lived 65 million to 70 million years ago, had feathered wings like a modern bird, but a long bony tail and a sickle claw like a meat-eating theropod dinosaur. Although it lived 80 million years after the first known bird, *Archaeopteryx*, *R. ostromi* may be one of the most primitive birds known and joins a gallery of recently discovered creatures that seem part bird and part dinosaur, researchers say. "It's a great discovery," says *Archaeopteryx* expert Peter Wellnhofer of the Bavarian State Collection of Paleontology and Historical Geology in Munich, Germany. "This fossil is very strong support for the theropod ancestry of birds." But this find won't end the fight over bird origins; researchers skeptical of a dinosaur ancestry say that Forster's team may have mistakenly combined bird and dinosaur bones.

In 1995, in their second field season in the sandstone hills of Madagascar, Forster and paleontologist Scott Sampson of the New York College of Osteopathic Medicine in Old Westbury, on a dig led by David Krause, also of Stony Brook, dug up a long, slender lower wing bone with quill knobs for feather attachment. It lay just above, although not attached to, several hind limb bones that fit together, as well as a long, bony tail like that of *Archaeopteryx*. The researchers knew they had something special, so they chopped out a 27-kilogram block of stone containing the bird and shipped the whole thing home to New York.

After preparing the specimen, they found that the bird's pelvic and pubic bones resemble those of *Archaeopteryx* and other early birds—making *R. ostromi* surprisingly primitive for its time in the late Cretaceous, when modern birds had already taken flight. What's more, the bird's last six dorsal vertebrae have an extra articular face, as seen in theropods but not in modern birds. These features, plus that sickle claw, make *R. ostromi* look even more like a theropod than *Archaeopteryx* does, says Forster.



FORSTER *ET AL.*

CATHERINE A. FORSTER

Bird of passage. A slashing claw (*above*) on an ancient bird dug up in Madagascar (*left*) suggests that it was in transition from dinosaurs to birds.

The new specimen joins a collection of strange-looking birds and dinosaurs, such as *Confuciusornis* and *Protoarchaeopteryx* from China, *Mononykus* from Mongolia, and *Unenlagia* from Argentina, whose combinations of features are hard to explain if birds evolved from some pre-dinosaurian reptile, argues University of Chicago paleontologist Paul Sereno. "In the past 5 years, we've discovered so many wonderful intermediate forms that are close to the transition from dinosaurs to birds," he says. The best way to explain these specimen's half-bird, half-dinosaur appearance, he says, is that birds evolved from dinosaurs. Animals such as *R. ostromi* then retained many primitive dinosaurian traits for millions of years, making it "a living fossil in its own time," says Wellnhofer.

Researchers like John Ruben of Oregon