MEETING BRIEFS

Primordial Soup Researchers Gather at Watering Hole

SARATOGA SPRINGS, NEW YORK–In a symposium held here on 23 and 24 June as part of the Northeast Regional Meeting of the American Chemical Society, two dozen researchers met to discuss the events that could have transformed a lifeless Earth into a rich biochemical broth, which could have given rise to the first living organisms. They described experiments pointing to ways in which conditions on a young Earth, such as sunlight and mineral surfaces, could have fostered the first steps toward life, including the formation of the first information-carrying molecules and the metabolic cycles that provide energy for living things. They also discussed a new technique that could pin down when Earth first became hospitable to life.

RNA Makes Connections

Cornell University chemist David Usher calls himself an "RNA optimist." A decade ago, Harvard University's Walter Gilbert and others anointed RNA as the probable first information-carrying molecule of life, playing the same role as DNA does now. Researchers worried, however, that early RNAs would not have formed the kinds of chemical bonds that enable modern versions of the molecule to resist being dismantled by water. But, at the meeting, Usher described work suggesting that under early-Earth conditions, the kind of bonds still seen in today's RNA would have been formed, creating long-lasting polymers.

Usher's lab recreated RNA polymerization with a "day-night" machine—a glass apparatus exposed to a rotating light source to simulate a cycle of 6 hours of daylight followed by 6 hours of darkness. "We run through lots of cycles of heating and cooling and wetness and dryness, which is exactly what you wouldn't have been able to avoid on the early Earth," he said.

When Usher and his colleagues added a mixture of nucleosides (RNA building blocks, each consisting of a sugar bound to one of the four bases found in RNA) and phosphates to the system, phosphate bonds formed both between the number 3 and number 5 carbons of adjacent five-carbon sugar rings—the kind of bonds seen in RNA today—and also between carbons 2 and 5. But the accumulating nucleic acids preferentially contained the 3-to-5 links, because the 2-to-5 links distorted the growing polymers, making them more likely to be broken down by water during the wet cycles. The result: short RNA helices and double-stranded RNAs containing precisely the kinds of durable phosphate linkages seen in today's nucleic acids formed in the cycler.

Other work suggests that the formation of RNA polymers may have been given a boost by the clays or pyrite minerals that might have been available wherever life got started, such as in warm pools or deep-sea hot springs. A decade ago, researchers had noted that the minerals could have provided a kind of scaffolding on which nucleic acids could assemble. At the meeting, James Ferris and Gözen Ertem, chemists at Rensselaer Polytechnic Institute in Troy, New York, presented evidence showing just how effective such mineral templates can be.

Last year, Ferris and Leslie Orgel at the Salk Institute reported in the 2 May issue of *Nature* that RNA monomers trapped between the alternating alumina and silica sheets of common montmorillonite clay can link into chains up to 50 units long, containing a single type of base. "We do not know precisely how clay catalyzes the reaction," said Ertem. "But, in general, monomers that adsorb on a clay surface are in close proximity to each other, and are oriented in [the right] geometry for [phosphate] bonds to form."

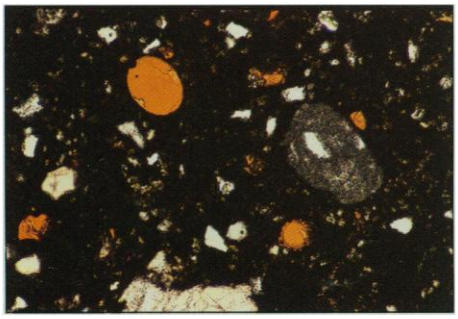
At the meeting, she filled out this picture by reporting evidence that polymers formed on clay can reproduce themselves—a crucial step toward life—by aiding the formation of polymers with complementary bases. For example, if the polymer contains only cytidines—one of four kinds of bases found in RNA—it can in turn serve as a template for formation of a second polymer, containing only guanine bases. The finding suggests, said Ferris, that "a community of interacting oligomers may have formed on mineral surfaces," ready to take on the next steps toward becoming living cells.

Biochemist Stanley Miller of the University of California, San Diego, whom many credit with founding the field of prebiotic simulations when he generated amino acids in his classic 1953 "primordial soup" experiment, says simulations like these can't offer definitive answers. But they are still valuable, he says. "How do we know whether simulation experiments really recreate what happened? We don't. But the alternative is to sit around and speculate about it."

Clues in Moon Beads

When did life first arise? Although the planet formed 4.6 billion years ago, the earliest hints of life—skewed carbon-isotope ratios in ancient sediments from eastern Greenland—date back only 3.85 billion years. Just how much earlier life could have gotten started depends on when the rain of asteroids and comets that pelted early Earth relented. At the meeting, John Delano of the State University of New York, Albany, proposed a new place to find clues to the end of the bombardment: the tiny glass beads found in samples of lunar soil.

Looking to the moon is nothing new for investigators trying to reconstruct Earth's history of bombardment. The moon's history of impacts presumably parallels Earth's, but unlike Earth, it doesn't experience the erosion and other geologic processes that tend to erase the evidence—rocks melted in impact cataclysms. Radioactive dating of rocks brought back by the Apollo astronauts suggests that the bombardment of Earth and the moon didn't abate until about 3.8 billion to 3.9 billion years ago, implying that life could not have arisen much earlier than that. But Delano questions these dates.



J.W. DELANO/STATE UNIV. OF NEW YORK

Moon shine. Glass spherules seen in this millimeterwide sample of lunar soil record the ancient bombardment of Earth and the moon.

Delano, who has been a lunar sample principal investigator for NASA since 1984, notes that the rocks on which the current dates are based are now known to consist of two or more types of materials that may have formed at different times. "Such a 'melt rock' might consist of 4.5-billion-year-old crystals in a matrix that is 3.9 billion years old. That could be averaged to an age of 4.2 billion years ago, which would have no physical meaning," Delano said at the meeting.

In contrast, each of the beads of glass found by the thousands in the Apollo samples, says Delano, "has an isotopic memory of when it was produced in [a single] impact event." What's more, since tiny droplets of molten glass can spray long distances from an impact, a single sample of lunar soil can carry records of many different impacts.

Delano plans to analyze the chemical composition of several hundred glass beads, to be certain they did not pick up impurities after they formed, then send them to Paul Renne at the Berkeley Geochronology Center for argon-argon dating. For now, he says, "Origin-of-life investigators should be reluctant to cede the interval of 4.4 billion to 3.9 billion years ago as having been too hostile for sustainable life." Says James Kasting, a geoscientist at Pennsylvania State University, State College, "It's hard to prove [the timing of impacts] from a small collection of moon rocks from 6 or 7 locations. If Delano has a better way to look at the data concerning bombardment, that would be very interesting."

Mimicking Metabolism

Anyone who has taken Biology 101 has become painfully familiar with the Krebs or citric acid cycle (CAC). This complex loop of reactions is part of aerobic respiration, which extracts energy from glucose far more efficiently than do alternative pathways that do not require oxygen. To biochemists pondering early life, aerobic respiration poses the same problem as RNA polymerization: How could this sophisticated chemistry have gotten started?

Maybe sunlight helped set the CAC, or parts of it, in motion, says Tom Waddell, an organic chemist at the University of Tennessee, Chattanooga. At the meeting, Waddell described experiments he did with undergraduates Tod Miller, Barry Henderson, and Sunil Geevarghese. To recreate parts of the CAC, they placed appropriate chemical intermediates from the cycle on a sunny rooftop. "We set up a simple experiment, watched what happened, and let nature teach us," Waddell said. They found that, in some cases, solar energy drove chemical reactions that produced further intermediates of the cycle. For example, oxaloacetic acid, a compound at the cycle's "end," broke down in sunlight, releasing citric acid, the compound that starts the cycle anew.

The findings mesh with analyses of the Murchison meteorite, found in Australia in 1969. In 1974, J. G. Lawless and co-workers at the Ames Research Center, in Moffett Field, California, identified a zoo of organic molecules in the 100-kilogram meteorite, including amino acids, nucleotides, and CAC intermediates. Solar radiation might have driven CAC-like reactions in space, Waddell thinks. His rooftop experiments show that these sun-inspired reactions could have occurred on Earth as well, perhaps in the chemical systems that were precursors to life.

Although Waddell has reproduced only a few steps of the citric acid cycle, he can't help imagining how the pieces might fit into a bigger picture. "Perhaps evolving cells [relied on] photochemical reactions that were the ancestors of the modern CAC," he says. Eventually, as enzymes evolved that could harness chemical energy to drive the CAC, organisms no longer had to rely on the sun to keep their metabolisms churning. "It is certainly a reasonable proposal," says James Ferris of Rensselaer Polytechnic Institute in Troy, New York.

–Ricki Lewis

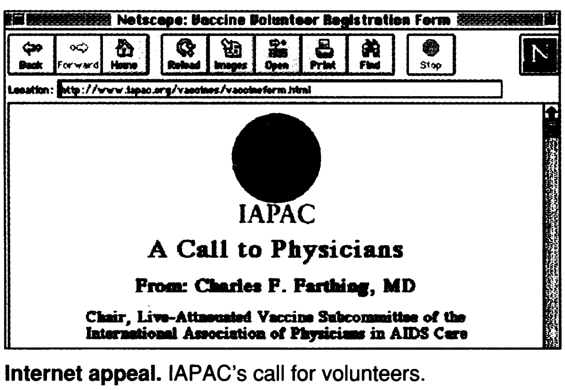
Ricki Lewis is the author of Life, *published by McGraw-Hill College Publishers.*

AIDS RESEARCH

Novel Campaign to Test Live HIV Vaccine

An AIDS vaccine that, hands down, has had more success in monkey experiments than any other approach has never been tested in humans. The reason: many researchers believe the vaccine, based on a weakened, or attenuated, live virus, would be too risky. Now, the little-known International Association of Physicians in AIDS Care (IAPAC), convinced that the potential benefits outweigh the risks, is conducting an unusual campaign to recruit "a few hundred" volunteers for a safety study of this approach that the group hopes to organize by the year 2000.

Heading the drive to sign up volunteers is AIDS clinician Charles Farthing, one of IAPAC's 5500 members and medical director of the AIDS Healthcare Foundation in Los Angeles, California. Farthing says he has been "progressively irritated" by the lack of movement toward clinical trials of an attenuated HIV vaccine—an approach that has worked wonders against diseases such as smallpox and polio. The Chicago-based IAPAC made the call for a live, attenuated HIV trial in the August issue of its journal; the editor, Gordon Nary, announced that he would be among the volunteers. IAPAC also has posted a registration form for the trial on its Internet site (http://www.iapac.org), and says more than a dozen people already have stepped forward.



Internet appeal. IAPAC's call for volunteers.

Ronald Desrosiers of the New England Regional Primate Research Center in Southborough, Massachusetts, first showed the power of the live, attenuated approach in a monkey study published in *Science* nearly 5 years ago (18 December 1992, p. 1938). Monkeys given the vaccine did not become infected later, when given a lethal strain of SIV, the simian cousin of HIV. Desrosiers, who has worked with Therion Biologics of Cambridge, Massachusetts, to develop a potential product, has spent the past several years deleting various genes from SIV and HIV to find a weakened form that is as safe as possible, yet still able to protect animals from disease-causing isolates of the virus.

A live, attenuated AIDS vaccine would have three potential pitfalls, however. The weakened virus would still be able to replicate and might cause AIDS after, say, 30 years. It's also possible the virus could mutate into a virulent form, although Desrosiers thinks this risk can be all but eliminated by deleting enough genes. Finally, the weakened HIV would still integrate with a host cell's DNA, which theoretically could trigger cancer by a process known as insertional mutagenesis.

Farthing says he hopes the safety trial will show after a year or two that people, like the monkeys, can control replication of the vaccine virus and not suffer any immunological damage. Still, AIDS experts say the trial won't answer some of the biggest safety questions. "We're really concerned with what happens when you vaccinate 20 million people and 10 years later, 5% or 10% get lymphoma," says Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases. "You're not going to know that from [IAPAC's proposed test]."

Farthing recognizes the risks, and acknowledges that regulatory agencies such as the Food and Drug Administration may never approve his proposed test. But "if you just assume everybody's going to say no, you don't do anything," he says. Margaret Johnston, head scientist for the International AIDS Vaccine Initiative, a group started by the Rockefeller Foundation to speed the search, thinks the safety issue are paramount, but says IAPAC's efforts might help. IAPAC's move, says Johnston, "will stimulate debate, which I do think is sorely needed."

–Jon Cohen