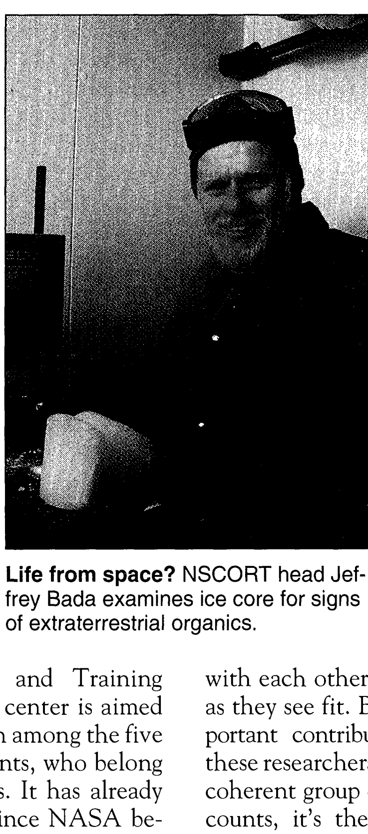
INSTITUTIONAL PROFILE

Novel Center Seeks to Add Spark to Origins of Life

LA JOLLA, CALIFORNIA—For more than 4 decades, a small band of researchers has been trying to explore a question that is about as fundamental as you can get: How did life begin? So far, they have only nibbled at the edges of the topic. Part of the problem is simply the difficulty of peering 4 billion years into the past, which is roughly when life on Earth likely originated. But another, more human, dilemma has held back origin of life studies, too: It isn't really a field. There is no degree in the discipline; although there is an international society, it has all of 300 members; and funding for origin of life studies is pathetic. Still, despite this harsh climate, an intellectual primordial soup made up of five leading origin of life researchers and their 20 students is now simmering here, and it may yet give life to a bona fide field.

The spark that could start off a self-perpetuating academic process was a decision 3 years ago by the National Aeronautics and Space Administration (NASA) to designate this "exobiology" group as a NASA Specialized Center of Research and Training (NSCORT). This "virtual" center is aimed at encouraging collaboration among the five participants and their students, who belong to four separate institutions. It has already enlivened the discipline: Since NASA began funding the center 3 years ago, the group has published a bevy of high-profile papers and thrown fuel on a number of long-smoldering debates. "It's a terrifically excellent group," says William Schopf, a geologist at the University of California, Los Angeles, who has helped review this NSCORT. "They're pushing the limits of problems that are of high quality."

If it seems odd that the space agency is spending nearly $1 million a year to investigate the origin of life, NSCORT member Stanley Miller of the University of California, San Diego, stresses that looking for life on other planets is part of NASA's mission. And, says Miller, "if you're going to search for life on other planets, understanding how it started on Earth is essential." Miller and his NSCORT colleagues are tackling a diverse set of issues, ranging from the chemistry of Earth's early atmosphere, to the notion that life may have been seeded from space, to the conditions that might give rise to robust RNA molecules.


SUSAN R. GREEN

Life from space? NSCORT head Jeffrey Bada examines ice core for signs of extraterrestrial organics.

Even without NASA's help, the five principal investigators (PIs)—all chemists of different stripes—would be in the forefront of origin of life studies. In addition to Miller, the group consists of Leslie Orgel at the Salk Institute for Biological Studies, Gustaf Arrhenius and Jeffrey Bada from the Scripps Institution of Oceanography, and Gerald Joyce of the Scripps Research Institute. "These are all-stars," says Schopf. "You'd assume they'd be affecting the field regardless." Yet you would not necessarily assume that they would be collaborating, because some of the PIs share little intellectual common ground—which sits fine with Orgel. "Why have several people in a field if you all think the same thing?" he asks.

The five PIs hook up with each other to do specific experiments, as they see fit. But the NSCORT's most important contribution, says Schopf, is that these researchers have been able "to attract a coherent group of students." And, by all accounts, it's the intermingling of the students—who mix it up at a biweekly journal club to which the PIs specifically are "disinvited"—that makes the NSCORT tick. "I think it's worked extremely well for the younger people," says Orgel.

Spark of life. San Diego's status as world headquarters for origin of life studies is linked strongly to Miller, who rose to fame in 1953 while still a graduate student in the lab of Nobel Prize–winning chemist Harold Urey. The so-called Miller-Urey experiment simulated the prebiotic atmosphere by mixing molecules they presumed were present on the early Earth: methane, ammonia, hydrogen, and water. They then zapped this soup with an electrical charge to mimic lightning, which in turn produced small amounts of amino acids—the building blocks of proteins, which are critical to all living things. "[That study] had a tremendously important role in making chemists aware that the whole question of origin of life could be approached by lab experiments," says NSCORT's Arrhenius. "It became an acceptable field."

Yet today, Arrhenius and many other researchers dismiss the experiment itself because they contend that the early atmosphere looked nothing like the Miller-Urey simulation. Basically, Miller and Urey relied on a "reducing" atmosphere, a condition in which molecules are fat with hydrogen atoms. As Miller showed later, he could not make organics in an "oxidizing" atmosphere.

Arrhenius's objection "starts from the observation that Earth now has such a high proportion of water," he says, noting that H_2O is a strong oxidizing agent. "And there's no theory to say the early Earth was deficient in water." Indeed, he believes it had much more water than was simulated in the Miller-Urey experiment. Also, methane and ammonia are easily obliterated by ultraviolet light, which makes it difficult to see how they could have hung around long enough to form organics.

Others balk at the notion of a reducing atmosphere because of what is known as the "faint young sun" paradox. As geologist James Kasting of Pennsylvania State University explained 2 years ago in *Science* (12 February 1993, p. 920), the sun likely had about 30% less luminosity when Earth was formed. If the planet had the same atmosphere as today, its mean surface temperature would have been below the freezing point of water; it would be a giant iceball. As geologic evidence suggests that Earth had liquid water early in its history, Kasting and others maintain that Earth's early atmosphere must have been rich in carbon dioxide (CO_2), which, through the greenhouse effect, would have kept the surface toasty. But these high levels of CO_2, a neutral agent, also would have prevented a Miller-Urey scenario.

Not that the first biomolecules had to have formed in an environment exposed to the atmosphere. One alternative explanation to the Miller-Urey scenario for life's origin focuses on deep-sea vents that cycle hot fluid in a reducing environment. Another is the theory promoted by A. Graham Cairns-Smith of the University of Glasgow in Scotland that life began as inorganic clays that passed on information in their crystalline structures. The NSCORT researchers are skeptical of both ideas, but they do take more seriously a proposal first made by the late British crystallographer John Desmond Bernal that minerals might have acted as catalysts to help build the first organic molecules.

Life from space. Then again, the building blocks for life might not have taken shape on Earth at all. A possibility that Arrhenius strongly favors and Orgel says he'd choose "if I really had to" is that comets, meteorites, and interplanetary dust particles shuttled in the organic molecules from which life on Earth evolved.

Bada, who heads NSCORT and is himself a former Miller graduate student—and who shares many of his mentor's views—puts little stock in this idea, yet he has been seriously investigating the possibility. Bada's working hypothesis is that if significant quantities of extraterrestrial organic molecules arrived 4 billion years ago, the supply should have continued at a reduced level in the recent past. To address this question, he has relied on α-aminoisobutyric acid (AIB), which is the most common amino acid found in meteorites containing carbon but is rarely found on Earth. He reasoned that if he repeatedly found AIB in polar ice, a medium that contains minuscule amounts of confusing terrestrial organic matter, that would strengthen the argument for an extraterrestrial origin.

In five dozen ice samples dating back more than 6000 years, Bada's group has only found one with high AIB levels. "This suggests to me that [extraterrestrial organics] would not have been important on the early Earth," says Bada. The one positive sample, he says, supports the idea that "delivery of organics to the Earth was not very robust and was very episodic."

Miller, who still believes his original work is valid, insists that no one knows what Earth's early atmosphere contained. "There's no evidence," says Miller. And he argues that the faint young sun paradox would not exist if the oceans went through several freeze-thaw cycles. As Miller, Bada, and Charles Bigham in his lab postulated in the 15 February *Proceedings of the National Academy of Sciences* last year, only the upper layer of the early Earth's oceans might have been frozen over, with the bottom layers constantly heated by radioactive decay from Earth's interior. Giant fiery meteorites, or bolides, might have repeatedly struck the upper ice layer, melting huge holes in the ocean surface. This could have created a plausible setting for the origin of life by freeing into the atmosphere methane, hydrogen, and ammonia that had been produced by hydrothermal vents on the ocean's floor. Then again, life might have started in the ocean itself if the bolides contributed organics and the ocean surface then refroze, trapping concentrations of methane and ammonia in the water. "That's where some interesting chemistry can take place," says Bada.

The pre-RNA world. Wherever and however the "interesting chemistry" took place, the organic molecules it spawned would ultimately have formed larger molecules able to hold information and copy themselves—the first life forms. What they might have looked like is another focus of NSCORT's "intensely experimental" approach, says Scripps Research's Joyce.

Joyce cut his scientific teeth as a graduate student in the lab of Orgel, who in the late 1960s was a co-proponent of the theory that life began with RNA, genetic material that today is best known as an intermediary in the process that transforms DNA into proteins. Orgel and others postulated that life more likely began in what has become known as the "RNA world" because RNA was easier to synthesize than DNA and because it made sense that the more stable DNA could eventually evolve from RNA. Their proposal required that some early form of RNA must have behaved as an enzyme, a critical function that would allow the molecule both to store genetic information and to act as a catalyst to help other RNA molecules copy themselves. In 1983, the University of Colorado's Thomas Cech and Yale's Sidney Altman independently made a breakthrough that lifted enzymatic RNA out of the speculative realm: They found that enzymatic RNAs, now called ribozymes, exist on Earth today.

The scenario that life began with ribozymes raises significant problems, too, however. RNA is a complex molecule that contains the sugar ribose linked on one side to a phosphate and on the other to bases known as purines (adenine and guanine) or pyrimidines (cytosine and uracil). As Orgel puts it, "There were no chemical supply houses on the primitive Earth." What's more, even if the ingredients had been present, the chemical steps needed to assemble them would have been difficult if not impossible in a prebiotic world, Orgel has shown. "The central problem is to see how you get to the RNA world," he says.

Miller's lab has been interested in fashioning a pre-RNA that does not rely on the traditional pyrimidines and purines. For example, he reported last year in the *Journal of Molecular Evolution* that urazole, a mimic of the pyrimidine uracil, binds much more easily with ribose.

Another possible pre-RNA that the NSCORT researchers have been studying is the peptide nucleic acid, or PNA, which Peter Nielsen of Denmark's Panum Institute and co-workers first reported in *Science* (6 December 1991, p. 1497). Like DNA and RNA, this synthetic molecule forms a double helix, but it uses simple amides rather than complicated ribose-phosphates for its backbone. Working with Nielsen, Orgel and Christof Böhler in his lab reported in the 17 August *Nature* that pieces of RNA can provide the template for pieces of PNA and vice versa. This demonstrates that "genetic takeover" of a pre-RNA by RNA could have occurred.

Yet Orgel is far from convinced that PNA preceded RNA. "Even PNA still looks fairly complex," he says. Building off Bernal's original idea, Orgel's and Arrhenius's labs are now collaborating in attempts to synthesize other pre-RNAs by using mineral surfaces to construct molecules with simple backbones.

The evolution of creation. Over at Scripps Research, Joyce is addressing a question further downstream. Rather than concentrating on where the original material came from, Joyce wants to unravel how RNA by itself could have been a life form. Which raises a fundamental question: What is life?

"The origin of life is synonymous with the origin of Darwinian selection," says Joyce. In Joyce's view, life is defined by repeated cycles of replication and mutation. Using the tools of molecular biology, he grows large populations of RNAs—on the order of 10^{14}—and attempts to select for the traits that the molecule ultimately would need to be a life form all by itself. For example, Joyce has shown that with "directed evolution" he can select for ribozymes that cleave DNA and incorporate other "coenzymes." But he envisions much fancier tricks. "We would like to teach the ribozyme to take over replication," says Joyce.

As with everyone else in NSCORT, Joyce firmly believes that while science may not unravel the precise origin of life, it is constantly moving closer to a plausible explanation. "Life will be made in the lab," predicts Joyce. "There's a reasonable chance it will be made by the end of the decade. ... It isn't something we need to talk about sitting in front of the fireplace sipping brandy. It's doable." Especially if the NSCORT succeeds and spawns a new generation of origin of life–ologists to take up the cause.

–Jon Cohen

THE NSCORT EXOBIOLOGY PROGRAM

Principal Investigator	Affiliation	Research Area
Gustaf Arrhenius	Scripps Institution of Oceanography	Formation and growth of RNA precursors
Jeffrey Bada	Scripps Institution of Oceanography	Organic material on primitive Earth
Gerald Joyce	Scripps Research Institute	Evolution of protein synthesis using RNA
Stanley Miller	University of California, San Diego	Nucleotides on primitive Earth
Leslie Orgel	Salk Institute for Biological Studies	Catalysis of nucleic acid replication by minerals