From Primordial Soup to the Prebiotic Beach

An interview with exobiology pioneer, **Dr. Stanley L. Miller**, University of California San Diego

By Sean Henahan, Access Excellence

1n 1953, a University of Chicago graduate student named Stanley Miller working in Harold Urey's lab flipped a switch sending electric current through a chamber containing a combination of methane, ammonia, hydrogen and water. The experiment yielded organic compounds including amino acids, the building blocks of life, and catapulted a field of study known as exobiology into the headlines. Since that time a new understanding of the workings of RNA and DNA, have increased the scope of the subject. Moreover, the discovery of prebiotic conditions on other planets and the announcement of a bacterial fossil originating on Mars has brought new attention to the study of life's origins. I spoke with Dr. Miller in his lab at UCSD about the field he has helped to make famous, exobiology.

Let start with the basics. Can you give a simple definition of exobiology?

The term exobiology was coined by Nobel Prize winning scientist Joshua Lederberg. What it means is the study of life beyond the Earth. But since there's no known life beyond the Earth people say its a subject with no subject matter. It refers to the search for life elsewhere, Mars, the satellites of Jupiter and in other solar systems. It is also used to describe studies of the origin of life on Earth, that is, the study of pre-biotic Earth and what chemical reactions might have taken place as the setting for life's origin.

Some 4.6 billion years ago the planet was a lifeless rock, a billion years later it was teeming with early forms of life. Where is the dividing line between pre-biotic and biotic Earth and how is this determined?

We start with several factors. One, the Earth is fairly reliably dated to 4.55 billion years. The earliest evidence for life was 3.5 billion years based on findings at the Apex formation in Western Australia. A new discovery reported in the journal Nature indicates evidence for life some 300 million years before that. We presume there was life earlier, but there is no evidence beyond that point.

We really don't know what the Earth was like three or four billion years ago. So there are all sorts of theories and speculations. The major uncertainty concerns what the atmosphere was like. This is major area of dispute. In early 1950's, Harold Urey suggested that the Earth had a reducing atmosphere, since all of the outer planets in our solar system- Jupiter, Saturn, Uranus and Neptune- have this kind of atmosphere. A reducing atmosphere contains methane, ammonia, hydrogen and water. The Earth is clearly special in this respect, in that it contains an oxygen atmosphere which is clearly of biological origin.

Although there is a dispute over the composition of the primitive atmosphere, we've shown that either you have a reducing atmosphere or you are not going to have the organic compounds required for life. If you don't make them on Earth, you have to bring them in on comets, meteorites or dust. Certainly some material did come from these sources. In my opinion the amount from these sources would have been too small to effectively contribute to the origin of life.

So while these are potential sources of organic compounds they are not essential for the creation of life on Earth?

As long as you have those basic chemicals and a reducing atmosphere, you have everything you need. People often say maybe some of the special compounds came in from space, but they never say which ones. If you can make these chemicals in the conditions of cosmic dust or a meteorite, I presume you could also make them on the Earth. I think the idea that you need some special unnamed compound from space is hard to support.

You have to consider separately the contributions of meteors, dust and comets. The amount of useful compounds you are going to get from meteorites is very small. The dust and comets may provide a little more. Comets contain a lot of hydrogen cyanide, a compound central to prebiotic synthesis of amino acids as well as purines. Some HCN came into the atmosphere from comets. Whether it survived impact, and how much, are open to discussion. I'm skeptical that you are going to get more than a few percent of organic compounds from comets and dust. It ultimately doesn't make much difference where it comes from. I happen to think prebiotic synthesis happened on the Earth, but I admit I could be wrong.

There is another part of the story. In 1969 a carbonaceous meteorite fell in Murchison Australia. It turned out the meteorite had high concentrations of amino acids, about 100 ppm, and they were the same kind of amino acids you get in prebiotic experiments like mine. This discovery made it plausible that similar processes could have happened on primitive Earth, on an asteroid, or for that matter, anywhere else the proper conditions exist.

The Murchison meteorite is a large meteorite that fell to earth near Murchison, Victoria, in Australia, in 1969. It is one of the most studied meteorites due to its mass, the fact that it was an observed fall, and that it belongs to a group of meteorites rich in organic compounds. Wikipedia

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Doesn't the Panspermia theory looks at the question of ultimate origins of life in a slightly different way?

That's a different controversy. There are different versions of the theory. One idea is that there was no origin of life, that life, like the universe, has always existed and got to the Earth through space. That idea doesn't seem very reasonable since we know that the universe has not always existed, so life has to happen some time after the big bang 10 or 20 billion years ago.

It may be that life came to Earth from another planet. That may or may not be true, but still doesn't answer the question of where life started. You only transfer the problem to the other solar system. Proponents say conditions may have been more favorable on the other planet, but if so, they should tell us what those conditions were.

Along these lines, there is a consensus that life would have had a hard time making it here from another solar system, because of the destructive effects of cosmic rays over long periods of time.

What about submarine vents as a source of prebiotic compounds?

I have a very simple response to that . Submarine vents don't make organic compounds, they decompose them. Indeed, these vents are one of the limiting factors on what organic compounds you are going to have in the primitive oceans. At the present time, the entire ocean goes through those vents in 10 million years. So all of the organic compounds get zapped every ten million years. That places a constraint on how much organic material you can get. Furthermore, it gives you a time scale for the origin of life. If all the polymers and other goodies that you make get destroyed, it means life has to start early and rapidly. If you look at the process in detail, it seems that long periods of time are detrimental, rather than helpful.

Can you review with us some of the history and basic background of your original prebiotic experiments?

In the 1820's a German chemist named Woeller announced the synthesis of urea from ammonium cyanate, creating a compound that occurs in biology. That experiment is so famous because it is considered the first example where inorganic compounds reacted to make a biological compound. They used to make a distinction between organic, meaning of biological origin, and inorganic- CO_2, CO and graphite. We now know that there is no such distinction.

However, it remained a mystery how you could make organic compounds under geological conditions and have them organized into a living organism. There were all sorts of theories and speculation. It was once thought that if you took organic material, rags, rotting meat, etc, and let it sit, that maggots, rats etc. would arise spontaneously. It's not as crazy as it seems, considering DNA hadn't been discovered. It was then reasonable to hold those views if you consider living organisms as protoplasm, a life substance. This all changed in 1860 when Pasteur showed that you don't get living organisms except from other living organisms. This disproved the idea of spontaneous generation.

But spontaneous generation means two things. One is the idea that life can emerge from a pile of rags. The other is that life was generated once, hundreds of millions of years ago. Pasteur never proved it didn't happen once, he only showed that it doesn't happen all the time.

A number of people tried prebiotic experiments. But they used CO_2F, nitrogen and water. When you use those chemicals, nothing happens. It's only when you use a reducing atmosphere that things start to happen.

Who came up with the idea of the reducing atmosphere?

Oparin, a Russian scientist, began the modern idea of the origin of life when he published a pamphlet in 1924. His idea was called the heterotrophic hypothesis: that the first organisms were heterotrophic, meaning they got their organic material from the environment, rather than having to make it, like blue-green algae. This was an important idea. Oparin also suggested that the less biosynthesis there is, the easier it is to form a living organism. Then he proposed the idea of the reducing atmosphere where you might make organic compounds.

He also proposed that the first organisms were coacervates, a special type of colloid. Nobody takes that last part very seriously anymore, but in 1936, this was reasonable since DNA was not known to be the genetic material..

In 1951, unaware of Oparin's work, Harold Urey came to the same conclusion about the reducing atmosphere. He knew enough chemistry and biology to figure that you might get the building blocks of life under these conditions.

Tell us about the famous electrical discharge experiment.

The experiments were done in Urey's lab when I was a graduate student. Urey gave a lecture in October of 1951 when I first arrived at Chicago and suggested that someone do these experiments. So I went to him and said, "I'd like to do those experiments". The first thing he tried to do was talk me out of it. Then he realized I was determined. He said the problem was that it was really a very risky experiment and probably wouldn't work, and he was responsible that I get a degree in three years or so. So we agreed to give it six months or a year. If it worked out fine, if not, on to something else. As it turned out I got some results in a matter of weeks.

In the early 1950s Stanley L. Miller, working in the laboratory of Harold C. Urey at the University of Chicago, did the first experiment designed to clarify the chemical reactions that occurred on the primitive earth. In the flask at the bottom, he created an "ocean" of water, which he heated, forcing water vapor to circulate through the apparatus. The flask at the top contained an "atmosphere" consisting of methane (CH_4), ammonia (NH_3), hydrogen (H_2) and the circulating water vapor.

Next he exposed the gases to a continuous electrical discharge ("lightning"), causing the gases to interact. Water-soluble products of those reactions then passed through a condenser and dissolved in the mock ocean. The experiment yielded many amino acids and enabled Miller to explain how they had formed. For instance, glycine appeared after reactions in the atmosphere produced simple compounds - formaldehyde and hydrogen cyanide. Years after this experiment, a meteorite that struck near Murchison, Australia, was shown to contain a number of the same amino acids that Miller identified and in roughly the same relative amounts. Such coincidences lent credence to the idea that Miller's protocol approximated the chemistry of the prebiotic earth. More recent findings have cast some doubt on that conclusion.

(Taken from Leslie Orgel's Scientific American article, "The Origin of Life on Earth", Scientific American, October, 1994)

You must have been excited to get such dramatic results so quickly, and with what, at the time, must have seemed like an outlandish hypothesis?

Oh yes. Most people thought I was a least a little bit crazy. But if you look at methane/ammonia vs. CO_2/nitrogen there was no doubt in my mind. It was very clear that if you want to make organic compounds it would be easier with methane. It's easy to say that but it is quite a bit more difficult to get organized and do the experiment.

The surprise of the experiment was the very large yield of amino acids. We would have been happy if we got traces of amino acids, but we got around 4 percent. Incidentally, this is probably the biggest yield of any similar prebiotic experiment conducted since then. The reason for that has to do with the fact that amino acids are made from even simpler organic compounds such as hydrogen cyanide and aldehydes.

That was the start. It all held together and the chemistry turned out to be not that outlandish after all.

What was the original reaction to your work in the science community?

There was certainly surprise. One of the reviewers simply didn't believe it and delayed the review process of the paper prior to publication. He later apologized to me. It was sufficiently unusual, that even with Urey's backing it was difficult to get it published. If I'd submitted it to "Science" on my own, it would still be on the bottom of the pile. But the work is so easy to reproduce that it wasn't long before the experiment was validated.

Another scientist was sure that there was some bacterial contamination of the discharge apparatus. When you see the organic compounds dripping off the electrodes, there is really little room for doubt. But we filled the tank with gas, sealed it, put it in an autoclave for 18 hours at 15 psi. Usually you would use 15 minutes. Of course the results were the same.

Nobody questioned the chemistry of the original experiment, although many have questioned what the conditions were on pre-biotic Earth. The chemistry was very solid.

How much of a role did serendipity play in the original setup?

Fortunately, Urey was so adamant at the time about methane that I didn't explore alternate gas mixtures. Now we know that any old reducing gases will do. CO_2/hydrogen and nitrogen will do the trick, although not as well.

There was some serendipity in how we handled the water. If we hadn't boiled it and run it for a week, we wouldn't have gotten such good yields of amino acids. We knew right away that something happened rather quickly because you could see a color change after a couple of days.

The fact that the experiment is so simple that a high school student can almost reproduce it is not a negative at all. That fact that it works and is so simple is what is so great about it. If you have to use very special conditions with a very complicated apparatus there is a question of whether it can be a geological process.

The original study raised many questions. What about the even balance of L and D (left and right oriented) amino acids seen in your experiment, unlike the preponderance of L seen in nature? How have you dealt with that question?

All of these pre-biotic experiments yield a racemic mixture, that is, equal amounts of D and L forms of the compounds. Indeed, if you're results are not racemic, you immediately suspect contamination. The question is how did one form get selected. In my opinion, the selection comes close to or slightly after the origin of life. There is no way in my opinion that you are going to sort out the D and L amino acids in separate pools. My opinion or working hypothesis is that the first replicated molecule had effectively no asymmetric carbon

You are talking about some kind of pre-RNA?

Exactly a kind of pre-RNA. RNA has four asymmetric carbons in it. This pre-RNA must have somehow developed into RNA. There is a considerable amount of research now to try and figure out what that pre-RNA compound was, that is, what was the precursor to the RNA ribose-phosphate.

Peter E. Nielsen of the University of Copenhagen has proposed a polymer called peptide nucleic acid (PNA) as a precursor of RNA. Is this is where PNA comes in?

Exactly, PNA looks prebiotic. Currently that is the best alternative to ribose phosphate. Whether it was the original material or not is another issue.

Can you clarify one thing? Have all of the amino acids been synthesized in pre-biotic experiments, along with all the necessary components for making life?

Just turning on the spark in a basic pre-biotic experiment will yield 11 out of 20 amino acids. If you count asparagine and glutamine you get thirteen basic amino acids. We don't know how many amino acids there were to start with. Asparagine and glutamine, for example, do not look prebiotic because they hydrolyze. The purines and pyrimidines can alos be made, as can all of the sugars, although they are unstable.

Your original work was published only a month apart from Watson and Crick's description of the DNA molecule. How has the field of molecular biology influenced the field of exobiology?

The thing that has probably changed the outlook the most is the discovery of ribozymes, the catalytic RNA. This means you can have an organism with RNA carrying out both the genetic functions and catalytic functions. That gets around the problem of protein synthesis, which is this incredibly complicated thing. There is a problem with RNA as a prebiotic molecule because the ribose is unstable. This leads us to the pre-RNA world.

The idea of the pre-RNA world is essentially the same as the RNA world, except you have a different molecule that replicates. Another thing worth remembering is that all these pre-biotic experiments produce amino acids. To have these amino acids around and not use them in the first living organism would be odd. So the role of amino acids in the origin of life is unknown but still likely.

Tell us about your recent work and the lagoon idea.

The primitive Earth had big oceans, but it also had lakes, lagoons and beaches. Our hypothesis is that the conditions may have been ideal on these beaches or drying lagoons for prebiotic reactions to occur, for the simple reason that the chemicals were more concentrated in these sites than in the middle of the ocean.

Is this because of the temperatures and also the presence of minerals as well?

Temperature is an important factor. Minerals have been thought by some to play a role in the origin of life, but they really haven't done much for us so far. People talk about how minerals might have helped catalyze reactions, but there are few examples where the mineral makes any difference.

Our most recent research tackled the problem of making pyrimidines- uracil and cytosine, in prebiotic conditions. For some reason it just doesn't work very well under dilute conditions. We showed that it works like a charm once you get things concentrated and dry it out a bit. This changed my outlook on where to start looking for prebiotic reactions.

Another example is our work with co-enzyme A. The business end of co-enzyme A is called pantetheine. We showed you could make this under these kind of pre-biotic "dry beach" conditions. We found that you didn't need it to be very hot, you can make it at 40 degrees C. This indicates the ease with which some of this chemistry can take place.

Temperature seems to be a talking point regarding prebiotic hypotheses.

We know we can't have a very high temperature, because the organic materials would simply decompose. For example, ribose degrades in 73 minutes at high temperatures, so it doesn't seem likely. Then people talk about temperature gradients in the submarine vent. I don't know what these gradients are supposed to do. My thinking is that a temperature between 0 and 10 degrees C would be feasible. The minute you get above 25 degrees C there are problems of stability.

How does the discovery of the Martian meteorite factor in to the discussion? Are you convinced these are the fossilized remains of extraterrestrial microorganisms?

I think the data is interesting and suggestive, but not yet conclusive. Let's accept that the meteorite does come from Mars. You have apparently got very small bacterial fossils also iron sulfide and magnetite sitting next to each other. Then there are these PAHs (polycyclic aromatic hydrocarbons). All of this is suggestive but not compelling.

There are just two possibilities. Either there was life on Mars or there was not. I have no problem with the idea of life on Mars, the question remains whether this evidence is adequate. If it is correct, it has an implication for one of the big questions of prebiotic research. That is, is it easy or difficult to produce life from prebiotic compounds in prebiotic conditions? It seems that it would be difficult on Mars. If it turns out to be the case on Mars, where the conditions do not look very favorable, then it should apply to anywhere in the universe, or any planet with a suitable atmosphere and temperature.

Can you tell us about the field of exobiology today in context of the world of science research?

It is a very small field. There is a society, the International Society for the Study of the Origin of Life. It has only 300 members, a rather small society. My own lab is part of program called NSCORT (NASA Specialized Center of Research and Training). This program is conducted in close cooperation with NASA and supports five researchers along with graduate students, post-docs and undergraduate students.

The more important research are the experiments these days, rather than the trading of ideas. Good ideas are those that when reduced to an experiment end up working. Our approach is to do experiments and demonstrate things, not just talk about possibilities.

What advice do you have for students interested in pursuing studies in exobiology?

Well we are talking about solving chemical problems. Therefore a background in basic chemistry is essential along with knowledge in the fields of organic chemistry, biochemistry and some background in geology and physics. Exobiology is a small field with a lot of interaction. It is one of few fields where an undergraduate would be able to work with top people in the field almost immediately.

This interview was conducted in October, 1996

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Study Questions:

1. What is exobiology?
2. Where is the dividing line between pre-biotic and biotic Earth
3. What is the Murchison meteorite and why is it important to this work?
4. What is the Panspermia theory?
5. Are submarine vents as a source of prebiotic compounds?
6. What was the surprising key result of the Miller and Urey experiment?
7. Is temperature a factor in the Miller and Urey experiment?