to withhold sequence data by somehow denying Japan access to U.S. databases.

"It is a very bad letter," concedes Norton Zinder of Rockefeller University, a longtime friend of Watson and chairman of the genome advisory committee at NIH. "You should have seen the original draft," he moans. "Had he sent that, Japan would have withdrawn its ambassador. The trouble with Jim is he is often right but not very polite." Meanwhile, McKusick, who says he has no complaints with the Japanese, is in Japan on a fence-mending mission.

In private Matsubara, who has been pushing for a bilateral agreement on the genome project, has characterized Watson's letter as "Japan-bashing." To *Science*, however, Matsubara strikes a diplomatic tone, saying that "there are certainly some tensions between Watson and Japan over the genome efforts. However, I believe the problems are not really serious." But should Watson make good on his threat, says Matsubara, "we shall be extremely annoyed."

One of Matsubara's colleagues in the Human Genome Program, Nobuyoshi Shimizu of Keio University School of Medicine, likens Watson's comments to "blackmail." Shimizu does not argue with Watson's point that Japan should repay the generosity shown it since World War II, "but in what way and in what capacity is our decision."

Shimizu and Matsubara are also somewhat perplexed about whether Watson actually has the authority to make good on his threat. Nor are they clear about whether he is writing as the director of the NIH genome project, a member of HUGO, or a private scientist. Says Shimizu: "I am concerned, even if it is his private view, because he is very influential."

To Shimizu fell the thankless task of delivering Matsubara's response to Watson, which he did at the San Diego meeting in early October. The message, in brief, was that while Japan is in the throes of setting up its own project, "we do not have the time or money to contribute to any other country yet." Shimizu and Matsubara say that Japan fully intends to contribute its fair share to the worldwide genome project, but that it may take a few years. Shimizu asked Watson to be patient, explaining that the Japanese bureaucracy runs very slowly.

Watson, however, is clearly exasperated with talk of bureaucratic obstacles. "Just because the Japanese bureaucracy runs slowly, there is no reason for the U.S. to carry the burden," he told *Science*. "The Japanese must face up to the fact that they are a wealthy nation and act accordingly. When they have the money, we can talk."

Watson apparently has no qualms about retreating from the stance of scientific openness that he has always defended, though he admits it is not a popular position. "The genome project is an immense opportunity. . . . The thought that we might keep the data secret is terrible, but I don't see an alternative," he told *Science*. "If we have done it and paid for it, why give it up? We would have to have holes in our head. Sharing is sharing cost as well."

How, exactly, Watson would deny Japanese scientists access to U.S. databases is not clear, "but there are ways to make it difficult for them," sighs Zinder, who, along with everyone else *Science* spoke with, opposes the idea. Nor is Watson worried about offending his Japanese colleagues. "I believe the message should be unambiguous, otherwise you can waste a lot of time."

Meanwhile, Watson's colleagues are doing their best to distance themselves from his remarks. "Watson is speaking for himself," says George Cahill of Howard Hughes Medical Institute and treasurer of HUGO. "He does not speak for NIH or HUGO. He does not speak ex cathedra like the Pope."

Not everyone takes offense at Watson's saber-rattling, however. In fact, one Japanese biologist at the recent San Diego meeting said he loves it, noting that every time Watson says something outrageous, the Japanese government boosts its support for the genome project.

And that, after all, is what Watson wants.

■ **LESLIE ROBERTS**

How Do You Read from the Palimpsest of Life?

A controversial new theory says that organisms of the ancient RNA world had a complex metabolism and used DNA—but had almost no protein enzymes

ABOUT 2.5 BILLION YEARS AGO, give or take a billion, Earth was populated by a one-celled organism that was very much like the bacteria of today, and yet eerily different. It obtained its energy much as today's lifeforms do. It probably even encoded its genetic information the same way, using DNA. And yet it had none of the protein enzymes that catalyze chemical reactions in modern organisms; instead it did its catalytic work with complex RNA molecules. It was also the ancestor of all modern life. It was "the breakthrough organism."

Or—maybe it wasn't. Building biochemical models of early organisms is an active and fractious growth industry these days. And the model above, which was recently proposed by organic chemists Steven A. Benner and Andreas Tauer of the Swiss Federal Institute of Technology in Zurich, and molecular biologist Andrew D. Ellington of the Massachusetts General Hospital in Boston, is more controversial than most.

"In reading their paper I wasn't sure if they were listening to nature or telling nature what to do," declares molecular biologist Alan Weiner of Yale University, their chief critic and a man who has done quite a bit of theorizing about early life himself. If nothing else, he says, "I find the whole notion of a 'breakthrough' organism ridiculous. It's unbiological. Things happen much more slowly than that."

Nonetheless, other researchers defend the work of Benner and his colleagues as one of the most ambitious and provocative reconstructions of early life to date. "The Benner paper is as rigorous as can be," says Harvard University emeritus chemist Frank H. Westheimer, who was an adviser for Benner's 1979 Ph.D. thesis. "It would be extraordinary if they got everything right. But they will certainly stimulate a lot of work."

"It's an extreme point of view," agrees chemist Leslie Orgel of the Salk Institute in La Jolla, California. "But I'm not willing to say it's wrong, either."

Benner, Ellington, and Tauer start out conventionally enough. Like most other origin-of-life researchers these days, they accept the idea that the primeval Earth was an "RNA world"—that is, a world in which RNA sequences were both a medium for storing genetic information and molecular workhorses directing the cell's metabolism through catalysis. Indeed, Thomas Cech of the University of Colorado and Sidney Altman of Yale University were just awarded the 1989 Nobel Prize in Chemistry for their discovery that RNA *can* function as a catalyst (*Science*, 20 October, p. 325).

Where the group goes well out on a limb, however, is in their attempt to describe what the RNA world was like. Instead of accepting most researchers' tacit assumptions that RNA catalysts were primitive and ineffectual, their model depicts an RNA world that was rich, complex, and vital. "If you believe

our model, then you have to believe that the RNA world had a sophisticated metabolism," says Benner.

Benner and his colleagues knew, of course, that the RNAs of modern life-forms are part of the elaborate machinery that the organisms use to decode the genetic information stored in DNA. The information in a gene is first copied into an RNA, which then directs the synthesis of a specific protein in a process called translation. The researchers therefore decided to reconstruct the biochemistry of what they call the breakthrough organism—that is, the first organism to invent that process of translation.

Obviously, they say, this kind of reconstruction is full of pitfalls: the only record of the RNA world—namely, the biochemistry of present-day organisms—has been written over by 2 or 3 billion years of evolution. The researchers compare the problem to deciphering a "palimpsest," a parchment that has been inscribed two or more times, but with the earlier texts imperfectly erased.

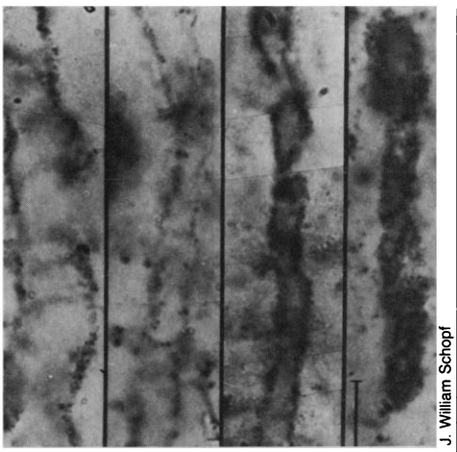
Benner and company accordingly break the reconstruction process into two steps. First, they try to reconstruct the "progenote," which is their name for the last common ancestor of modern forms of life. Presumably the progenote is a descendent of the breakthrough organism and is therefore much more recent in time. It is also much more accessible, because its metabolic pathways can be deduced from modern organisms in much the same way that ancient languages such as Indo-European can be deduced from modern languages such as English and Russian.

To take a very simple example, says Benner, all modern forms of life use DNA as their genetic material and have similar ways of decoding the information it contains. So these abilities must have evolved first in the progenote and then been passed along to its descendants. In general, says Benner, the most probable form for the progenote is the one that could produce modern life forms with the fewest mutations.

Proceeding in this way, Benner and his colleagues build up a reasonably detailed picture of the progenote's genetics and metabolism. Even Weiner says he finds this part of their work intriguing.

But Benner and his colleagues hit a roadblock in trying to take the next step back to the breakthrough organism. The extrapolation fails, Benner says, if there is only one known descendant. And by their definition the progenote is the only descendant of the breakthrough organism.

To get around this roadblock, Benner, Ellington, and Tauer propose what might be called the rule of non-uniqueness. Suppose, for instance, that a piece of RNA plays a role in a modern cell that might have been played just as well by a protein. Adenosine, for example, is a building block of RNA that is also found in a variety of small molecules, including adenosine triphosphate (ATP), that are crucial to the cell's metabolism. Since it is hard to see how such an RNA fragment could have displaced a protein that was already in use, argues Benner—proteins can generally do a given job much better than RNA—the logical conclusion is that ATP and other small adenosine-containing molecules are relics of the pre-protein RNA world.



J. William Schopf

Relics of an RNA world? *These bacterial fossils are 3.5 billion years old.*

Alternatively, suppose a piece of RNA plays a role for which it is uniquely suited. In that case, says Benner, it could have arisen at any time in the course of evolution. Indeed, it could have arisen several times in several different forms, which would then have converged by natural selection.

It is by reasoning such as this that Benner, Ellington, and Tauer come to their most startling conclusion: that the breakthrough organism had DNA and the mechanisms for transcription in place *before* it made extensive use of proteins as catalysts. That conclusion runs counter to most other views of the RNA world.

The researchers' argument starts with ribonucleotide reductase, the enzyme that converts the ribose sugars in RNA building blocks to the deoxyribose sugars found in DNA. There are at least three and possibly four kinds of these reductases known in the modern world, they point out, and each is quite different in structure and mechanism of operation. So where did they come from?

It's hard to see how these reductases could have evolved independently, Benner says, because that would mean that they had no common ancestor in the progenote—even though the progenote certainly used DNA and therefore must have had some way to make it. And yet it's just as hard to see how the different reductases could have evolved from a single ancestral protein, because that would have required massive changes in the protein—even though there was no obvious selective pressure to do so.

So the most plausible alternative, say Benner and company, is that the modern enzymes evolved from an ancestral reductase made of RNA. Indeed, this has long been thought to be how RNA-world enzymes gave way to protein enzymes in general: over time, the various sections of RNA would have been replaced by more efficient protein segments, which would thereby confer a selective advantage on the organism in which the replacements occurred. Eventually the RNA would vanish entirely.

But this alternative also leads to an obvious conclusion, say the researchers: if an RNA-based reductase was present in the RNA world, then it must have had something to do—namely, make DNA.

Weiner, however, doesn't buy it. "They want the RNA world to be very complex? Okay," he says. They want to have DNA appear early? That's a surprise to most people, he says, but again, okay.

"But this breakthrough organism—it's social Darwinism! What they're saying is that there were no proteins up to that point, and then some organism invented protein translation and just took over." Weiner finds it much more plausible that protein translation was invented jointly by many RNA-based organisms, which were constantly cross-fertilizing each other in a kind of long-term, community effort.

Nonsense, replies Benner: a sudden appearance of protein is precisely what he and his colleagues are not claiming. "There does have to be a first protein synthesized by translation, just as there was a first airplane and a first pilot," he says. "But that doesn't mean that the whole aviation industry was invented at that moment."

Clearly, this debate is not going to get resolved any time soon. But at least the Benner group's theory has a testable prediction: that some bacterium, somewhere, will be found to have a reductase that retains a fragment of catalytic RNA.

As Ellington says, "I'm the first to admit that this is just a theory. It all happened billions of years ago, and there's no way you can prove anything. But perhaps [research like this] can tell you something about the rules by which evolution operates."

■ **M. Mitchell Waldrop**

ADDITIONAL READING

S. A. Benner, A. D. Ellington, and A. Tauer, "Modern metabolism as a palimpsest of the RNA world," *Proc. Natl. Acad. Sci. U.S.A.* **86**, 7054 (September 1989).