in a very difficult stage, and we don't know where we are going," says a frustrated Masatake Fukugita, a cosmologist from the University of Kyoto.

Few of the models are fatally wounded—at least in the eyes of their creators. Between the possible errors in the COBE results and the room for adjustment in the models, there's enough wiggle room for even the most hard-pressed cases to squeeze by. "One thing I was surprised to see was that COBE has not ruled out huge classes of models. People can force them to fit," says Dick Bond of the Canadian Institute for Theoretical Astrophysics, Toronto.

But some cosmologists, unwilling to force existing models to work, have started getting serious about models they previously considered ungainly, such as a mixture of hot and cold particles or a combination of these and a mysterious antigravity factor called the cosmological constant. "These are not the most elegant models," says Davis, "but the data have gotten so good that you have to consider these theories on the merit that they fit the data."

New Ferment

The combination of new data and unsettled theories should make for some exciting times in cosmology. "This is one of those breakthroughs that turn the field red hot," says University of Pennsylvania's Steinhardt. The heat may increase another notch with results from other microwave experiments. COBE can only measure the very biggest "bumps" in this microwave background. Detectors at the South Pole, for example, can trace finer scale details. And so far, says Steinhardt, the South Pole instruments see only perfect evenness. This lack of structure, he says, "is getting a little painful." Reconciling COBE's broad-scale map with the finer scale results from the South Pole, says Steinhardt, may call for one of the complex explanations of the cosmic background—possibly the one he's been developing, in which the "lumps" COBE has mapped contain the signature of gravitational waves generated by the Big Bang.

Before such strange beasts can be either banished or welcomed into the fold of competing theories, there's also more work to be done on the calculation side, says Bond. He adds that cold dark matter appeared to suffer such a blow from the COBE results only because it was the best thought-out model, with the sharpest predictions. "It's easy to say something is possible when not enough calculations have been done," he says.

The one thing Bond and his colleagues are sure of is that a theoretical shake-out is coming, and the COBE results will help drive it. But they aren't holding their breath. Says Princeton's David Spergel, "I don't know whether we're really close to an answer or nowhere near it."

–Faye Flam

Biologists Trace the Evolution of Molecules

An unusual mix of 300 molecular biologists, population geneticists, and evolutionary biologists came together from 11 to 14 June at Pennsylvania State University for the International Conference on Molecular Evolution. Though their disciplines go by different names, all use the tools of molecular biology to sort out evolutionary history—whether they are trying to decipher the evolution of molecules such as RNA and DNA or reconstruct the family ties of humans and other organisms (see story on page 32, for example). Though the meeting was rife with disagreements about findings and even about methods, the participants did cover more than 3 billion years of evolution in 3.5 days. What they missed, they'll pick up on next year: They agreed to form a new Society for Molecular Biology and Evolution, which plans to meet annually.

Creation of the Exon Universe

When Nobel–Prize winning molecular biologist Walter Gilbert glanced at the program at the start of last week's conference on molecular evolution, he got a surprise: There, in the abstracts, was a description of a poster confirming a key prediction Gilbert had made in 1986—one that had been based on a highly controversial theory about how genes were put together in the earliest cells. "It's just what the doctor ordered," exclaimed Gilbert as he met the Canadian graduate student presenting the poster.

The student, molecular biologist Claus Tittiger of Queen's University in Kingston, Ontario, has discovered a piece of apparently senseless DNA, called an intron, in exactly the spot in the mosquito genome where Gilbert had forecast it would be. Like a piece of tape splicing together sections of movie film, the intron falls where Gilbert's "exon shuffling" hypothesis suggests two protein-coding modules called exons were joined together early in the evolution of the gene for the enzyme triosephosphate isomerase (TPI). But even as Gilbert delightedly embraced the new evidence, some scientists at the meeting were unconvinced: "This is just one example that supports his theory," says Indiana University evolutionary biologist Jeffrey Palmer, who criticized the hypothesis in an invited talk and in lively discussions that spilled out into the hallways during the conference.

Gilbert has had to get used to sniping ever since he argued in *Science* (7 December 1990, p. 1377) that genes were constructed from a surprisingly small number of genetic building blocks that have been around for 3 billion years. The Harvard University biologist proposed that several thousand of those blocks—the ancestors of exons—were shuffled and recombined in new ways over the millennia by introns, whose role has puzzled scientists for decades. By separating the protein-coding exons, he hypothesized, introns made it easier and faster for the exons to move about through recombination, thereby permitting rapid evolution of novel forms.

But that proposal put Gilbert at the center of an ongoing controversy. If introns played the role he described, they would have to be as old as the genes they are found in. As early as 1978, W. Ford Doolittle of Dalhousie University in Nova Scotia had proposed that introns were always part of the ancestral genome. Supporting that view, Gilbert found introns in identical locations in the genomes of distantly related organisms, such as corn, chickens, and humans. This, the "introns-early" school argued, provided evidence that the introns must have been inherited from a common ancestor of plants and animals.

Wrong, insist doubters, including Palmer. The trouble is that examples of introns showing up in identical locations in the genomes of plants and animals are the "exception, not the rule," says Palmer. The vast majority of the hundreds of thousands of introns in animal genomes are found in different positions than the introns in plant genomes. Moreover, introns are missing from the protein coding genes of many ancient organisms, including all prokaryotes (organisms with nonnucleated cells) and all of the earliest known eukaryotes (which have nucleated cells).

Gilbert responds that introns would have been lost from some genes after their assembly as they were "streamlined" for more efficient transcription of the genetic message. And now he can point to Tittiger's poster for support. In a 1986 article in *Cell*, Gilbert had noted that in such distantly related organisms as corn, the fungus aspergillus, and chickens, the TPI gene has a total of 11 exons and 10 introns—although not all appear in any one creature. He proposed that the ancestral gene had included all of those introns, plus one extra, to break up one of the exons that

was much longer than the others in the genes of the modern organisms. The missing intron, he said, must have been lost from the studied organisms, but he predicted that it would turn up in the TPI gene of some other organism that had preserved it over the millennia.

And that's just what Tittiger, with the help of geneticist Virginia Walker, his supervisor, and graduate student Steve Whyard, found in the mosquito genome, in precisely the predicted spot. Not only does the discovery provide additional evidence for the ancient origins of those introns, but it also shows that they can be lost from many organisms over time.

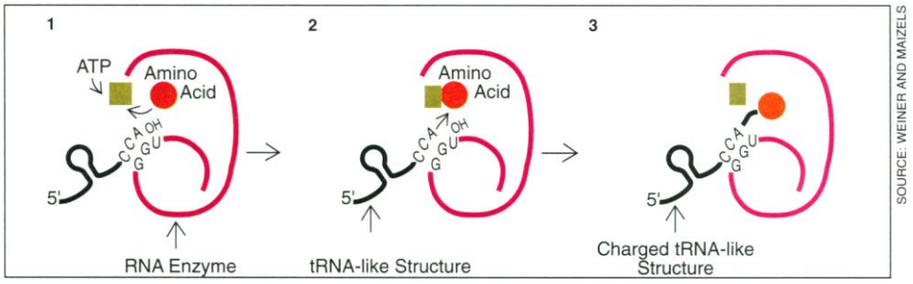
But this latest example won't be enough to convince members of the "introns-late" school, who say that it's hard to swallow the notion that tens of thousands of introns have vanished over and over again. Instead, Palmer thinks, introns are much more likely to have been inserted later in a single group of higher eukaryotes. He predicts that as more TPI genes are sequenced in other organisms, many other new introns will be found that were not predicted by Gilbert—and in locations that are awkward for the exon shuffling hypothesis. "Exon shuffling played no major role in the assembly of primordial genes," says Palmer. And that means "there is no universe of exons to be analyzed" outside of those organisms that actually have introns.

But Gilbert isn't swayed, saying that for now, he is reassured—and downright thrilled—by the Tittiger poster: "It is very rare in biology to make a prediction and have it work out." As for the young Ontario molecular biologist who landed in the middle of the debate, he isn't about to guess who is right: "This was an overwhelming experience," he says.

Excavating the Molecular Fossil Record

Yale University molecular biologists Alan Weiner and Nancy Maizels are searching for clues about the origin of life. But they aren't looking at ordinary fossils made of mineralized bone. Instead, they are studying what they call "molecular fossils"—modern biomolecules whose parts appear to be frozen in time, preserving remnants of the ancient events that forged the first living molecules. Earlier excavations of this molecular fossil record had convinced many researchers that the first molecules able to store information and catalyze their own reproduction were made of RNA. Now Weiner and Maizels are trying to fill in some major gaps in the picture of that "RNA world."

If RNA came first, how, for example, did it begin copying itself, which it had to do to transmit genetic information from one generation to the next? And how did RNA devise the machinery needed to build the first proteins? Weiner and Maizels think they can answer those questions with a model they have been developing over the past 5 years. And at the International Conference on Molecular Evolution, Weiner argued that new work from several labs lends persuasive and unexpected support to the central hypothesis of their "genomic tag model"—namely that a small RNA loop that appears in modern RNA species is in fact an ancient structure that played a major role in replication in the RNA world.



Origin of protein synthesis? An RNA-replicating enzyme charges a tRNA ancestor by attaching an amino acid.

In developing their model, the Yale pair took their cues from the structures of the RNAs in the genomes of modern retroviruses and certain RNA viruses that infect bacteria and plants. They realized that all these unrelated viruses use a similar structure to initiate the copying of a single strand of RNA into another complementary strand of RNA or DNA. That structure is a length of RNA that folds into a stem and a loop at the 3' end of the RNA. The fact that this same structure is found in these apparently unrelated viruses suggested to Weiner and Maizels that its role in copying RNA must be ancient. Billions of years ago, the same structure might have served as a "genomic tag" to highlight a region of RNA as a starting point for duplication by an early RNA-replicating enzyme (itself made of RNA).

But once they developed their model to explain how RNA replicated itself, Weiner and Maizels thought they saw evidence that the genomic tag could have had another role as well. That genomic tag structure also looks a lot like the structure of modern transfer RNA (tRNA), which translates the nucleic acid language of the genome into the sequences of amino acids that make up proteins. The similarity, they thought, was too remarkable to be coincidental, so they proposed that in the earliest era of life, these genomic tags gradually expanded their purview from RNA replication to protein synthesis. The expansion began, they suggested in a 1987 paper, when the RNA-replicating enzyme evolved the ability to attach an amino acid to the tRNA-like genomic tag, giving it a charge. That step would have made replication more efficient—and it also prepared the genomic tags for their later role in assembling amino acids into the first peptides. Weiner points out that a recent paper in *Science* (5 June, p. 1420) by Joseph Piccirilli, Thomas Cech, and others at the University of Colorado, Boulder, demonstrated that an RNA enzyme can indeed do that job.

The whole scenario, of course, assumes that the tRNA-like genomic tags truly are relics of the RNA world. And as Weiner reported at the conference, independent studies by Alan Lambowitz's group at Ohio State University and Elizabeth Blackburn's group at the University of California, San Francisco, have recently found that tRNA-like genomic tags play critical roles in transcribing RNA into DNA in the mitochondria and nuclei of higher organisms, not just viruses. The findings suggest that, rather than being something recently invented by viruses, the structure is probably ancient and has survived over 3.5 billion years of evolution.

Weiner and Maizels are also encouraged by some other recent work that is filling in gaps in their scenario. When primordial tRNAs laden with amino acids came together, assembling a protein would have required an enzyme capable of forming a bond between the amino acids. According to recent work by University of California, Santa Cruz, molecular biologist Harry Noller, such an enzyme may well have been present in the RNA world. Last month he presented evidence that a ribosomal RNA itself is the enzyme that catalyzes the assembly of amino acids (*Science*, 5 June, p. 1416).

Taken together, says Weiner, the research begins to fill in the missing pieces in the history of RNA. "Harry's work meets us halfway," says Weiner. "We're speculating that RNA catalysis gave us tRNA and tRNA charging. Now Harry proves that the enzyme that catalyzes the peptide bond formation is made of RNA." What all this means, he adds, is that the case is getting stronger and stronger for the RNA world. "RNA is doing all the interesting things."

–Ann Gibbons

Additional Reading

For "Exon": J.D. Palmer and J. Logsdon Jr., "The recent origins of introns," *Curr. Opin. Genet. Dev.* **1**, 470 (1991).

For "Molecular Fossils": A. M. Weiner and N. Maizels, "t-RNA-like structures tag the 3' ends of genomic RNA molecules for replication: Implications for the origin of protein synthesis," *Proc. Natl. Acad. Sci. U.S.A.* **84**, 7383 (1987).