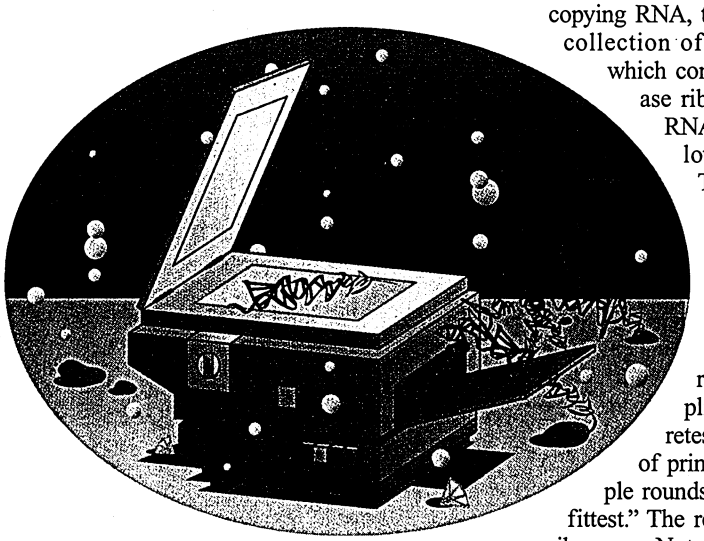
RIBOZYMES

Making Copies in the RNA World

By mimicking evolution in the lab, scientists have produced the first RNA enzyme that can make copies of other RNA molecules. The discovery provides a missing piece of evidence for a primitive biological world that existed before DNA and proteins entered the scene.

The discovery nearly 2 decades ago of ribozymes—RNA molecules that can catalyze chemical reactions—led to the idea



that modern life could have evolved from a primitive "RNA world." Doing the job of both DNA and proteins, RNA would carry genetic information and replicate that information to pass on to future generations. Subsequent discovery of additional ribozymes—including the heart of the protein-synthesizing ribosome (*Science*, 31 July 1998, p. 658, and 11 August 2000, p. 878)—has added to the credibility of the RNA world hypothesis. But scientists have been unable to show that molecules of RNA are actually capable of copying other RNA sequences, a job performed in the modern biochemical world by protein enzymes called RNA polymerases. That activity would be a critical component of an RNA world.

On page 1319 of this issue, Wendy Johnston and colleagues at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology (MIT) in Cambridge have now filled that key gap. They describe an enzyme, consisting of a stretch of RNA produced by in vitro evolution, that can make complementary copies of RNA molecules up to 14 nucleotides long, regardless of sequence, with impressive accuracy.

"The engine of the RNA world" would have to be able to do better than 14 nucleotides, says Gerald Joyce of the Scripps Research Institute in La Jolla, California, "but there's no doubt [now] that RNA [itself] is capable of doing polymerization."

David Bartel, leader of the Whitehead group, had previously selected from random RNA sequences an RNA molecule that could join two RNA strands end to end. He later discovered that this "RNA ligase" could also add a few nucleotides, the individual building blocks of RNA, onto the end of RNA molecules with specific sequences. Although not very robust, the ribozyme was performing the same chemical steps as "modern" protein enzymes that synthesize RNA.

To search for ribozymes that are better at copying RNA, the Whitehead team made a collection of RNA molecules, each of which consisted of Bartel's RNA ligase ribozyme linked to a 76-base RNA with random sequence followed by an RNA "primer." They screened 10^{15} of these randomized molecules for those that could add nucleotides to the end of the RNA primer, in a specific sequence dictated by an RNA template added to the reaction. The researchers amplified working molecules and retested them with different sets of primers and templates in multiple rounds of in vitro "survival of the fittest." The result was a vastly improved ribozyme. Not only could it make complementary copies of RNA templates 14 bases long, but most important, it could use any RNA sequence as a template, a generality that would be critical for a replicating ribozyme in an RNA world.

Bartel notes that the ribozyme stops adding bases not because it can't hold onto long pieces of RNA but because the best reaction conditions for polymerization are also optimal for chemical breakdown of RNA. That suggests that by tweaking the reaction conditions it should be possible to make RNA molecules longer than 14 nucleotides—a prerequisite for the RNA world. (The Whitehead team's ribozyme itself, for instance, is 189 nucleotides long.)

The ribozyme adds the right base onto RNA about 98.5% of the time. That pales in comparison to protein polymerases, which can achieve 99.99% accuracy. But, speculates Phillip Sharp of MIT, ribozymes in the RNA world may have only had to copy RNA sequences a few hundred bases long; longer units could have been spliced together by other ribozymes. That would make higher error rates tolerable.

The ribozyme's ability to generically recognize any RNA sequence is likely due to its interaction with chemical groups on an RNA molecule's backbone. The details of that interaction, however, await further structural studies. Those studies could reveal similarities with protein polymerases, says biochemist Tom Cech of the University of Colorado, Boulder, president of the Howard Hughes Medical Institute and co–Nobel Prize winner for the discovery of ribozymes. He notes that protein polymerases commonly resemble a hand, with catalysis occurring in the "palm" and a "thumb" and "finger" holding the substrate in place: "Maybe they started with a palm [the RNA ligase] and evolved a thumb and finger." **–R. JOHN DAVENPORT**

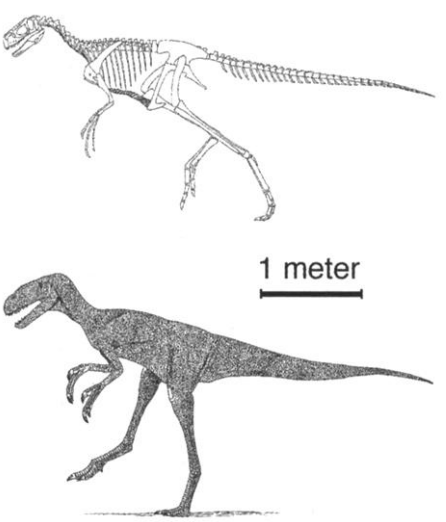
PALEONTOLOGY

Early Tyrannosaur Was Small But Well Armed

For all the fame of *Tyrannosaurus rex* and its relatives, their origins have been difficult to pin down. Now paleontologists have unveiled a skeleton of a primitive tyrannosauroid that backs up what many have suspected: The hulking predators evolved from smaller, long-armed creatures with grasping hands.

The classic view of *T. rex* ancestry held that it evolved from a long line of large meat eaters that stretched back about 80 million years to the Jurassic. An alternative idea, proposed in the 1920s, suggested that the tyrannosaurs of 65 million years ago descended from a group of more diminutive predators called the coelurosaurs, which is now known to include *Velociraptor*. The theory didn't catch on at the time, but it was revived in the 1990s and sometimes dubbed the "tyrannoraptor hypothesis." Yet despite the many anatomical similarities between tyrannosaurs and smaller coelurosaurs, no one had found a dinosaur that seemed transitional.

That gap is now filled by the 132-million-year-old *Eotyrannus*, found by an



Hands up. Unlike its later *T. rex* kin, *Eotyrannus* sported long, grasping forelimbs.

CREDITS: (TOP TO BOTTOM) ILLUSTRATION: TERRY SMITH; COURTESY OF DARREN NAISH/UNIVERSITY OF PORTSMOUTH

amateur collector in 1997 on the Isle of Wight, off the southern coast of England. Although isolated bones of primitive tyrannosaurs had been reported before, this 5-meter-long skeleton beats them hands down. It's about 40% complete and includes the front half of the skull. In the April issue of *Cretaceous Research*, a group from the University of Portsmouth, United Kingdom, and the Museum of Isle of Wight Geology describes several features that link *Eotyrannus* with tyrannosaurs, such as fused nasal bones and teeth with a "D"-shaped cross section. Other traits are much more primitive, and it has long arms and hands like *Velociraptor*—just as the tyrannoraptor theory predicts. "This is one of the first specimens to confirm that," says team member Darren Naish of the University of Portsmouth.

The new specimen will help clarify how tyrannosaur traits evolved, says paleontologist Tom Holtz of the University of Maryland, College Park, who gave the tyrannoraptor hypothesis its name. For example, *Eotyrannus* implies that the advanced biting style of the tyrannosaurs evolved in a predator that could still grab with its arms. As for the tyrannoraptor idea, Holtz says *Eotyrannus* "is great confirmation." –ERIK STOKSTAD

ANIMAL RESEARCH

Charles River Labs to Care for NIH Chimps

After a yearlong search, the National Institutes of Health (NIH) has found a new caretaker for nearly 300 chimpanzees once used in medical research. The decision is a mixed blessing for animal activists. They had long accused the animals' current caretaker, the Coulston Foundation of Alamogordo, New Mexico, of unsafe and negligent veterinary practices, but they had hoped the chimps would be released to a retirement sanctuary. And they were especially upset by a separate NIH decision to purchase 14 young chimpanzees from Coulston for possible research.

As *Science* went to press, NIH was set to sign a 10-year, $42.8 million contract with Charles River Laboratories, a company based in Wilmington, Massachusetts. The corporation would assume care for 286 NIH-owned chimpanzees at the Holloman Air Force Base in New Mexico, most of them infected with HIV or hepatitis in NIH protocols. "This isn't an official sanctuary, but the idea is that at this facility, [chimpanzees] will be cared for, given social enrichment, and allowed to live out their natural lives," says Charles River senior vice president Dennis Shaughnessy about the colony. No experiments will be conducted at Holloman, says Judith Vaitukaitis, director of NIH's National Center for Research Resources, although

High priced? NIH is reportedly planning to buy 14 young chimpanzees for $30,000 each.

NIH-funded scientists interested in conducting research on the chimps may arrange for animals to be transported to other sites.

Animal-welfare groups have complained loudly about the privately owned Coulston Foundation, charging that it provides inadequate veterinary care and keeps its animals in unsafe conditions. The foundation has denied those charges. In 1999, Coulston settled one investigation by the U.S. Department of Agriculture (USDA) into animal welfare violations (*Science*, 10 September 1999, p. 1649) by agreeing to give up 300 of the approximately 600 chimpanzees the foundation owned.

NIH acquired 288 Coulston chimps last May and since then has conducted several unsuccessful searches for a caretaker. Coulston put in a bid, but NIH rejected its application (*Science*, 13 October 2000, p. 247). The USDA still has an open investigation on Coulston, and two of the NIH-owned animals have died in the last year. Animal-welfare groups have claimed that the deaths were due to negligence, whereas Coulston spokesperson Donald McKinney says that the animals died of routine health complications.

Linda Brent, president of Chimp Haven, an organization in San Antonio, Texas, that hopes to build retirement sanctuaries for former research chimpanzees, says finding an alternative provider was a positive interim step. "I am hopeful that in the future [the chimpanzees] will be able to be moved out and fully retired," she says.

Indeed, NIH is reluctantly moving forward to set up a system of retirement sanctuaries. Last month, it requested that interested organizations describe their ability to care for at least 75 chimpanzees as part of the so-called CHIMP Act, which President Clinton signed into law last December (*Science*, 22 December 2000, p. 2233). The law requires NIH to set up a system of retirement facilities for animals no longer needed in research. At least two organizations, Chimp Haven and Primarily Primates, also in San Antonio, filed the required statement by the 15 May deadline.

ScienceScope

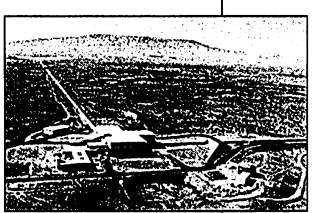
Measuring Up What good is a painfully detailed review of a research agency's activities if it's ignored by the politicians who draw up the agency's budget? That's what a National Academy of Sciences (NAS) panel asks in a new report on a 1993 law aimed at making the federal government more efficient.

The Government Performance and Results Act (GPRA) requires each agency to set annual goals, define how it plans to achieve them, and then measure the outcome. For years, researchers have worried that the act would trivialize federally funded research by forcing agencies to show a short-term payoff from basic research. Now they have a new fear—that agency officials are wasting time preparing reports that lawmakers don't read.

The annual GPRA reports "have not been used for a political purpose, which is the ultimate goal," says Enriqueta Bond. Bond co-chairs the NAS panel that looked at how five leading research agencies deal with the act, which kicked in a few years ago. A White House budget official agrees, adding that "the measures used by most agencies aren't particularly helpful" in setting funding levels.

The annual exercise does help the agency evaluate research quality and relevance, according to the academy panel, but falls short in deciding if the work is world-class. Still, the burden of preparing the reports may soon outweigh the benefit, Bond warns, unless policy-makers start paying more attention.

Quake-Proof LIGO has been shaken and rattled, but it is nearly ready to roll again. On 28 February, a magnitude-6.8 earthquake struck Washington state and took a toll on the Laser Interferometer Gravitational-Wave Observatory in Hanford (right), a sensitive detector designed to detect the warping of space-time by gravitational waves (*Science*, 21 April 2000, p. 420). The shaking knocked equipment out of alignment and damaged some mirror attachments, says site chief Fred Raab, derailing a scheduled joint observation session with a twin facility in Louisiana. But repairs should be completed by the end of the month, and the project is still on track to begin its gravitational-wave search next year.



Contributors: Andrew Lawler, Charles Seife, Jeffrey Mervis

CREDITS: (TOP TO BOTTOM) ROBERT MAASS/CORBIS; LIGO/CALTECH