beacon got brighter, the frequency increased. Then, to their delight, the brightness increased, but the frequency seemed to hit a ceiling at about 1000 cycles per second. It would go no higher, implying that no smaller orbit was possible.

The group measured the ceiling on four different occasions, and they also saw it in a second, slower flicker, which originates as the accretion disk signal modulates another x-ray signal from a hot spot on the surface of the spinning star. "I'm convinced it's not a fluke," says NASA Goddard's William Zhang, who presented the findings. Zhang says the innermost orbit is about 20 kilometers from the star's center.

"These are extremely exciting results," says Massachusetts Institute of Technology (MIT) physicist Paul Joss, explaining that the innermost orbit is direct evidence of the drastic warping of space-time expected near a massive object. Similar observations, says MIT physicist Wei Cui, could provide a stringent test for Einstein's theory. "Everyone assumes relativity is right," he explains, "but there are so many theories of gravity around."

Most of these variants of relativity are indistinguishable from Einstein's except around dense objects like neutron stars. The innermost orbit, "literally a few kilometers above this strange object," he says, is just the place where the theories' predictions might differ. If Einstein's theory is right, the position of the innermost orbit means the star's mass is about 2.3 times that of the sun. Unfortunately, there are no independent measurements of the mass to test that conclusion. But by studying other x-ray emitters, physicists may be able to confirm Einstein or rule out his competition.

Relativity specialists aren't the only ones delighted with the data. The position of the innermost orbit implies that the neutron star is surprisingly hefty. By some estimations, that much mass packed into so small a volume should have collapsed into a black hole. The fact that it hasn't means that the strong nuclear force holding the particles apart is stronger than some had expected. "The nucleons want to stay farther away from each other," staving off further collapse, says NASA Goddard physicist Jean Swank.

University of Illinois astrophysicist Frederick Lamb is delighted with another feature of the data, the correlation between brightness and frequency. It supports his contention that the star's radiation plays a crucial role in controlling the infall of matter. "These data are like a dream come true," he says. But he cautions that they "have only been around for 2 weeks. We need to kick the tires and see that they stand up."

–David Kestenbaum

EVOLUTIONARY BIOLOGY

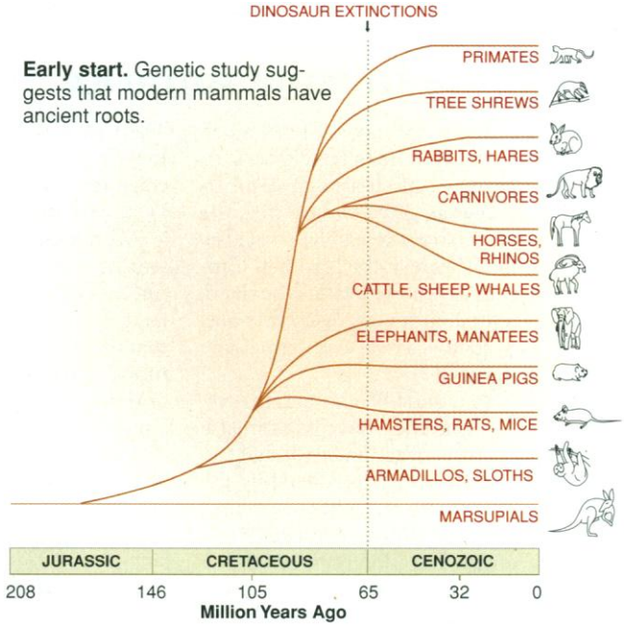
Genes Put Mammals in Age of Dinosaurs

It's hard to imagine humbler beginnings than those usually assigned to mammals. The long-standing view from the fossil record is that our furry ancestors first appeared 225 million years ago as small, shrewlike creatures living in the shadow of the dinosaurs. Only after a mass extinction 65 million years ago at the end of the Cretaceous period killed off the dinosaurs were mammals able to evolve into everything from primates to rodents to carnivores. But a new genetic study is challenging that view, saying mammals were already a diverse lot during the age of dinosaurs.

In this week's issue of *Nature*, evolutionary biologist S. Blair Hedges and molecular evolutionist Sudhir Kumar of Pennsylvania State University, University Park, describe how they compared genes from hundreds of vertebrate species and used the differences as a molecular clock to date when animal lineages originated. The molecules show, say Hedges and Kumar, that the modern orders of mammals go back well into the Cretaceous period, in some cases to more than 100 million years ago. "The thought of all these different creatures living under the feet of the dinosaurs is intriguing," says Hedges.

But many paleontologists are deeply skeptical. "It suggests that the fossil record is horribly incomplete," says Michael Benton, a paleontologist at the University of Bristol in the United Kingdom. "They're saying side by side with lower Cretaceous dinosaurs, we should be finding ducks and hens and squirrels and rabbits." Instead, he thinks that the molecular clock can't keep time.

The new report is the latest of several molecular studies to suggest that many animal lineages are older than the fossil record shows (*Science*, 21 February 1997, p. 1109). Most of these studies have relied on just a handful of genes and have not persuaded many doubters. But Hedges and Kumar analyzed a prodigious number of genes—658 in all—and counted sequence differences between 207 vertebrate species. They assumed that the more differences between two species, the more time had passed since they diverged from a common ancestor. To calculate how fast the molecular clock ticks, the team started with a reliable date from the fossil record: 310 million years ago, when the mammal-like reptiles split from the birdlike reptiles. From the sequence differences seen between animals in these two groups, the team calculated a rate of change for each gene, then used those rates to calculate divergence times among other species of vertebrates.



Early start. Genetic study suggests that modern mammals have ancient roots.

SOURCE: S. KUMAR AND S. B. HEDGES/PENN STATE

For most species, the molecular dates matched those from fossils—but not for mammals. According to the genes, the modern orders of mammals arose much earlier than expected (see graph). Marsupialia (kangaroos and opossums) are pegged as originating 173 million years ago, rather than 94 million years as indicated by fossils, and Archonta (primates and tree shrews) at 86 million years ago, rather than 64 million years ago. "This doesn't mean that elephants and tigers were running around," says Hedges. "The animals themselves were probably small. But the lineages leading to different modern orders of mammals were already distinct."

Paleontologist Philip Gingerich of the University of Michigan, Ann Arbor, however, protests that if the molecules are right, the fossil record has a gap as big as 70 million years. "You can imagine how maddening this stuff is to a paleontologist," he says.

The missing mammals may have been overlooked because they were small and harder to find, or because they were scarce and lived in terrain less likely to be preserved, suggests Hedges. But Benton says that's unlikely because the Cretaceous fossil record reveals many lizards, snakes, birds, and other small vertebrates. And paleontologists have turned up

only a few controversial Cretaceous specimens linked to modern mammals (*Science*, 21 November 1997, p. 1438), although they have hunted intensely. "There's a huge premium on finding a Cretaceous rabbit or other mammal," says Benton.

Instead, most paleontologists argue that the molecular clock is unreliable. Perhaps the mutation rate sped up and slowed down at different times in mammalian history, suggests Benton. For example, a population explosion during the rapid radiation of mammals 65 million years ago might have allowed their DNA to accumulate mutations more quickly, speeding up the clock.

But Hedges and other molecular evolutionists say their clock is reliable, noting that their study agrees with most dates from the fossil record and with other genetic work. "It's entirely consistent with what we found," says Simon Easteal, a molecular evolutionist at Australian National University in Canberra who also found earlier origins for mammals. And if the clock sped up during the early mammalian radiation, then the later dates for divisions between various mammalian species, such as primates, sheep, and cows, wouldn't match those from fossils—unless the clock later slowed down by precisely the same amount in each of many different lineages. "That is really stretching," says Hedges.

For now, the debate goes on. "We have two fairly entrenched positions," says Benton. "The exciting thing is within our lifetimes, we can hope to see which one is right."

–Ann Gibbons

MICROBIOLOGY

New Clue to How Anthrax Kills

The deadly disease anthrax has been much in the news lately—thanks largely to fears that rogue leaders or international terrorists will attempt to wage germ warfare with the anthrax bacillus. Now, a research team led by George Vande Woude at the National Cancer Institute (NCI) in Frederick, Maryland, has made a serendipitous discovery that may someday give doctors a new countermeasure against the disease.

On page 734, Vande Woude and his colleagues report that they have identified a possible mechanism of action for "lethal factor" (LF), a toxic protein produced by the anthrax bacillus that is thought to be one of the principal causes of death in infected individuals. Scientists have long suspected that LF is a protease, an enzyme that cuts other proteins, but they have not been able to identify its targets. The Vande Woude team has found that LF cleaves and inactivates an enzyme in one of the cell's key signaling pathways, the mitogen-activated protein kinase (MAPK) pathway, which helps control cell growth, embryonic development, and the maturation of oocytes into eggs.

Although it makes sense that disrupting such a critical pathway could kill cells, researchers have not yet shown that this effect is what makes LF so toxic. Regardless, the result may aid the development of new treatments that work by neutralizing the toxin. As Vande Woude puts it, "Conceivably, we could find a drug that would make anthrax as a weapon of destruction as powerful as a water pistol."

He and his colleagues had no intention of studying anthrax pathogenicity. They were interested in the MAPK pathway, named for one of its constituents, a so-called kinase that regulates the activity of other molecules by attaching phosphate groups to them. To find out more about the pathway's role in oocyte maturation, Nick Duesbery, a postdoc in Vande Woude's lab, was seeking compounds that block MAPK's activity. The group knew of one such chemical, PD09859, which is one of more than 60,000 agents the NCI has screened for antigrowth activity on human tumor cell lines. The Vande Woude team asked NCI chemist Ken Paull to search that database for other compounds with effects similar to PD09859's. LF proved to have the highest score.

Working with LF provided by anthrax researcher Steve Leppla at the National Institute of Dental Research in Bethesda, Maryland, Duesbery and colleagues then showed that the toxin prevents frog oocytes from maturing into eggs, indicating possible blockage of the MAPK pathway. The jam apparently happens, the researchers found, because LF clips off a piece of the enzyme responsible for activating MAPK, thereby crippling it. When they sequenced two forms of this enzyme—MAPK kinase (MAPKK)—from LF-treated cells, for example, they found that the amino terminals of the proteins were missing either seven or nine amino acids.

ARTHUR M. SIEGELMAN / VISUALS UNLIMITED

Deadly bug. Lung infections by *B. anthracis* (shown here) can kill rapidly.

Biochemist John Collier at Harvard University Medical School in Boston says that killing the host may be a key advantage of targeting this essential molecule. Unlike many microbial pathogens, *Bacillus anthracis* seems to depend on the death of its host to propagate. "As the animal decays, the bacteria are exposed to oxygen; they turn to spores and repopulate the soil," says Collier. "The host has to die for transmission to occur."

The identification of an LF target molecule represents the first step toward developing an antidote to the toxin. Natural anthrax infections, which are usually transmitted by animal products, are rare, but having such an antidote could be a boon if the pathogen were to be used in a terrorist attack. Although antibiotics kill *B. anthracis*, by the time characteristic symptoms appear, the bacteria are already multiplying wildly in the bloodstream and have produced massive amounts of circulating toxin, which can't be eliminated by killing the bacteria. Antibiotic treatment at this point doesn't help. "A drug that inhibits LF enzymatic activity might be able to act very quickly to block any further effects of LF on susceptible cells," says microbiologist Randall Holmes at the University of Colorado Health Sciences Center in Denver.

Still, the researchers aren't certain that LF owes its toxicity to its ability to cleave MAPKK. In fact, it's hard to explain how inactivating MAPKK would result in some of the known physiological effects of LF. In 1993, for example, Collier and Philip Hanna, currently at Duke University Medical Center in Durham, North Carolina, found that immune cells called macrophages mediate the harmful effects of LF in mice at least partly by producing inflammatory cytokines, immune cell–activating molecules that in excessive concentrations can cause some of the toxic reactions, including shock, seen in anthrax. Duesbery is now looking to see whether MAPKK inactivation is linked to overproduction of these compounds.

To try to show directly that MAPKK inactivation is responsible for LF's physiological effects, he is also investigating whether a MAPKK mutant that resists cleavage by LF can protect cells from the toxin. At the same time, the team is looking for other cellular substrates of LF.

As they pursue the many questions their findings have generated, the researchers seem to be enjoying the adventure. "I started out as a virologist and ended up studying oocyte maturation," says Vande Woude. "Now suddenly I'm looking anthrax in the face. It's pretty amazing."

–Evelyn Strauss

Evelyn Strauss is a free-lance writer in San Francisco.