tumor blood vessel growth. It also blocks apoptosis, or programmed cell death, perpetuating cancer cells. By forcing the buildup of a protein that prevents NFκB activation, PS-341 seems to starve tumors of their blood supply and growth stimuli, thereby promoting their self-destruction.

On a cellular level, blocking the proteasome generally stresses cancer cells by jamming them with proteins. Adams believes that cancer cells may be selectively vulnerable to PS-341 because they can't handle the stress of the protein buildup as easily as normal cells can. This stress causes "catastrophic signaling events, which drive the tumor cell to die," explains Adams. "A normal, untransformed cell can withstand the stress response, at least for short periods of time." For that reason, intermittent dosing—once or twice weekly, for a limited time—is crucial. The rest periods are designed to allow the proteasome in normal cells to recover. "We keep patients' dose below a level of 80% proteasome inhibition," says Adams. "There's a stress to the host, but a tolerable stress."

The clinical results, from a multicenter trial sponsored by Millennium and headed by Dana-Farber, announced at ASH seem to bear this out. Of 54 myeloma patients, more than half experienced major tumor shrinkage, and the drug halted tumor growth in most of the others. Because myeloma is currently incurable, oncologists are jubilant, although they express some misgivings. "We have something to whack myeloma with we didn't have a year ago," says James Berenson, director of myeloma programs at Cedars-Sinai Medical Center in Los Angeles. "That's pretty cool." But, he adds, "this is not an easy drug." Some patients experience such severe pain after taking PS-341 that they refuse to continue treatment. But enough have benefited that more than 30 separate clinical trials are now under way, sponsored by the NCI and by Millennium, in a wide range of cancers, including breast, colon, lung, and prostate.

Even if acute side effects can be managed, the long-term effects of partial, periodic proteasome inhibition in humans are unknown. "We definitely need to understand the effects of partial inhibition before we can make sweeping statements about why it's not toxic to normal cells," says McConkey. Primate studies have only gone out 3 months.

Already, it's clear that PS-341 is not the ideal proteasome inhibitor, because the drug indiscriminately raises levels for hundreds of proteins without regard to their anticancer effect. Millennium is now trying to develop inhibitors upstream of the proteasome, by tagging proteins for survival even before they're sent to the proteasome for destruction. If a drug could inhibit specific enzymes that attach ubiquitin to individual proteins (ubiquitin chains mark proteins for destruction in the proteasome), it could, in theory block degradation of only those proteins thought to have a direct anticancer effect—for example, tumor suppressor gene products.

So proteasome inhibition, in all its guises, has arrived as an anticancer strategy, although no one, including Millennium, is quite sure how best to apply it. "They have a golden nugget, but they're going to have to figure out how to make it into a golden ring," says Berenson. Only time will tell if PS-341 ultimately proves useful in the clinic, but the drug has already shown that playing with garbage has its rewards.

–KEN GARBER

Ken Garber is a science writer in Ann Arbor, Michigan.

MEETING **PRIMATE ORIGINS**

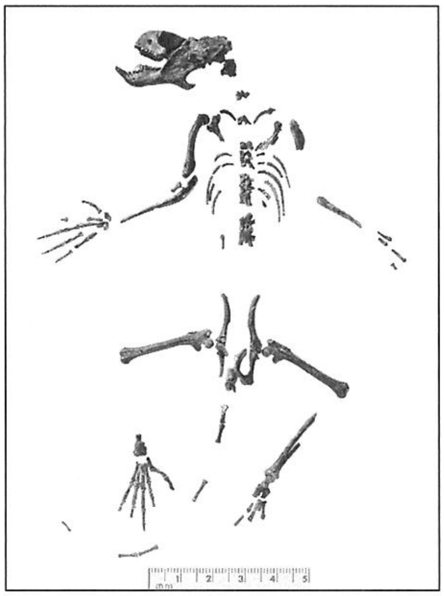
New Fossils and a Glimpse of Evolution

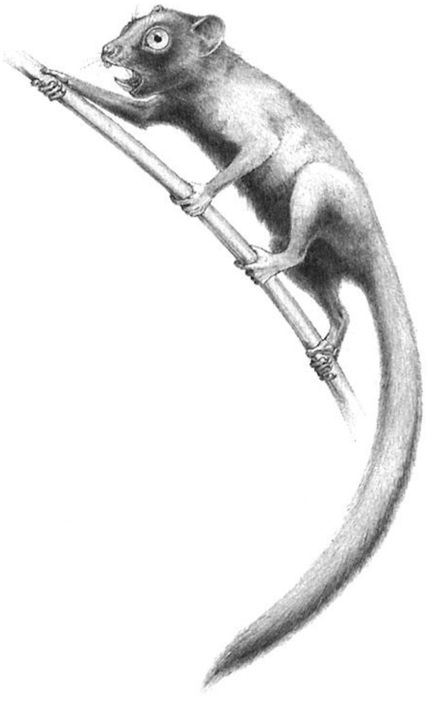
CHICAGO—In an all-too-rare occurrence, paleontologists and molecular biologists met here 13 to 15 December 2001 to share their data and their often very different perspectives. The gathering, the "First-Ever International Conference on Primate Origins and Adaptations: A Multidisciplinary Perspective," was organized by the Field Museum and Northwestern University. Hot topics included descriptions of six exceptionally well-preserved fossils of archaic primates and of how primates evolved color vision.

Fresh Look at Primate Ancestors

Small, furry, with large eyes, grasping hands, and a fondness for hunting insects: That's one of several popular images anthropologists have painted of the ancestors to primates. The first undisputed primates appear in the fossil record about 55 million years ago in the Eocene. The problem, however, has been a dearth of fossils before that time, in the Paleocene, to back up conjectures about primate ancestors. Vast movements of rock, earth, and water over tens of millions of years crushed the fragile fossils, usually leaving only scattered bones and teeth as evidence. Worldwide, less than a half-dozen incomplete Paleocene primate skeletons have been described.

Now, vertebrate paleontologist Jonathan I. Bloch and undergraduate Doug M. Boyer of the University of Michigan, Ann Arbor, and their colleagues have added considerably to this data bank. At the meeting they described their full cache of six exceptionally well-preserved, complete skeletons, dissolved out of freshwater limestone in the





Arborealist. Fossils of *Carpolestes simpsoni* suggest that it had specialized tactile and grasping abilities, necessary for a life in the trees.

CREDITS: D. M. BOYER

brightly colored badlands of the Clarks Fork Basin of Wyoming—world-renowned fossil beds of the Paleocene and Eocene eras of 65 million to 53 million years ago.

The stone blocks, although stored in the museum basement for a decade or so, have been painstakingly probed for fossils only in the last 3 years. Already, the new fossils are forcing paleontologists to reexamine and expand their earlier conceptions about archaic primates. The newfound fossils represent four of the 13 families of plesiadapiforms, or archaic primates, dating to about 56 million years ago: *Carpolestes simpsoni*, a new species of *Ignacius*, *Plesiadapis cookei*, and an as yet unnamed genus and species of micromomyid. The skeletons "are amazingly complete, a rarity for fossils that old," says Northwestern University evolutionary morphologist Matt Ravosa. "They blew people away."

Here's what the new evidence suggests:

Carpolestes simpsoni was a committed arborealist, weighing about 100 grams and capable of moving on large vertical supports and of grasping slender supports with its hands and feet. It sported a nail on its big toe, indicating specialized tactile and grasping abilities. "This fossil documents the first evidence of strong pedal grasping with an opposing big toe in a Paleocene primate," says Bloch. Equally important, the morphology of the ankle bones, showing marked mobility, suggests that *Carpolestes* was not a leaper. And although some plesiadapiforms may have been gliders, closely related to the modern flying lemur, *Carpolestes*'s lack of slender limbs and relatively short fingers on this fossil show that it was not.

With its flexible back, the 400-gram *Ignacius* could scamper both on the ground and up trees, as do modern squirrels. Judging from its teeth, *Ignacius* ate a generalized diet of insects and fruits, with a large helping of tree sap. Instead of gliding, it probably had a bounding gait, propelled by its hindlimbs.

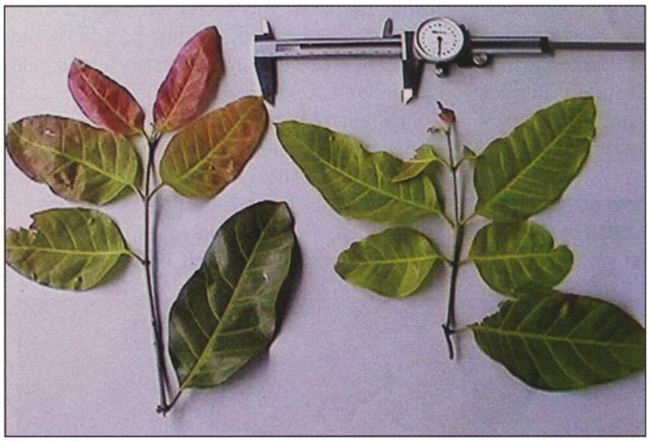
Plesiadapis cookei, the only skeleton of this species ever unearthed, spent most of its time in trees, unlike its European relatives, which may have lived on the ground like marmots. It weighed about 4 kilograms, was a relatively slow and deliberate climber, and may have suspended itself from trees, its limb proportions suggest.

Tiniest of them all was the micromomyid, weighing in at about 20 grams. Earlier fossils of this animal included only isolated specimens of bones, jaws, and teeth, including an oddly shaped premolar, leading paleontologists to suggest that it ate fruits and insects. This first known skeleton suggests a highly arboreal creature that also may have hung from trees.

"Before these discoveries, plesiadapiforms were thought to have a limited range of movement," says Ravosa. "This work shows they were diversifying in ways mirrored by later primates." Bloch goes one step further, suggesting that these plesiadapiforms are a sister group to primates, an idea that has been spurned in recent years.

Seeing Red

Back in the late Cretaceous, early placental mammals saw the world in limited colors, much like humans with red-green color blindness do. Then, about 35 million years ago, after New World monkeys set off on their own evolutionary path, the common ancestor of Old World monkeys and apes evolved full trichromatic vision. For more than 100 years, evolutionary dogma was that primates acquired Technicolor vision to enable them to find ripe fruit. But in the past few years, Peter Lucas and Nathaniel Dominy of the University of Hong Kong and their colleagues have argued that the driving force was leaf color, not fruit color—and they brought new evidence to the meeting to buttress their case.



CREDIT: N. DOMINY

Lunch. New evidence suggests that primates evolved full color vision to detect tender red leaves rich in protein, munched on here by a black-and-white colobus.

The first blow to the common wisdom came in 1996, when Gerald Jacobs of the University of California, Santa Barbara, found that both the males and females of one species of New World monkeys – howler monkeys (genus *Alouatta*)—also had trichromatic vision, showing that they had evolved this advantage independently of Old World monkeys. Lucas was intrigued, as these monkeys feed mainly on young leaves rather than fruit. Because tropical foliage often emerges red, not green, Lucas and his colleagues suggested in 1998 that early Old World primates evolved trichromatic vision to better search for these young, reddish leaves, which are remarkably tender and high in protein. Primates able to forage for valuable foliage not clearly visible to other mammals would have a clear nutritional advantage over other leaf-eaters. "If fruits are first in importance in the diets of most primates, then leaves run a close second for many larger species and dominate in some," says Lucas. And a simple gene duplication increasing the number of retinal cone pigments, he adds, was all that it took to transform a dichromatic primate into a trichromatic one.

Some evidence to support the idea that trichromatic vision evolved to help primates better search for reddish leaves, published last year in *Nature*, came from a survey of four Old World primates—chimpanzees, black-and-white colobus, red colobus, and red-tailed monkeys—at Kibale National Park in Uganda. Lucas's team observed that these trichromatic monkeys preferred tender, reddish younger leaves to mature green ones. They also asserted that trichromacy didn't evolve to allow primates to see ripe fruits better, because most fruit-eating Neotropical primate individuals are dichromatic.

The reaction to this paper, says Dominy, was mixed. "Lucas has presented a new idea, one that deserves to be taken seriously," says vision scientist Daniel Osorio of the University of Sussex, U.K. Others were less enthusiastic: "We were questioning dogma dating from Victorian times," explains Dominy.

At the meeting the team presented as yet unpublished evidence on primates to solidify their case. Some animals studied were dichromatic, some trichromatic, and some polymorphic (in which trichromacy is sex-linked, much as it is in humans). Lucas's colleagues, led by Kathy Stoner and Pablo Riba, gathered data on Costa Rican trichromatic howler monkeys and polymorphic spider monkeys, whereas Nayuta Yamashita studied the more primitive, dichromatic ring-tailed lemurs and polymorphic sifakas—another type of lemur—in Madagascar. Their collected data show, as before, that primates with full color vision prefer meals of redder leaves, and that diet can affect physical character in ways that are subtle but profound.

–ANNE SIMON MOFFAT

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