

ago at Hadar, 60 kilometers south of Mille. An older Kenyan species thought to be bipedal, 4.1-million-year-old *A. anamensis*, is also a possibility. Haile-Selassie says the new skeleton is slightly younger and distinct from the mysterious 4.4-million-year-old *Ardipithecus ramidus*, known from teeth and a crushed, still unpublished, skeleton that he also found; he adds that the new skeleton may connect the dots between

Ardipithecus and later australopithecines, revealing how the human mode of walking evolved. Three even earlier species have been proposed as bipedal hominids but are known only from fragmentary fossils or a skull.

The discovery of the new skeleton comes at a good time for Haile-Selassie, one of the first black Africans to launch his own fossil-hunting expedition (*Science*, 29 August 2003, p. 1178).

The U.S. National Science Foundation rejected his grant application last year to look for hominids in the localities around Mille. Instead, he and Latimer got foundation funding for a small team of mainly Ethiopian fossil hunters. With a find like this, Haile-Selassie hopes getting future grants will not be a problem. "We want to go out and see if we can find the head and mandible," he says.

—ANN GIBBONS

ALZHEIMER'S DISEASE

Play and Exercise Protect Mouse Brain From Amyloid Buildup

As the population ages, finding ways to stave off the debilitating brain degeneration of Alzheimer's disease becomes ever more critical. New results with a mouse model of the condition now provide further support for the idea that "use it or lose it" applies as much to the mind as to the body.

A leading explanation for Alzheimer's disease blames abnormal buildup of a small protein called β amyloid, which accumulates in pathological structures called plaques in patients' brains. Now, working with mice genetically engineered to produce similar β -amyloid plaques, a research team led by Sam Sisodia of the University of Chicago, Illinois, has found that the β -amyloid buildup can be greatly reduced by a lifestyle change: housing the animals in an enriched environment—one amply stocked with toys and exercise equipment—instead of in standard lab cages equipped with nothing more than food, water, and bedding material.

The experiments, reported in today's issue of *Cell*, also provide clues to how an enriched environment might protect against β -amyloid accumulation. Zaven Khachaturian, editor of the journal *Alzheimer's and Dementia*, calls the work "very provocative. ... It opens new ways of getting at the underlying mechanism" of plaque formation.

Several epidemiological studies have suggested that environmental enrichment, including education and intellectually challenging leisure activities such as reading and playing bridge, diminishes the risk of Alzheimer's disease. Others have pointed to a possible protective role of exercise. But lower activity levels could be an early symptom of the disease rather than a risk factor.

With mice, though, it's possible to study environmental influences on the earliest stages of plaque formation. Sisodia and his colleagues Orly Lazarow and John Robinson started their experiments when the mice were just 1 month old, many weeks before they nor-

mally show symptoms of Alzheimer's disease; the genetically modified animals they used ordinarily develop β -amyloid plaques by about 4.5 months of age. The researchers put seven animals in standard cages and another nine in the enriched environment, where the activities of the mice were closely monitored.

After 5 months, the researchers killed both sets of mice and examined their brains. Animals kept in the enriched environment showed "a marked reduction in amyloid burden," Sisodia says. The decrease appeared to be related to exercise. "The animals that were most active as

land, and their colleagues reported that enriched environments actually increase plaque formation. The reason for the discrepancy is unclear, although the design of the 2003 experiment was different. For one, that study involved only female mice, whereas the Sisodia team used males. The Jankowsky-Borchelt group also had many more animals in their enriched cages and added young mice as they removed older ones. "To me that spells stress," says David Arendash of the University of South Florida in Tampa, who also studies the effects of enrichment on Alzheimer's mice. That stress might have overcome any beneficial effects of the enhanced environments.

Sisodia's group didn't test whether the enriched cages improved learning and memory in their animals, although work by others suggests that it may. This was the case in

the experiments performed by Arendash. The improvement occurred even though the Tampa team did not see reductions in β -amyloid deposition in their mice. But those animals were very old—16 months at the start of enrichment—and they already had extensive β -amyloid deposition.

How much these mouse studies of enriched environments relate to Alzheimer's disease in people remains to be seen. Adding another clue, Constantine Lyketsos and his colleagues at the Johns Hopkins Medical Institutions in Baltimore will report in the April issue of the *American Journal of Epidemiology* that engaging in a variety of different physical activities can reduce the risk of developing Alzheimer's disease by as much as 50%, although only in people who did not carry a particular gene variant called *APOE4* that increases Alzheimer's risk.

Lyketsos says that his team's results and Sisodia's provide an "interesting convergence" about the possible effects of physical exercise on Alzheimer's risk. So while you're out running to save your heart, you might also be saving your brain.

—JEAN MARX



Fun and games. Mice in cages with toys and exercise equipment develop less β amyloid than do ones in standard cages (inset).

determined by their time on the running wheels had the least [β -amyloid] burden," Sisodia adds. He notes, however, that other aspects of the enrichment, such as increased visual stimuli and social interactions, could still account for the reductions.

The researchers also identified changes in the brain that might explain a lessening of β -amyloid deposition. They saw increased activity of a β -amyloid-degrading enzyme called neprilysin in the brains of the enriched mice, as well as changes in gene expression that could promote neuronal survival and enhance learning and memory.

In late 2003, Joanna Jankowsky of the California Institute of Technology in Pasadena, David Borchelt of the Johns Hopkins University School of Medicine in Baltimore, Mary-