Former residents? These burial pits are pegged to the Hellenistic period.

character of many of these ‘carvings,’ ” says archaeologist Pierre Lombard of Lumière University in Lyon, France. Although impressed by the site and the Armenian team’s work, Lombard, an expert on the ancient Middle East, suggests that the “animal heads” could possibly be an effect of erosion. Others, however, argue that weathering alone is unlikely to have produced such features.

Also mysterious are thousands of tiny round pits, ranging from the size of silver dollars up to teacup saucers, which are scattered across much of the exposed top of the bluff. “We can’t explain these,” says Gasparyan, who speculates that they might have been used for anchoring posts. “They are far too regular” to have been simply from erosion, says Smith, but when they were made might be an “irresolvable issue,” he says.

If the Early Bronze Age finds aren’t tantalizing enough, the Armenian team has also uncovered evidence of habitation from more recent periods: Urartian amphoras from the 8th to 6th century B.C.; coins bearing the profiles of Alexander the Great and Octavian Augustus, and sarcophagi with skeletons buried with either pagan or Christian ritual that span a period from the 4th century B.C. to the 4th century A.D.; glazed and cooking pottery from the 12th to 14th centuries; and ceramics and coins of the Khanate of Yerevan from the 17th and 18th centuries. “I cannot think of a site anywhere in the Caucasus with such a millennia-long length of occupation,” says Kohl, who is eager to see Agarak for himself. “That fact alone makes the site important and noteworthy.”

After the threat of destruction just a few years ago, Agarak’s future now seems secure. The Armenian government has designated much of the site a national park, and the Gfoeller Foundation has put up $60,000 to fund the first few years of a long-term excavation. It’s also funding preliminary excavations elsewhere in Armenia and claims to have found a cavern with paintings that could date from the Stone Age, as well as a site in northern Armenia with evidence of early hominids—an important find if true, but not a big surprise considering its proximity to the famed Dmanisi site in neighboring Georgia. The foundation’s support, predicts Smith, “will be a magnet for researchers and students from around the world.” And that’s exactly what Armenia’s suddenly resurgent community of archaeologists and anthropologists is hoping for.

–RICHARD STONE

ANIMAL MODELS

Can a Mouse Be Standardized?

With new generations of mutant mice on the horizon, some researchers question the meaningfulness of standard behavioral tests and the wisdom of minimizing the mouse environment

OXFORD, UNITED KINGDOM—Georgia Mason moves quietly from cage to cage, peeking in on mice dimly visible by the glow of a red lamp. “This one spends her time ‘route tracing,’ ” says Naomi Latham, one of Mason’s graduate students at the University of Oxford, as she slides a cage from the rack. Within the shoebox-sized cage, a mouse appears to perform a slapstick comedy in fast-forward mode, chasing herself around and around in a tight circle. “She does that for hours at a time,” Latham says. Mason points out a mouse with all its whiskers missing. “Sometimes they pluck out all the fur from the face.” By filming their mice in near darkness with a sensitive camera, Latham and Mason are cataloging a variety of such repetitive behaviors collectively known as stereotypy.

Studying bizarre mouse habits might seem obscure, but the need to work out which aspects of a mouse’s environment cause such behavioral quirks is becoming urgent. New techniques are speeding the creation of mutant mice used to study the links between genes and behavior. But there’s accumulating evidence that the typical living conditions of lab mice might induce odd behaviors, from the subtle to the profound, that might obscure genetically based differences. The result: The same experiment can have different outcomes in different labs.

Idiosyncratic. Despite seemingly standardized environments, mice sometimes behave unpredictably.

That point was driven home 3 years ago in a project led by John Crabbe, director of the Veterans Affairs’ Portland Alcohol Research Center in Oregon (*Science*, 4 June 1999, p. 1599). This was the experiment no one in the field wanted to do: Mice of the same strains, born on the same day, were tested with a standard array of behavioral tests in three independent laboratories. To the horror of behavioral geneticists, the results varied wildly between labs, despite efforts to rear the animals in the same way and test them at the same time under seemingly identical conditions. Following up on this study, Crabbe and his colleagues report in the January 2003 issue of the *Journal of Neuroscience* that certain strains of mice are much more active in some laboratories than others, and this confounds certain behavioral tests. But the critical differences between laboratory environments remain a mystery.

One ultimate aim of research such as Mason’s is to figure out those differences and use that knowledge to improve standards for the mouse environment. But that will involve “a balancing act,” says Pat Nolan, a geneticist at the U.K. Medical Research Council’s Mammalian Genetics Unit near Oxford. The advantage of simplifying the

CREDITS: (TOP TO BOTTOM) DMITRI ARKAKELYAN AND ARTHUR GYULGAZIAN; DAVID A. NORTHCOTT/CORBIS environment in which mice are housed and tested, says Nolan, is that results are more easily replicated. But too narrow an environment limits the range of behavioral phenotypes that mice can exhibit. What's more, Mason points out, keeping mice in cramped and barren quarters elicits behaviors such as stereotypy that interfere with gathering meaningful data. Mason argues that "noisier" environments that mimic a mouse's natural habitat—offering, for example, places to hide—could reduce noise in mouse behavior.

The pharmaceutical industry is taking a keen interest in these efforts to understand the behavior of *Mus musculus*. Big pharma devotes most of its $30 billion research budget to diseases of the central nervous system (CNS) and uses the mouse almost exclusively as its model organism. As in other mammals, between 30% and 40% of mouse genes are responsible for the development and maintenance of the CNS. Aided by the publication of the mouse genome—which is 80% similar to our own—researchers are racing to produce mutant mice that mimic human CNS diseases.

To determine whether a particular gene is important for schizophrenia, for example, researchers compare the behavior of mice with normal or mutated forms of the gene. But this step, explains Mason, can be a stumbling block, because behavior is variable and highly sensitive to interactions between genes and environment.

Crabbe has firsthand experience with these vexing problems. He had created a strain lacking the gene for a receptor of serotonin, a neurotransmitter thought to be important in addiction, and in 1996 demonstrated that these mice drink more alcohol than other mice—a result he replicated four times. But when mice from this strain were raised elsewhere as part of the comparative study Crabbe conducted 3 years later, they had no particular fondness for alcohol. Crabbe concluded that subtle differences between laboratory environments were behind these divergent results.

Mason believes that stereotypy could be part of the explanation. Joseph Garner, a former student of Mason's who is now at the University of California, Davis, has recently shown that stereotyping C57 mice—the strain most commonly used for genetic experiments—differ profoundly from their normal-seeming cage mates, in that they get "stuck in ruts." Garner found that stereotyping mice have difficulty switching to a new task, even when the old task goes unrewarded, Mason reported in September at the Festival of Science in Leicester, U.K. Although recognized years ago, says Mason, stereotypy is "often overlooked because it happens at night." According to Garner and Mason, it is caused by early separation from mothers, a lack of sensory stimulation, and cages 1/20th the size of a mouse's natural territory.

Adding to the problem, even lab-bred mice are social animals. "After 4 weeks in isolation, mice become very strange. It's better to study their behaviors in a social context," says Hans-Peter Lipp, a biologist at the University of Zürich, Switzerland. To this end, he has invented a computerized cage that keeps track of the location and behaviors of individual mice within groups (see sidebar).

Lipp admits that his approach is not amenable to the high-throughput testing of mutant mice that many researchers are calling for. According to the National Association for Biomedical Research in Washington, D.C., well over 20 million laboratory mice are produced annually in the United States alone. The numbers are expected to balloon with new breeds of mutant mice created using ethylnitrosourea (ENU), which mutates the DNA in sperm. Whereas most breeds of mutant mice have been produced by "knocking out" a specific gene, researchers are using ENU to build huge libraries of mice containing single, random mutations.

To run each mouse produced by ENU through time-consuming tests in search of often-subtle behavioral differences would be impossible, says Robert Gerlai, a biotech consultant formerly of Eli Lilly Research Laboratories in Indianapolis, Indiana, so the system needs to be automated—but just how is unclear. Large-scale behavioral testing of mutants can produce misleading results, claims Hanno Würbel of the University of Giessen, Germany, the first to observe nocturnal mouse stereotypy. Such testing is likely to use simple environments, explains Würbel, "but this is naïve. The behavioral effect of a gene should be tested in many contexts, not just a single, standard laboratory environment."

Others are adopting these ideas. Nolan's research group is developing ENU mouse models of human disease as part of a European Union consortium formed last month called Eumorphia. One of its goals is to develop new environmental and phenotype-testing standards. The research showing that mice are exquisitely sensitive to their environments will guide the group's efforts, Nolan says, and he hopes new techniques will improve the data mining of ENU mice.

–JOHN BOHANNON

John Bohannon writes from Lyon, France.

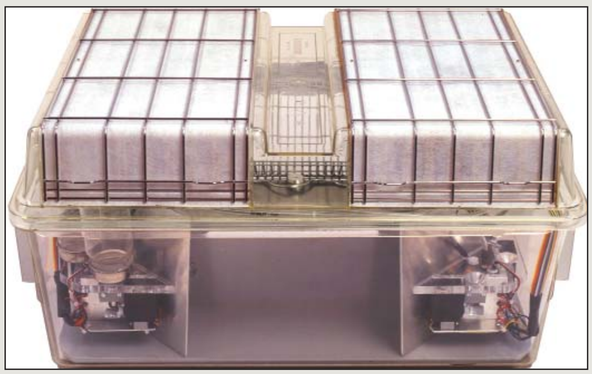
To Build a Better Mouse Cage

When it comes to mouse behavior, a perennial source of experimental "noise" is the scientist herself. Mice are sensitive to differences between people, such as their handling techniques or scents. And not only do humans complicate experiments by their presence, they limit the pace of research by observing no more than one mouse performing one task at a time. "Behavioral analysis is space and time intensive," says Robert Gerlai, a biotech consultant formerly with Eli Lilly Research Laboratories in Indianapolis, Indiana. That's why many mouse researchers would like to remove humans from the picture altogether.

One attempt to create a standard human-free mouse environment is the SmartCube, a high-tech testing environment for a single mouse being developed by PsychoGenics in Hawthorne, New York. According to its creators, by keeping track of many parameters over time—the order and duration of certain behaviors, along with physiological variables such as heart rate—the SmartCube will detect subtle effects that would be invisible to an old-fashioned human researcher.

Whereas the SmartCube observes a single mouse with better-than-human watchfulness, the IntelliCage keeps track of up to 16 mice living in the same cage. A computer follows the location of mice by means of microchips implanted in the loose skin at the back of their necks and records their interactions with various behavioral testing modules at each corner of the cage. Hans-Peter Lipp of the University of Zürich, Switzerland, created the IntelliCage to observe mouse social behavior while reducing the total number of mice needed for his research. Mice behave strangely unless given the illusion of privacy from people, says Lipp, "because, after all, humans are seen as dangerous predators."

–J.B.



Big Brother. The IntelliCage records the behavior of several mice while they socialize.

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