As time goes by, mutant mice face problems

Mice lacking an important enzyme go gray and lose their hair earlier than normal, frequently develop sores as they age, and have unusually short life spans. They also suffer more tumors than normal mice do, raising questions about a much-hyped idea for treating cancer.

These age-related conditions showed up in a new long-term study of mice that have a mutation in a gene for telomerase, an enzyme that affixes protective DNA segments to ends of chromosomes. Scientists know that if this enzyme doesn't work, the chromosomal tips, called telomeres, usually shorten whenever a cell divides, ultimately disappearing.

In 1997, Ronald A. DePinho of the Dana-Farber Cancer Institute in Boston, Carol Greider of Johns Hopkins Medical Institutions in Baltimore, and their colleagues described the development and surprisingly healthy early life of six successive generations of mice that lacked telomerase. Each generation had shorter telomeres than the previous one, and the sixth turned out infertile (SN: 10/11/97, p. 228).

Now, in the March 5 CELL, the scientists describe what happens as these mutant mice age and their telomeres shrink further in many cells. "Over the course of their 2-year lives, [the mice] walk this telomere plank into genetic instability, loss of cell viability, and so on," says DePinho.

A few scientists have speculated that many ravages of aging result because telomeres shrink over time in mammalian cells. Yet as the telomerase-lacking mice grew older, they didn't experience a greater-than-normal incidence of some age-related conditions, such as osteoporosis, cataracts, and atherosclerosis.

Nonetheless, telomere shortening may play a role in certain aspects of aging. In addition to premature graying and hair loss, the aging mutant mice have an increased rate of skin ulcers and are slower than normal to heal wounds—traits also common in elderly people. Moreover, when treated with blood-depleting agents, the mice have trouble recovering, an impairment resembling the difficulties that many elderly people face after chemotherapy or surgery.

In general, says DePinho, the mutant mice resemble aged individuals in their reduced ability to respond to physiological stresses. However, young sixth-generation mutant mice did not have the same impaired stress responses as 2-year-old third-generation mice, even though the groups had telomeres of similar length. Other, still undetermined, age-related changes in cells must combine with shortened telomeres for such symptoms to emerge, says DePinho.

Third-generation telomerase-lacking mice had an unusually large incidence of cancer, and the sixth generation showed a higher rate still. The lack of telomeres triggers chromosomal fusions and other genetic abnormalities that foster tumors, concludes DePinho.

The cancer finding adds a new wrinkle to the debate about whether depriving malignant cells of telomerase will prevent them from growing. John P. Murnane of the University of California, San Francisco and other scientists had previously found that cells can maintain telomeres through a mechanism not involving telomerase. Since this mechanism seems to depend upon chromosomal rearrangements, cancer cells employing it may undergo additional mutations that make them more malignant.

"You might actually make matters worse if you knock out telomerase in a tumor because you would select for cells that use the alternate mechanism," says Murnane.

Still, both Murnane and DePinho stress that mice sometimes poorly reflect human biology and that tests of telomerase inhibitors are warranted in people with cancer. Brief, localized use of the inhibitors may destroy or reduce the size of existing tumors without significantly increasing the risk of new cancers developing. —*J. Travis*

Chemistry diagnoses a painting's ills

A doctor giving a lecture in anatomy points to the dissected arm of a cadaver while his pupils look on intently. The Dutch artist Rembrandt van Rijn painted this scene in 1632. Now, nearly 4 centuries later, the canvas known as "The Anatomy Lesson of Dr. Nicolaes Tulp" has itself gone under the scalpel.

New techniques developed by a team of Dutch scientists have helped art conservators in their recent restoration of this 17th-century masterpiece. By examining tiny paint chips with various spectroscopic methods, the scientists determined the chemical compositions of the paint, glaze, and varnish layers on the canvas. This information provided insight into artistic techniques and guidance to conservators deciding how to clean and repair the artwork.

"There's a big gap in the understanding of the basic processes of aging in painted art," says Ron M.A. Heeren of the FOM Institute for Atomic and Molecular Physics in Amsterdam. To fill that gap, researchers are working with MOLART, a Dutch project to "provide the art conservation community with tools and fundamental research capabilities," Heeren explains. He described the group's techniques this week at the Pittsburgh Conference in Orlando, Fla.

"What they have done is much more fundamental chemistry than what has been done previously" in art conservation, says David Erhardt of the Smithsonian Center for Materials Research and Education in Suitland, Md.

With microscope and scalpel, the Dutch researchers remove flakes of paint about 1 millimeter across, routine practice in restoration projects. The scientists mount them in resin and polish the samples with fine aluminum oxide particles in water. By studying how the surfaces then interact with light, the scientists can explore the chemical composition of the paint chips. "The sensitivity of analytical techniques has improved so much that you don't need large quantities of material," Heeren says.

The Mauritshuis

Chemical analysis helped to restore Rembrandt's 367-year-old painting "The Anatomy Lesson of Dr. Nicolaes Tulp."

Before it reached its current home in the Mauritshuis, a museum in The Hague in the Netherlands, "The Anatomy Lesson" hung for many years in the Amsterdam surgeon's guild where Nicolaes Tulp lectured. There the painting experienced mishaps that would make any art lover cringe. It had been rained upon and dirtied by smoke from a fire, for example, says Heeren.

When conservators began examining the painting a few years ago, they noticed many holes. The scientists have now found that the white material in these microscopic craters consists of carboxylates making up a benign soap containing lead. A chemical reaction in or on the painting created this substance, but whether the constituents came from Rembrandt's brush, the environment, or previous restoration efforts remains unknown. The conservators decided that the best strategy was to leave the holes alone.

In another case, the MOLART group detected protein, confirming that Rembrandt used eggs to improve the consistency of paints. With analytical methods, Heeren says, scientists can reveal the secrets of artists from another age. —*C. Wu*