ther discovered that the bacteria survive the insult by repairing the damage—snipping the damaged regions from one strand of their double-stranded DNA. Then, in 1968 at the University of California, San Francisco, James Cleaver found that a genetically impaired DNA repair apparatus underlies xeroderma pigmentosum, a human disease that predisposes affected individuals to skin cancer. A link was thus solidly forged between unrepaired DNA damage and human cancer.

The legacy of these landmark discoveries is striking. The role played in hereditary cancers by defective repair genes—the genes that direct the production of the enzymes responsible for the actual repair work—is now a focus of research around the world. And OBER-supported scientists continue to be leading players. At Livermore and Los Alamos, for example, researchers have isolated and cloned several repair genes, including the very one whose defects lead to xeroderma pigmentosum. But the clear picture that unrepaired DNA damage was the insidious culprit in the long-term consequences of radiation exposure had far deeper ramifications. It was now seen that x-rays, ultraviolet light, and cancer-causing chemicals worked in similar ways, subverting or overwhelming the natural DNA repair mechanisms that our health relies upon. So central is the role of DNA repair, and so active is today's research community in seeking to understand it better, that in 1994 the prestigious journal *Science* designated the entire class of DNA repair enzymes as its "Molecule of the Year."

Another upshot of the earliest research on DNA repair was the development of new screening tests for possible cancer-causing chemicals. If unrepaired DNA damage was at the source of most cancer, then detectable cellular mutations were danger signs to be heeded. In short order, then, the seventies produced a number of new tests for cancer-causing potential, the best known of which is the Ames test, developed with AEC support in 1973 by Bruce Ames at the University of California, Berkeley. Some strains of bacteria, hobbled by an inability to produce an essential molecular building block, can reproduce only if something alters them genetically. Thus, any chemical that produces a flourishing colony of these bacteria is a potential human mutagen. Today, around the world, the Ames test is one of the first hurdles a new chemical or pharmaceutical must clear on its way to regulatory and public acceptance.

A Logical Consequence: The Human Genome Project

A surprising but cogent thread links the atomic bombs that ended World War II with today's most ambitious health research effort, the Human Genome Project. One of the unanswered questions of radiation research is the extent to which the descendants of bomb survivors harbor DNA mutations as a legacy of their par-

DNA SNAPSHOTS

■ Another window into the workings of the cell opened in 1956 at Brookhaven, when W. L. (Pete) Hughes synthesized tritium-labeled thymidine, a highly specific precursor of DNA. (Tritium is a radioactive isotope of hydrogen.) Cells take up thymidine in preparation for cell division, build it into their DNA, and then hand it down to their daughter cells. The tritiated version emits low-energy electrons, which can be made to expose photographic film and thus to produce microscopic pictures showing where DNA synthesis has taken place. By observing the fate of tritiated thymidine in living cells, Brookhaven scientists were able to confirm the Watson-Crick hypothesis for DNA replication at the chromosomal level—and to "watch" chromosomes exchange genetic material during the process of cell division. Their careful experiments also elucidated many of the details of the cell cycle, the sequence of observable stages a cell passes through between cell divisions. Today, tritiated thymidine is a standard tool around the world in studies of how cells proliferate and how cancer develops and responds to treatment. ■

1966 Argonne radiation biologist Miriam Finkel isolated the murine osteosarcoma virus, the source of a gene that would be widely used in subsequent research. The *fos* gene plays a prominent role in the regulation of cell proliferation.

1967 At Los Alamos Mack Fulwyler and Marvin Van Dilla developed the fluorescence-activated flow cytometer.

1968 James Cleaver at the University of California, San Francisco, showed for the first time that a human disease (xeroderma pigmentosum) associated with a susceptibility to cancer is caused by a genetically impaired ability to repair damaged DNA.