

A Healthful Dab of Radiation?

The notion that certain toxic chemicals can be healthful in small doses is stirring new controversy (see main text), but a similar debate about low-dose ionizing radiation has been raging for decades. Now, research that could shed light on possible "radiation hormesis," much of it funded by the U.S. Department of Energy (DOE), is well under way. Although these studies may not soon alter regulators' assumption that any dose of radiation is harmful, the findings about low-dose effects may be provocative.

Radiation risks are now calculated based mainly on cancers among 86,600 survivors of the two atomic bombs dropped on Japan. These human data "are the gold standard," notes carcinogenesis expert Julian Preston of the U.S. Environmental Protection Agency (EPA). The incidence of solid cancers in the survivors rises in a straight line with dose. This suggests that any increase in dose delivers an increase in risk, with no safe level of radiation. But at the lowest doses, there are too few cancers to calculate the actual risks. "The numbers are just not there," says radiobiologist Eric Hall of Columbia University in New York City. To be cautious, public health agencies extrapolate risk in a straight line from higher to lower doses. That leaves open the possibility that something unexpected is going on below the threshold of measured effects.

In this zone, there are hints that a little radiation could even be beneficial. The Japanese bomb survivors who received the lowest doses are living longer than controls, for example. Some studies have found a slightly lower incidence of cancer in people living in places such as western China and Colorado, where natural background radiation levels are three to four times higher than the global average of 2.4 millisieverts per year. And studies dating back to the 1950s report that rodents live about 10% to 20% longer if exposed to small amounts of radiation, notes cancer researcher Arthur Upton of the University of Medicine and Dentistry of New Jersey.

In the mid-1980s, Nobel Prize-winning cytogeneticist Sheldon Wolff of the University of California, San Francisco, offered one explanation: When his team "tickled" cells with a low dose of radiation, waited a few hours, then applied a high dose, the cells showed fewer DNA strand breaks than did cells hit only with the high dose. Wolff described it as an "adaptive response," suggesting that the low-dose radiation had stimulated the cells' DNA repair enzymes. Wolff, however, felt it was too soon to conclude that radiation hormesis was real, arguing in a 1989 debate in *Science* with Leonard Sagan of the Electric Power Research Institute in Palo Alto, California, that other damage caused by low-dose radiation might overwhelm the beneficial effects.

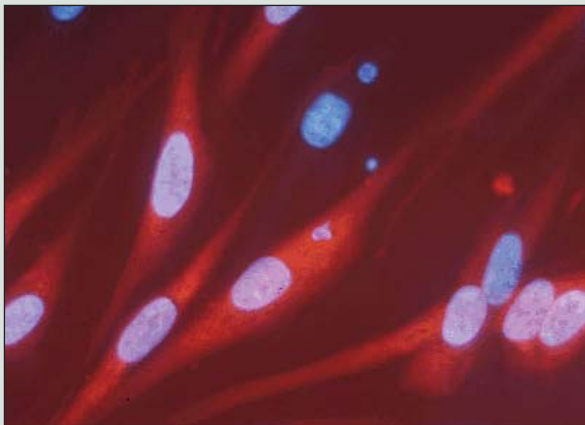
After a funding slump, research on this topic picked up again a few years ago as DOE faced skyrocketing costs to clean up its radioactive waste sites. In 1997 Senator Pete Domenici (R-NM) persuaded Congress to create a new DOE program to study low-dose radiation. Approved through 2007, it has spent nearly \$100 million so far, mostly on cellular studies.

Ironically, some new findings have heightened concern. For example, Hall and other Columbia researchers using a new technique that can hit a dish of cells with a single alpha particle reported a bizarre result in 1999: Even cells not directly hit sustain damage. Other labs have found that supernatant from such an experiment

can also cause this so-called bystander effect, suggesting that radiation creates a harmful molecule that seeps from irradiated cells into neighboring cells. Adaptive responses only partially repair the damage, the Columbia team has found. The implications, Hall says, are that "low-dose risk may be being underestimated."

Others don't dispute this result but note that alpha particles make up only a portion of the low-level radiation that people are exposed to, and they are particularly damaging—"like a baseball bat through a cell," says radiation oncologist William Morgan of the University of Maryland, Baltimore. Adaptive responses may offset harmful bystander effects in cells dosed with gamma rays and x-rays, Morgan suggests.

Whether any of the changes seen in cell studies actually lead to cancer is unknown. Genomically unstable cells created by bystander effects might be more likely to die through apoptosis, or programmed cell death, for example. The net result could be that low-dose radiation helps remove potentially cancerous tissue, says molecular biologist William Bonner of the National Cancer Institute in Bethesda, Maryland. "What you really want to know is what's happening in an animal." The DOE program aims to learn more by funding carcinogenesis modeling studies and single-particle experiments on three-dimensional



Bystander effect. Only pink cells were hit by alpha particles, but both a radiated cell and an unirradiated cell (blue) have fragments that indicate broken chromosomes.

tissues, says program director Noelle Metting.

Other researchers are revisiting past animal studies that showed beneficial effects. Radiobiologist Ron Mitchel of the company Atomic Energy of Canada Limited is seeing evidence for protection against cancer in transgenic mice that lack one copy of the *p53* tumor suppressor gene and are highly prone to developing tumors. Mitchel's group reported in the March issue of *Radiation Research* that a tickle dose of gamma rays significantly delays the development of spontaneous lymphomas and bone tumors in these mice. Low-level radiation isn't always bad, Mitchel says: "There's obviously a threshold for harm."

Hoping to resolve conflicts in earlier mammal data on low-dose radiation and cancer, a team at the University of Ottawa is scrutinizing details such as tissue and radiation type in 750 data sets. The team sees protective effects, but only for some strains and species. That suggests variability in humans: "A little radiation may be good for some people but bad for others," says lead investigator Philippe Duport.

Some scientists, including members of the Health Physics Society, already believe that there's enough evidence to assume that radiation is harmless below a certain level. But the National Council on Radiation Protection and Measurements in its latest report in 2001 said that the linear-no-threshold model should be retained for now. A National Academy of Sciences panel known as BEIR-VII is examining the latest data and could issue its verdict as soon as next year, says academy staffer Evan Douple. But even if animal data and new mechanistic studies give support to the hormesis theory, nobody thinks BEIR-VII will abandon the current linear model of risk just yet. That would be a "complete shift" for public health, says Preston, adding: "If you've got human data, you use it."

—JOCELYN KAISER