

CATCHING  
SOME RAYS

At typical background levels of radiation near sea level in the U.S., each cell in your body sees on average about seven secondary electrons a day. Those electrons will come, however, in bunches of 1,000 per cell every few months.

The dose averages to a scary-sounding (but actually relatively harmless) 200 mega-electron volts per kilogram per second.

About 40 percent of that dose comes from radioactive nuclei naturally present in the human body. Lung tissue would experience much more because of short-range alpha particles (helium nuclei) emitted by inhaled radon and its daughter nuclei.

The electromagnetic fields emitted by power lines, cell phones and other consumer electronics are emphatically *not* ionizing radiation. According to the American Physical Society, scientific research shows “no consistent, significant link between cancer and power line fields.”

dom held that DNA could be harmed by secondary electrons only while they had more than about 10 eV—enough energy to ionize the DNA. Then a collaboration led by Léon Sanche, Darel Hunting and Michael A. Huels of the University of Sherbrooke in Quebec studied the effects of electrons with as little as 3 eV and found that even those

could break both strands of a DNA molecule’s double helix. The electrons seem to exert their destructive power by attaching to one of the DNA’s component molecules; the resulting negative ion then breaks down. The decay fragments can in turn damage the other strand by chemical reaction. The cell’s DNA-repair machinery can correct a single lesion, but closely spaced or complex lesions are likely to defeat its restorative abilities.

Tilmann Märk’s group at the University of Innsbruck in Austria has now extended the lower energy limit to well below 1 eV. Rather than studying whole DNA molecules, the group collided a low-energy electron beam with beams of gaseous uracil, thymine and cytosine (bases that form the information-carrying rungs of an RNA or DNA molecule) and deoxyribose (one of the backbone molecules). According to Märk, even electrons with near-zero energy “destroy deoxyribose very effectively, [producing] a number of fragment ions.” As in the whole-DNA experiments, the electrons appear to act by attaching to the molecules in question, which then break up by los-



URANIUM EMITS alpha particles (helium nuclei), each of which can generate 160,000 low-energy electrons in tissues.

ing a hydrogen atom or a larger fragment.

Both collaborations have also studied the effects of low-energy electron attachment to halo-uracil molecules, in which a halogen atom such as bromine replaces a hydrogen atom. More than 40 years ago researchers discovered that substituting bromo-uracil for thymine in DNA increases a cell’s

sensitivity to radiation (thymine is like bromo-uracil except that a methyl group replaces the bromine). Some studies have suggested that fluoro-uracil, used in chemotherapy, also radiosensitizes tumor cells. (Its main therapeutic effect, however, is inhibition of DNA or RNA synthesis.) This year the Innsbruck group found that chloro-uracil is 100 times as sensitive as ordinary uracil to breakup by electrons.

Of course, reactions in dilute uracil gas in a vacuum are a far cry from reactions within a DNA molecule in vivo with numerous closely attached water molecules. To address this issue, Märk says that his group “plans to enclose these molecules in a cluster of water molecules and then study the interactions with electrons.” Huels and his co-workers, meanwhile, are studying bromo-uracil in situ in strands of DNA with a view to enhancing its effectiveness in radiotherapy. They have found that bromo-uracil’s radiosensitizing effect depends on the DNA structure and the base sequence where the bromo-uracil is incorporated. “This may allow us to target specific sites in tumor cells directly,” Huels says.

U.S. DEPARTMENT OF ENERGY SPL/Photo Researchers, Inc.

## HORMESIS

## Nietzsche’s Toxicology

WHATEVER DOESN’T KILL YOU MIGHT MAKE YOU STRONGER BY REBECCA RENNER

If dioxin and ionizing radiation cause cancer, then it stands to reason that less exposure to them should improve public health. If mercury, lead and PCBs impair intellectual development, then less should be more. But a growing body of data suggests that environmental contaminants may not al-

ways be poisonous—they may actually be good for you at low levels.

Called hormesis, this phenomenon appears to be primarily an adaptive response to stress, says toxicologist Edward J. Calabrese of the University of Massachusetts at Amherst. The stress triggers cellular repair and

maintenance systems. A modest amount of overcompensation then produces the low-dose effect, which is often beneficial.

This idea may sound bizarre, but such adaptation to stress is common, says physiologist Suresh Rattan of Århus University in Denmark. Exercise, for instance, plays biochemical havoc with the body: starving some cells of oxygen and glucose, flooding others with oxidants, and depressing immune functions. "At first glance, there is nothing good for the body about exercise," he notes. But even couch potatoes know that moderate exercise is worthwhile. Rattan says that the cellular insults from exercise prompt the defense system to work more efficiently.

Over the past decade, Calabrese has compiled thousands of examples of hormesis from published scientific literature. Many findings challenge and even flout established theories about what is harmful. For example, the prevailing theory is that any increase in radiation exposure increases the risk of cancer. But biologist Ronald Mitchel of Atomic Energy of Canada has shown that a single low dose of ionizing radiation stimulates DNA repair, delaying the



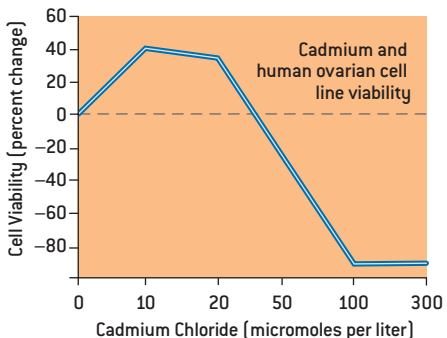
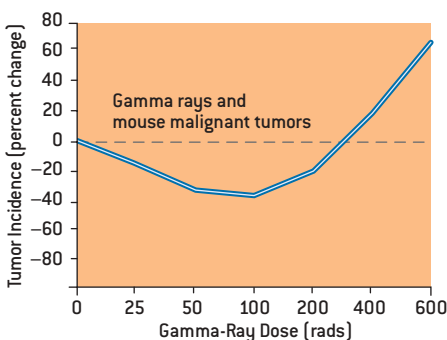
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LUCY READING, ADAPTED FROM J. R. MAISIN ET AL. IN RADIATION RESEARCH, FEBRUARY 1988 (top) AND TETSUYA ABE ET AL. IN BIOCHEMICAL PHARMACOLOGY, JULY 1, 1999 (bottom), AS REPRODUCED BY EDWARD J. CALABRESE AND LINDA A. BALDWIN IN TRENDS IN PHARMACOLOGICAL SCIENCES, JUNE 2001



**A PINCH OF POISON** seems beneficial in some cases when compared with control groups, as shown by the effects of gamma rays on the emergence of mouse tumors (top) and of cadmium exposure on human ovarian cells (bottom).

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**POLLUTION STANDARDS** that factories—such as this chemical plant on Lake Baikal, Russia—must meet may change if hormesis proves to be a widespread phenomenon.

onset of cancer in mice; high doses produced the opposite effect, as expected. Prolonged exposure to extreme temperatures is also harmful, but Rattan has found that heating up human skin cells to 41 degrees Celsius (106 degrees Fahrenheit) twice a week for an hour slows aging in the cells.

Even well-established environmental headaches display some hormesis. The definitive rat study that linked high doses of dioxin to cancer, published in 1978 by Richard Kociba of Dow Chemical and his colleagues, also found that low doses reduced the incidence of tumors.

“Adaptation to such stresses is absolutely essential,” Mitchel remarks. “If we couldn’t adapt to changes in our environment, we would die.” Such adaptation at the molecular level is seen in most primitive forms of life and has been evolutionarily conserved all the way up to humans, he adds.

Hormesis challenges the existing hazard-assessment process underlying environmental regulations, Calabrese says. Toxicologists usually determine the relation between exposure to contaminants and health risks by conducting animal experiments. They start out by giving lab animals a high dose that produces clear adverse effects. Then they work downward until they can estimate a concentration that doesn’t cause harmful effects. For chemicals that don’t cause cancer, they obtain a safe dose for humans by applying uncertainty factors to account for differences between mice and men and among individual people. The resulting safe dose for humans is then usually deemed to be about 0.01 to 0.001 the safe dose for mice. For carcinogens, toxicologists assume that exposure to any amount increases the risk.

But Calabrese suspects that in many cases, the benefits of hormesis may occur at levels higher than the recommended safe doses for humans. Thus, it might be

possible to refine pollution standards so that we can reap the benefits of hormesis while still being protected against adverse effects in the environment. Or at the very least, it might be reasonable to stop worrying about exceedingly low exposures.

Researchers investigating adaptive stress responses aren’t the only ones interested in effects at low doses. Scientists studying endocrine disruption are also joining in. They are concerned that contaminants that mimic hormones can have significant harmful effects at very low doses if exposure occurs during a susceptible developmental window. In some sense, endocrine disruption appears to be the opposite of hormesis, in which low doses could have unsuspected harmful effects because of the contaminant’s chemical similarity to hormones.

Advances in molecular biology are giving toxicologists the tools to investigate low-dose phenomena, according to Joseph V. Rodricks, health sciences director at Environ, environmental consultants in Arlington, Va. Instead of monitoring the onset of disease or cancer, toxicologists are beginning to use modern molecular biology tools to identify the critical early precursors to illness. They then monitor how the precursors vary at low doses.

Hormesis has much to prove if it is to revolutionize toxicology, Rodricks notes. Many of the hormetic dose-response relations that Calabrese has compiled raise more questions than answers, he says. For example, the dioxin study looks like hormesis if all types of cancer are combined, but hormesis doesn’t show for individual types of cancer. Despite such skepticism, Rodricks is one of many toxicologists calling for a National Research Council review of this phenomenon.

*Rebecca Renner writes about environmental issues from Williamsport, Pa.*