

Is Radiation Good for You

Or dioxin? Or arsenic?

The answer is yes but only in very small doses, says one of the country's most respected toxicologists. If he's right, environmental regulation will never be the same



By Will Hively

Photography by Dan Winters and Gary Tanhauser

ANY IDIOT SHOULD BE ABLE TO POISON A PLANT. That's what Edward Calabrese thought in 1966 as a junior at Bridgewater State College in Massachusetts. He was in a plant physiology class at the time, and his lab group had been told to dose some peppermint with an herbicide called Phosfon. The idea was to measure how much a given dose stunted the plant's growth, thereby demonstrating a fundamental tenet of biology: The more you poison something, the sicker it gets. In Calabrese's case, though, the lesson backfired. Instead of shriveling, the crop grew green and luxuriant. "Either you treated the plants with the wrong chemical, or you mislabeled them," the professor said. "God forbid, you discovered something new."

When Calabrese next tried to repeat the experiment, the peppermint shriveled as expected. But the professor had been right: Calabrese *had* discovered something new. When he sprayed the plants with a diluted dose of the poison, as he had done mistakenly the first time, the plants thrived. By every measure—height, weight, root length—they did about 40 percent better than those that did not get Phosfon.

Thirty-six years later, in his office at the University of Massachusetts at Amherst, Calabrese tells the story with matter-of-fact assurance. Slight of build and gray of mop, standing hip deep among stacks of scholarly publications, he hardly looks like a rev-

olutionary. He claims to have a "bland personality," and his owlish glasses and soft-spoken demeanor seem to bear this out. Yet his conclusions are as unflinching as they are controversial. Poisons that injure or kill at high doses can have the opposite effect at low doses, he says, and the paradox holds true for every conceivable measure of health—growth, fertility, life span, and immune and mental function. The effect is known as hormesis, from the Greek word for excite. "The implications," he says, "are enormous."

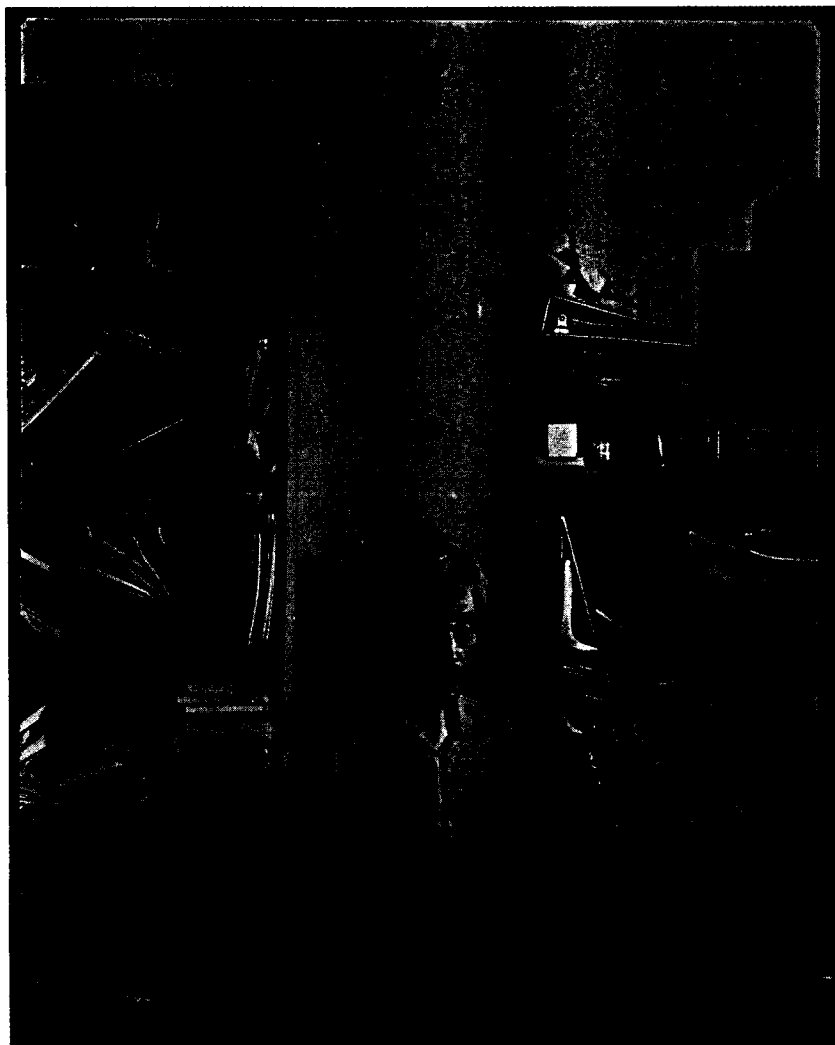
During the past decade, Calabrese has combed through tens of thousands of studies for examples of the effect, and he has

found them in impressive numbers. Worms exposed to excessive heat, rats given a little dioxin, mice and humans exposed to low-level radiation—all have lived longer, in controlled experiments, than they would have without the toxins. Now Calabrese and a small but growing number of researchers worldwide are zeroing in on the biological basis for this effect. “If you really understood the master switch,” he says, “it would become very powerful.”

It also becomes scary. Using toxins to improve health sounds both irresponsible and suspiciously convenient for polluters. If a little dioxin is good for you, why bother to clean up the Hudson River? If a touch of arsenic can fend off cancer, why lower the allowable amount in drinking water, as the Environmental Protection Agency has urged? “This is one of the major awakenings we are going through,” Calabrese says. “We really don’t see any exceptions, and that’s hard for people to deal with. But I have so much data—this is so overwhelmingly convincing—that I don’t think anyone rational could deny that hormesis exists.”

IF ANY OTHER RESEARCHER HAD CHOSEN TO CHAMPION HORMESIS, THE theory might still be languishing in 19th-century medical tomes.

Edward Calabrese has earned new scientific respect for the theory of hormesis. For too long, he says, the theory was tainted by its similarity to homeopathy. He calls this “guilt by association.”



What distinguishes Calabrese from a crank—what has earned him the respect of government regulators, scientific collaborators, and thousands of subscribers to his newsletter—is both his method and his background. “He is a mainstream toxicologist,” says Donald Barnes, former staff director of the EPA science advisory board. “Everyone knows him. He is not a flake. And everyone respects the work he has done.” It’s hard to dismiss Calabrese as an apologist for polluters: He spent the better part of his career proving exactly how dangerous pollutants can be.

After those early experiments with peppermint, Calabrese published a paper and then shrugged off his small discovery—a paradox without explanation. When he arrived at Amherst in 1976, he set up a conventional toxicology lab. In the mid-1980s, he began to study carcinogens. The wisdom of the time held that carcinogens could cause cancer only after repeated exposures. Calabrese decided to take a closer look. Moving from the lab to the library, he devoted much of the next 15 years to reviewing 6,000 previous cancer studies. In more than two-thirds of the studies, he found evidence that a class of chemicals known as mutagens could cause cancer with a single exposure.

This was a style of research that would later serve him well with hormesis, and the results were nearly as controversial. Among the mutagens he had studied were food preservatives and other common substances— aflatoxins, for example, produced by molds. “Usually, in the beginning, people thought I was crazy,” Calabrese says. “Industry was very upset.” But he persevered, and his findings soon filtered into the mainstream. Around 1990 he told the state of Colorado that the EPA’s limits for a toxic chemical leaching from an Army waste site were about a hundred times too lenient. After lengthy hearings in 1993, the state agreed. The Army faced an estimated cleanup cost of at least \$7 million at that site alone—and it had 21,000 others to worry about.

It was intensely gratifying, Calabrese says, to realize the difference that one researcher’s testimony could make. But by then he was already facing an even steeper challenge. In 1985 he had received an innocent-looking flyer in the mail that announced a conference on the stimulating effects of low-dose radiation. It may have mentioned hormesis, which he had never heard of before. He knows only that it sparked a memory. He called Leonard Sagan, an expert on radiation health effects, who was organizing the conference. He told Sagan he had seen a similar effect in peppermint plants 20 years before. “This was a transition for me to a phenomenon,” he says, “not just an event.”

HORMESIS, HE CAME TO LEARN, HAS A LONG BUT NEARLY forgotten legacy. Some trace its origins to Paracelsus, a 16th-century Swiss-German pharmacologist who declared: “All things are poison and nothing is without poison. It is the dose that makes a thing a poison.” This was common sense of a sort: We all know that even essential nutrients like sodium become toxic in high doses. But in the late 1800s, in Germany, sci-

entists took the idea a step further. Poisons, the psychiatrist Rudolf Arndt and the pharmacologist Hugo Schulz declared, simply have a lower threshold of toxicity than other substances; taken in the right quantity, they can do good. As the Arndt-Schulz law put it: Poisons are stimulants in small doses.

Arndt based his conclusions on animal experiments, Schulz on studies of yeast fermentation. Their findings agreed with other research, and their law was thought to apply to most chemical and environmental stresses. But both Arndt and Schulz went on to use their findings to champion the medical practice of homeopathy, and that's where the trouble started. Hormesis and homeopathy share similar trappings, but they are very different concepts. Homeopathy holds that diseases are best treated by stimulating the body's natural defenses with toxins that cause similar symptoms. If you have a stomach virus, for instance, a homeopath may prescribe a bit of arsenic because arsenic poisoning also causes abdominal pains and vomiting. It's a matter of analogy more than biology, and the actual dose is almost nil. Homeopathic remedies are thousands or even millions of times more dilute than the range in which Calabrese and others have observed hormesis. Some remedies contain barely a molecule of the toxin.

Scientists have long scoffed at homeopathy, saying its benefits, if any, are purely psychological. As hormesis acquired the same taint, it began to lose supporters as well. Then other forces pushed it toward extinction.

Soon after the discovery of X rays in 1895, researchers began publishing reports of radiation hormesis, claiming, for example, that low doses stimulated plants. At the same time, some quacks began touting radioactive patent medicines for every conceivable human ailment. It's not clear how many people exposed themselves to such elixirs, but the fad came to an abrupt halt with several well-publicized poisonings. In 1932, for instance, industrialist Eben Byers died from bone cancer presumably caused by his regular intake of radium supplements. Meanwhile, other researchers had shown that radiation causes chromosome damage in fruit flies—the higher the dose, the more mutations.

After World War II, physicists and others unhappy with the spread of nuclear weapons fanned the fear of radiation. By the time Calabrese's generation went to school, all mention of hormesis had dropped out of textbooks. Nevertheless, a handful of researchers still talked about hormetic effects. In 1985 one of them sent a flyer to Edward Calabrese.

"IF HORMESIS IS REAL AND SUBSTANTIAL," CALABRESE BEGAN TO THINK, "we should see it in all forms of life." But it wasn't until four years later, when he saw a debate in the journal *Science* between Leonard Sagan and a colleague more skeptical of hormesis, that he decided to bring the question to a wider scientific audience. In 1990 he and a few other researchers founded a newsletter, with Calabrese as its editor. They chose the name *BELLE*, for Biological Effects of Low Level Exposures, and Calabrese lined up an advisory committee of high-level academics, industry researchers, and government reg-

ulators. Among them were a number of skeptics. "I wanted a balanced group," Calabrese says, "to cancel out ideologies."

Within 10 years, *BELLE*'s circulation grew to 12,000—large enough to support a refereed scientific journal, which is scheduled to begin publication in January. Along the way, in 1996, the Texas chemical industry became a major supporter of Calabrese's research. His funders had an obvious agenda, Calabrese admits, but he didn't really care. "In the academic setting, I don't have to get the answer people expect," he says. "My salary comes through anyway."

Calabrese's sponsors wanted him to create a database of experimental evidence on hormesis in humans, to settle once and for all whether the effect is real. He persuaded them to broaden the scope to all organisms. During the next several years, he and his colleague Linda Baldwin systematically worked their way through the hormesis literature. They looked at each study's design; its data on low-dose exposures, the magnitude and statistical significance of that data, and their reproducibility. Then they tallied up their findings and assigned each study a score—one, they hoped, that any objective observer would agree with.

Studies designed to look for low-dose effects of toxins were few. Most researchers focused on high doses, tracing the effects from fatal exposures down to the so-called threshold of toxicity, and often a little below. Typically, too few subjects got the lowest doses for any meaningful statistics to emerge. But in 2 percent of the studies—the ones Calabrese and Baldwin assigned their highest score—the data were strong enough to analyze.

Calabrese insisted on including all studies that met the scoring criteria, whether their results supported hormesis or contradicted it. In the end, the positive results carried the day: Low doses were 2.5 times more likely to stimulate subjects than the risk-assessment models used by agencies such as the EPA had assumed. "Today we have 4,500 cases showing what we believe to be hormesis," Calabrese says. "If you see this pattern again and again and again, you really can't ignore it."

Findings in hand, Calabrese began to make the rounds of scientific meetings, just as he had with his carcinogen data. This time, though, he ran into a subtler resistance. When he had railed against single-exposure carcinogens in pollution, he says, it was as if he had been "defending mom and apple pie." His data on hormesis, by contrast, seemed like a license to pollute—even though his sponsors in Texas had, by then, bowed out. He remembers giving a talk on hormesis one day, when a troubled researcher stood up in the crowd. "Aren't you the same Calabrese of the single-exposure carcinogen?" the man said. "Isn't that a contradiction?"

TO WIN OVER SKEPTICS, CALABRESE REALIZED, HE NEEDED MORE THAN A good database. Statistics can associate almost anything with anything—poisoning with health, skin color with academic performance. What he needed was a good explanation: How, precisely, could a stress or poison promote health? "Toxicology today," as he puts it, "worships on the altar of mechanism."

The general principle behind hormesis, Calabrese believes, is

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homeostasis: the tendency of an organism to keep itself on an even keel. We respond to a rise in temperature by sweating. We respond to invading microbes by cranking up the immune system. Hormesis occurs when our bodies overcompensate, reaching a new and healthier equilibrium. When the immune system "remembers" foreign proteins, for instance, it can gear up quicker to cope with similar challenges, and the organism becomes more resistant to disease. Friedrich Nietzsche wasn't far off the mark, hormesis researchers say: What doesn't kill you makes you stronger. Some would even cite weightlifting, running, and character-building experiences as examples of stresses that produce hormesis.

Still, a general principle is not yet a mechanism. For that, Calabrese needed a specific sequence of cause and effect. Pharmacology seemed the natural place to look. Drugs typically lock onto receptors that signal the body to produce more of some needed chemical—a hormone, say—or to remove it from circulation. If low doses of poisons act just like medicines, then they should affect the same pathways. Calabrese and Baldwin have identified about 30 types of receptors that drugmakers target. They regulate important functions such as cell division, immune responses, and nerve signals, and they seem likely places where toxins would act.

Nevertheless, hormesis researchers have yet to run tests that would link low-dose toxins to these mechanisms, and it's easy to see why. For example, Calabrese sees evidence that low levels of carbon monoxide may help prevent heart disease. He believes that carbon monoxide reacts with nitrogen oxide in blood, which in turn activates receptors in artery walls that make blood vessels relax or contract. Arteries that are more relaxed are less likely to clog with plaque. But carbon monoxide also binds with hemoglobin, and at higher doses prevents the blood from carrying oxygen through the body. Just imagine asking a pharmaceutical company to fund experiments that prove the benefit of low-dose carbon monoxide. Where is the potential for profit? Could anyone patent, let alone market, a carbon-monoxide inhaler?

Other possible mechanisms for hormesis include heat-shock proteins and stimulations to the immune system. Heat-shock proteins are produced by cells in response to hyperthermia and other stresses. They help other proteins fold properly and may prevent damage from oxidation. As for immune-system stimulants, the best example may be radiation. While most scientists dismissed radiation treatments as quackery after World War II, a handful continued to test it as a way to prevent metastasis in cancer patients. In 1976 and 1979, two small clinical trials at Harvard found that low-dose radiation boosted four-year metastatic cancer survival rates from 40 to 70 percent and from 52 to 74 percent. Five years ago, a study at Tohoku University in Japan reported that patients who received low-dose radiation had an 84 percent chance of surviving for 12 years; those who didn't receive it had only a 50 percent chance of surviving nine years.

Myron Polycove, a professor emeritus of laboratory medicine and radiology at the University of California at San Francisco, has

studied radiation hormesis for decades. He finds that low-level radiation benefits the body in at least two ways: It stimulates the immune system in the constant search-and-destroy mission against cancerous cells, and it stimulates DNA repair. The oxygen we breathe is a highly reactive element, he points out, that breaks chemical bonds throughout our cells and in our DNA. The body is constantly repairing this damage, but mistakes accumulate as we age. Polycove believes that more efficient DNA repair explains why many organisms exposed to low-level radiation have lived longer than controls that were not irradiated.

Radiation hormesis is highly controversial. Polycove and others admit that all radiation causes damage, even at low doses, but they insist that the stimulation it provides more than compensates for the damage. For cancer therapy, they recommend the Japanese procedure, in which patients first get conventional high-dose radiation and/or chemotherapy to kill off tumors, then follow it up with low-dose treatments to stimulate hormesis and fight metastasis. In recent years, only one U.S. physician, James Welsh, practicing at the Johns

Hopkins Medical Center in Baltimore, has tried the procedure, and only on one patient, an 81-year-old man with lymphoma who refused to continue chemotherapy. His condition improved dramatically, but he later relapsed.

Europeans have a long history of seeking similar treatments. Every year, tens of thousands flock to spas like the one in Bad Gastein, Austria, to soak in water with naturally high radon content. In Montana, some abandoned mines, suffused with radon gas, have been refashioned as radon therapy centers. Moderate exposures supposedly promote overall health, but Calabrese is doubtful. "We have to be careful when calling hormesis beneficial," he says. You might end up stimulating a disease through hormesis—it might be "good" for the cancer cells or invaders—more

than you stimulate the body's defenses. Radon treatments are worth studying, he says. "But I am a cautious individual, and I usually require substantial amounts of data before I jump in the water, and I would call that jumping into the water."

LAST JUNE SOME 50 SPEAKERS, AND ANOTHER HUNDRED OR SO HORMESIS researchers in biology, toxicology, and medicine, came to Amherst for the first international conference on hormesis. They came from every relevant field of study and from all over the world: the United States and Canada, Europe, Russia, and Asia.

The crowd didn't look particularly daring or nonconformist, just the usual bearded professors and dapper consultants rattling around in a cavernous, neo-brutalist conference center. The presentations tended to be sober and scientific, but the talk between sessions plunged into familiar controversies. Once, during the twice-daily parade between auditorium and buffet tables, an advocate of nuclear power grumbled about the public fear of radiation. Another time, a researcher whose rats thrived on small doses of dioxin argued that "it's a ridiculous waste of money" to remove traces of chemicals from the environment.

"You can sense a lot of frustration and some anger here,"

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Calabrese remarked. Hormesis has been a "marginalized hypothesis" for decades, he said, yet the data suggest that it's a fundamental, unifying aspect of biology. In the studies that he and Baldwin reviewed, low doses of toxins typically improved a subject's endpoints by 30 to 60 percent. That's a small improvement if you're talking about the size of a tumor, but not if you're talking about some other conditions.

In one session of the conference, veterinarian Dennis Jones, of the Agency for Toxic Substances and Disease Registry in Atlanta, presented recent findings on low-dose mercury exposure. Jones analyzed data from a study at the Centers for Disease Control that tracked more than 100,000 infants. The infants were given thimerosal, an organic compound of mercury used as a preservative in vaccines. The researchers worried that giving the infants too many vaccines might harm them. But Jones found that limited exposure to mercury actually *lessened* the children's chances of developing neurological tics, delayed speech, and other pathologies. Jones's analysis is preliminary, so he declined to give concrete numbers. But he called the study "exquisite" and said that it "really amazed" him. Calabrese was not amazed. "In our most recent database search," he said softly into the microphone, "mercury is perhaps the most studied element showing a hormetic effect."

Unfortunately, benefits from hormesis may be practically impossible to harness. Hormesis usually occurs at doses about five times lower than the toxic threshold, Calabrese has found. (The EPA often sets acceptable exposure limits 20 times lower than that.) But sensitivities can vary from individual to individual by a factor of 10 to 100. A dose that stimulates hormesis in one person may well be toxic to another. That variability is a major reason why hormesis won't add new medicines to our cabinets anytime soon.

Still, hormesis may have an impact on environmental regulations. Pollution regulators work with risks so small, Calabrese says, that their numbers are calculated guesses. They measure how poisonous a toxin becomes at high doses and then draw a straight line—a "linear dose-response curve"—to predict the lesser poisoning effect at low doses. But what if low doses boost rather than harm well-being? Take the debate over arsenic. Based on a linear dose-response curve, the EPA believes that even trace amounts of arsenic can significantly increase the risk of cancer. As a result, the agency recommended lowering the legal limit in drinking water from 50 to 5 parts per billion in 1999. (It has since been raised to 10 parts per billion.) Yet a paper soon to be published by the journal *Ecotoxicology and Environmental Safety* shows a hormetic effect from a dose of 25 to 75 parts per billion. Biologist Gary Kayajanian combed through the results of two previous arsenic studies, one in Taiwan and the other in Utah. The Utah results were particularly telling: Raising arsenic levels back to 50 parts per billion, they suggested, would prevent 1,000 cancer deaths per day nationwide.

Yet another toxicologist, at the June conference, used his own observations of hormesis to support *stricter* limits on pollutants. Keith Solomon, director of the Centre for Toxicology at the Uni-

versity of Guelph, Ontario, has spent 30 years studying the effects of farm runoff on freshwater organisms. Runoff typically contains many low levels of pesticides, fertilizers, and antibiotics. But what turns out to be good for one species in the lab usually isn't good for all of them, Solomon says. The cloudier water forces some plants to grow taller and more vigorous, for instance, while killing off others. And when some populations explode at the expense of others, the balance of predator and prey can be thrown out of whack. "Bottom line," Solomon says, "you can say hormesis is a bad effect environmentally."

RECENTLY, DURING A QUIET WALK AROUND CAMPUS, CALABRESE'S MIND flirted with a dangerous question: Where is all this taking him? Hormesis might be a cruel joke—biology's equivalent of cold fusion—but he sees important differences. Cold fusion came out of one lab run by two researchers, and people could not reliably reproduce their results. With hormesis, 99.9 percent of the findings are not Calabrese's own, and they can be reproduced. "I believe that not only is hormesis real," he says, but it's also the most dominant biological effect at low exposures.

It's time for the EPA to develop a new paradigm for setting exposure limits, Calabrese says. Unlike the pollutants Solomon studied, the arsenic in drinking water and the radon gas that seeps into homes are natural toxins. Before advising homeowners and townships to spend fortunes on removing radon and arsenic, Calabrese thinks, the EPA should analyze the actual data on low-level exposures. "If hormesis is real," he says, "you can pretty much throw out what they are doing for risk assessments." If hormesis is the rule, rather than the exception, it should also prompt researchers to change the design of animal studies. Only then can we hope to find the master switch and how to exploit it—to improve the immune system, repair injury, and extend life.

Calabrese has yet to convince most mainstream scientists of that. Last year, for instance, a form of hormesis appeared in physicist Robert Ehrlich's book *Nine Crazy Ideas in Science*. "The idea of improving one's well-being through the nuclear version of tanning salons may sound patently absurd," Ehrlich wrote. Yet he gave it a rating of just one cuckoo on a scale of zero to four, meaning "probably not true, but who knows?" Such half-mocking reactions frustrate Calabrese, but they also push him toward new research, new evidence, and new surprises. Growth through adversity is his personal hormesis.

"How strange life is—not a straight line," he says. Little events deflected him enormously: a mistake someone made while diluting an herbicide, a flyer received in the mail. But beneath the superficial zigzags, there has always been a straight line: his search for truth. Sometimes, to refresh his sensibilities, Calabrese walks through his backyard, past a swing set his children have outgrown. In the garden, he stoops to his peppermint plants—the very same ones, he explains, from his undergraduate experiments at the state college, propagated all these years through root cuttings. He breaks off a leaf and inhales the essence of peppermint oil. ☐

A dose that stimulates one person may well be toxic to another. That's one reason hormesis won't lead to new medicines anytime soon