

Hotel Hormesis

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Imagine this: You have finally come back to your room after a long day of classes, and as you sift through your mail, you notice a brochure with a picture of a beautiful hotel in scenic Northern California called the Hormesis Spa and Resort. This brochure from the Background Radiation Enhancement Company (BREC) explains that increasing your background radiation exposure can actually heal your diseases and even make you live longer. Your eyes finally fall down to the testimonial below the picture, “I upped my background exposure. Now, up yours.”

Wow, you think, but why would I want to increase my background radiation? I always thought that background radiation was bad for you—that is exactly what the majority of the public thinks about radiation. If you walked up to random people on the street and asked what they associate with radiation, their response would probably include negative words such as mutant, dangerous, and cancer. Many of these images are generated by the media, which constantly discusses radiation in a negative light. For example, in the recent movie *Eight-Legged Freaks*, spiders exposed to radioactive waste turn into humongous people-eating mutants, and in Tom Clancy’s book, *The Hunt for Red October*, the Russian submarine has a nuclear reactor accident with radiation leakage that forces the crew to abandon ship.

However, the real root of public radiation fears rests in actual events. In 1945, thousands of people died in the atomic bomb explosions in Hiroshima and Nagasaki, Japan, and the lives of many were endangered during the nuclear accidents at Three Mile Island and Chernobyl. People are constantly bombarded with negative images of nuclear radiation. The popular belief now is that radiation, no matter the dose, is bad for you.

This theory is perpetuated by the LNT (Linear No-Threshold) model. Developed by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), this model states that there is no level of safe radiation because it is prudent to assume that radiation is linearly carcinogenic down to a dose of zero (Figure 1). These estimates are developed from extrapolating high-dose data from the Japanese bomb studies and nuclear accidents down to low doses.¹ Although it lacks low-dose data, this very conservative model was almost immediately accepted by committees around the world, such as the International Council for Radiation Protection (ICRP). It thereby stands as the leading model on which radiation exposure and protection is based. Proponents of the current standards claim that a conservative model must be used because it is so difficult to obtain actual low-dose data.²

However, research over the past few decades has indicated that low doses of radiation might actually benefit the body. Hormesis, which comes from the Greek word *hormaein*, meaning “to excite,” is the principle by which low doses of an agent cause stimulatory or beneficial effects that cannot be predicted by the extrapolation of detrimental or lethal effects induced by high doses of the same agent. Thus, small and large doses cause different physiological results. Although high doses of radiation increase the risk of cancer, low doses may boost the biological defense system, which would lead to fewer deaths from cancer and other causes. Additionally, these combined



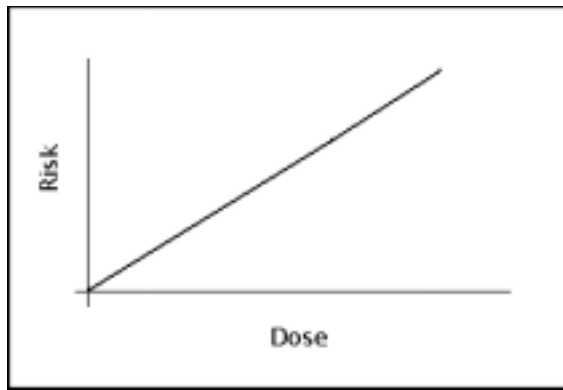


Figure 1. Linear extrapolation of high-dose cancer risk data to zero.

effects have the potential to lead to longer lives, according to studies performed by Sagan and Sugahara.³

Previous Studies

The principle of hormesis was first discovered by T.D. Luckey, who found that low doses of dietary antibiotics caused a surge of growth in livestock. An analogous principle is the purpose behind vaccination: after the immune system is introduced to pathogens at a low, relatively harmless level, it can more efficiently mount a response against “the real thing” when a harmful pathogen invades the body.

The same effect holds true for ionizing radiation. Though excessive exposure to ionizing radiation could lead to various complications, a low dose might actually encourage DNA repair, enabling the cells to cope with higher doses of radiation damage. Radiation hormesis is usually applied to physiological benefits stemming from low LET radiation in the range of 1-50 cGy total absorbed dose. Fitness, or ability of the organism to survive, is of optimal level when exposure levels fall in the hormetic zone (Figure 2).

According to T.D. Luckey, experiments in animals and animal cells exposed to radiation actually show an increase in cell growth and overall health. Invertebrates maintained in radiation-deficient conditions show a marked decrease in growth, which leads to the theory that radiation is in fact essential for growth.⁴

An article published in *Science* by Jocelyn Kaiser states that current radiation risks are based on the cancers occurring among the 86,000 survivors of the atomic bombs dropped on Japan in World War II. Carcinogenesis expert Julian Preston of the U.S. Environmental Protection Agency (EPA) declared that these survivors provide the “gold standard” in human data for radiation. Overall, the incidence of solid cancers among the survivors increases in a relatively straight line in accordance with the amount of radiation that the people received. However, at the lowest doses, too few cancers occur to accurately determine the risk at that level. As radiobiologist Eric Hall of Columbia University in New York City says, “The numbers are just not there.” Usually, public health agencies extrapolate the results of lower doses based on the data from higher doses.⁵

However, evidence shows that these lower doses of radiation may in fact be beneficial. For example, the Japanese bomb survivors who received the lowest doses are living longer than people denoted as “controls.” In western China and Colorado, where background radiation exposure levels are three to four times higher than the global average of 2.4 millisieverts per year, inhabitants have a slightly lower incidence of cancer.^{5,6}

Nobel Prize winner Sheldon Wolff of the University of California in San Francisco irradiated cells with a low dose of radiation. He discovered that cells that had been exposed to a low dose of radiation sustained a refractory response to higher doses of radiation; apparently, the induced response to the initial low dose led to the repair and rejoining of broken chromosome ends. Wolff declared that this induced response meant that “chromosome aberrations, deletional (or null) mutations, DNA double-strand breaks, and even cell survival that is dependent upon the genetic (cytogenetic) integrity of the cell can be endpoints that will show an adaptive response to ionizing radiations.”⁷

Wolff also explored the effect of radon and X-rays on human lymphocytes; exposure to low doses of X-rays resulted in a lower number of chromatid deletions induced by subsequent high doses of clastogens. Clastogens are substances that cause chromosomal breaks. Wolff attributed the high survival rate of his irradiated cells to the induction of a repair mechanism by the low-dose exposure. Before, the chromosome aberrations caused by radon’s radiation had been thought to be irreparable. However, Wolff irradiated human lymphocytes with low doses of X-rays (2 cGy) at 48 hours of culture and then exposed them to radon at 72 hours of culture. The number of radon-induced chromatid deletions decreased by a factor of two. Usually the number of aberrations per cell is overdispersed, due to the high relative biological effectiveness of alpha particles from radon. However, the pretreatment of cells exposed to the low-LET X-rays decreases the overdispersion. A lower number of pretreated cells exhibit chromosomal aberrations, compared with the number of aberrations present in cells that had been exposed solely to radon.⁸



Figure 2. The optimal range of exposure, known as the “hormetic zone,” promotes fitness until the transition point.

An experiment conducted by Vaiserman, Litoshchenko et al. measured the long-term effects of different radiation dosages to *Drosophila melanogaster*. At the one-hour egg stage, the scientists gave the male flies 0.25, 0.50, 0.75, 1.0, 2.0, and 4.0 Gy. After five to six days, DNA was isolated from the adult males and digested by S1-nuclease. A decrease in the life span of the flies was only observed at the largest dose, 4.0 Gy. In the males, 0.25 and 0.5 Gy caused the maximum life span possible. The DNA samples taken from the irradiated flies proved to be more stable when exposed to the S1-nuclease. The scientists concluded that “the higher stability of DNA originated from the irradiated flies could be the result of repair system activation.”⁹

Radiobiologist Ron Mitchel performed an in vivo study on heterozygous Trp53 mice, which are radiation sensitive and cancer prone, specifically to spinal osteosarcomas and lymphomas. The low doses of radiation had no effect on the frequency of tumor formation, showing that the low doses did not initiate tumor formation. However, at a 10 mGy, low-dose rate (0.5 mGy/min), ⁶⁰Co γ irradiation exposure increased the tumor latency, reducing the risk of both lymphomas and osteosarcomas and reducing the rate at which the tumors became malignant. With exposure to 100 mGy (0.5 mGy/min), ⁶⁰Co γ radiation delayed the lymphoma latency longer than the 10 mGy exposure, but increased the spinal osteosarcoma risk by decreasing the overall latency. This data shows that a transition zone exists between reduced and increased risk, but the dose for this transition differs by tumor type.¹⁰

The concept of radiation hormesis is currently considered a radical theory; therefore, scientists still disagree about the optimal dose for a person. In general, the optimal dose has been found to be approximately 10 cSv/yr. T.D. Luckey published the following table outlining the effects of various doses in his book *Radiation Hormesis*.

Table 1. Effects of dose¹¹

mGy/y	Designation	Comments
10 ⁻³	Lethal	Extreme conditions
10 ⁻²	Moribund	Laboratory conditions
10 ⁻¹	Deficient	Unusual environments ¹
1	Minimal	Low background
10	Marginal	High background
10 ²	Optimal	Recommended allowance
10 ³	Acceptable	Work limit
10 ⁴	Maximal	Health limit ²
10 ⁵	Excessive	Chronic radiation syndrome
10 ⁶	Lethal	Acute radiation syndrome

If the notion of hormesis for ionizing radiation is accepted, then accurately quantifying the beneficial dose for radiation would be necessary. Two issues hinder a more reliable definition: reliability of human studies and correlations between animal and human studies.

Limited studies have been conducted on human specimens in the laboratory. Due to ethical issues and the uncertain risk surrounding radiation hazards, human

beings are not considered appropriate subjects for experimental research on controlled dose studies. Generally, when a study of hormesis on humans was conducted, the subject received the dose through some uncontrollable exposure. For example, atomic bomb survivors, people living in high radium areas, and medical radiation patients have all been monitored for hormesis. The problem is the lack of sufficient controls in the studies to ensure that outside effects do not distort the observation of biological processes. At this point, no reliable studies have involved irradiated humans in a laboratory setting to specifically study hormesis.

Reliable studies have been performed on mice and other laboratory animals. Does hormesis in various laboratory animals directly correlate to hormesis in humans? A specific difference in the studies is the average life span of different animals; a mouse may only live a few years, but a person lives for decades. Current research does not suggest how exposure to radiation correlates between the two beings; however, murine research does often have implications on the human body due to similarities in their biological mechanisms. For example, adenomas of the lung in mice progress similarly to human lung tumors.

Researchers still need more information before they can identify an accurate optimal dose of radiation. Are hormesis studies on humans sufficiently controlled to be reliable? How does data from laboratory animals used in radiation studies correlate to humans? These questions must be answered before an optimal dose can be reliably defined.

In general, scientists performing experiments on low-dose ionizing radiation exposure have found that the low doses of radiation stimulate DNA repair mechanisms that allow cells to live longer than controls. However, though various studies have found that low doses of radiation induce a DNA repair response that aids further exposure to radiation, the side effects of radiation exposure might outweigh the good. In 1997, the Department of Energy approved a new program to study low-dose radiation. Approved through 2007, it has cost about \$100 million thus far and has focused mainly on cellular studies.

Molecular Mechanisms of Hormesis

The current model, put forth by UNSCEAR, promotes the Linear No-Threshold (LNT) model, which suggests that any dose of radiation, however small, may have negative biological consequences. At high radiation doses, especially with regard to high-LET radiation, biological processes are disturbed. This has been proven by animal experiments using rats and epidemiological studies based on data from Hiroshima and Nagasaki. The mechanisms behind the damage involve the ionization and excitation of either DNA or cellular water. A direct effect of radiation constitutes the ionization and subsequent break in DNA; an indirect effect occurs when daughter products of the original radiation interact with the DNA to produce double- or single-stranded breaks. Such breaks can lead

Receptor-Mediated Activation of PKA

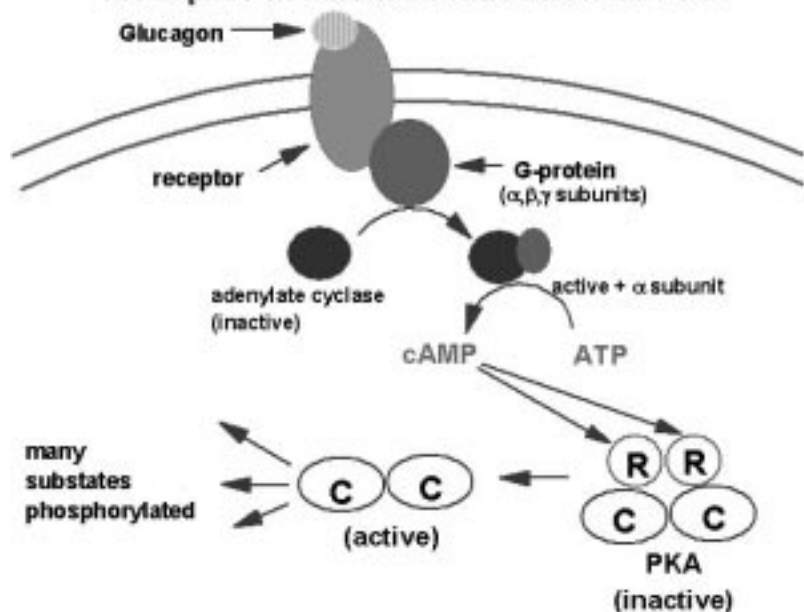


Figure 3. Representative pathway for the activation of cAMP-dependent protein kinase (PKA). In this example glucagon binds to its cell-surface receptor, thereby activating the receptor. Activation of the receptor is coupled to the activation of a receptor-coupled G-protein (GTP-binding and hydrolyzing protein) composed of 3 subunits. Upon activation the alpha subunit dissociates and binds to and activates adenylate cyclase. Adenylate cyclase then converts ATP to cyclic-AMP (cAMP). The cAMP thus produced then binds to the regulatory subunits of PKA leading to dissociation of the associated catalytic subunits. The catalytic subunits are inactive until dissociated from the regulatory subunits. Once released the catalytic subunits of PKA phosphorylate numerous substrate using ATP as the phosphate donor. Source: Michael W. King, Ph.D, IU School of Medicine, copyright 1996.

to chromosomal aberrations, which in turn may lead to cancer.

Proponents of the LNT theory have done dose-sensitive experiments on DNA, revealing that even doses below 1 eV of electrons result in DNA breaks. Tilman Mark's group at the University of Innsbruck in Austria has demonstrated that electrons less than 1 eV cause damage by reacting with the deoxyribose component of DNA. The newly formed ion then breaks apart, producing fragments that can further react with the complementary strand of DNA. Although DNA repair machinery is very efficient, it cannot fix breaks that occur in close proximity to one another. Thus, a double-stranded break can occur from even low doses of electrons.

Supporters of the growing theory on hormesis have conducted experiments showing that low doses in fact boost the biological defense system. On a molecular level, radiation at low doses may help the body in the following ways: stimulating the immune system, inducing the transcription of DNA repair proteins, producing radical scavengers, and temporarily halting DNA synthesis until the cell can recover.

Effects on the immune system have been demonstrated by Shu-Zheng Liu. When administering whole body low doses to rats, Liu measured the amount of cAMP and cGMP in thymocytes, which are immune system cells. He found that there was a decrease in cAMP levels and an increase in cGMP levels after doses within 0.2 Gy X-rays were given. In regular cells, cAMP induces

the catalytic activity of protein kinase A. When cAMP levels are reduced, PKA is down regulated and the thymocytes increase production of transcription factors involved in generating an immune response. On the other hand, when cAMP levels are high, PKA inhibits production of these transcription factors. This pathway explains the effect of low doses on the immune system.

The mechanism underlying the synthesis of novel DNA repair proteins in response to low-dose radiation remains unknown. The existence of these proteins is largely based on biochemical analysis of the protein content of cells before and after low-dose radiation. One such protein, RIP10, was found to interact both with cytoplasmic and nuclear proteins. This means that RIP10 translocates into the nucleus and probably affects transcription. Another possibility is the increased activation of ADP-ribose-transferase, which normally repairs DNA strand breaks. In some studies, ADP-ribose-transferase is found to be less active in cells after receiving low doses of radiation because there are fewer DNA strand breaks in these cells as compared to cells receiving no radiation.

Each mammalian cell goes through 70 million instances of oxidative damage per year. Most of this damage is caused by oxygen metabolism. Often, free radical oxygen species leak out of mitochondria and travel into the cell's nucleus where the DNA is housed. To protect itself from such free radicals, the mammalian cell has a biodefense system in place. This system consists of DNA repair proteins, antioxidants, and apoptosis (cell suicide) signaling. The antioxidant system includes antioxidant vitamins, glutathione (glutathione peroxidase), sulfhydryls (superoxide dimutase, SOD), and antioxidant enzymes. The theory behind hormesis suggests that the production of few free radicals produced by low-dose radiation triggers the antioxidant defense system to super-normal levels. Although the mechanism is not fully understood, it most likely involves the free radicals indirectly signaling intermediary molecules to increase transcription of antioxidant enzymes and production of molecules such as glutathione and sulfhydryls. Moreover, some studies suggest that apoptosis is more efficient. This means that damaged cells will initiate suicide protocols instead of continuing to proliferate.

Finally, in order for these processes (transcription of DNA repair proteins, stimulation of immune system specific proteins, and antioxidant molecule production) to occur, DNA synthesis is temporarily halted in the presence of low-dose radiation for an estimated five hours, so that the cell can recover more effectively from the administered radiation.

Conclusion

At the present time, the Linear No-Threshold (LNT) model is firmly established and accepted as the best way to analyze the risk of radiation. Through the years, hormesis has made the occasional push to gain acceptance, most recently in the early nineties. However, the

general public is firmly convinced that radiation is dangerous regardless of the circumstance. This stereotype is stressed both in the media and in professional training programs. The concept of ALARA (As Low As Reasonably Achievable) is one of the first things that radiation workers learn in their training.

The commitment to LNT is reflected in radiation regulation. There is a striking relationship between this optimal value and the limits for radiation workers. The Nuclear Regulatory Commission limits people to an equivalent dose of 0.05 Sv/yr. This clearly coincides with LNT, as proponents of hormesis suggest that the optimal dose is approximately 0.10 Sv/yr. The dose to the general public beyond background radiation is required to be below 0.001 Sv/yr: This is two orders of magnitude short of Luckey's optimal dosage.

The possibility of hormesis should be somewhat intuitive. Consider the following: Muscles require exercise; by exercising the muscles, greater strength and endurance is built. Perhaps this is analogous to DNA repair. As DNA is damaged in small amounts, the DNA repair mechanisms may become more efficient at repairing future damage. It is certain that DNA repair is induced by radiation. As Zbigniew Jaworowski states in his article "Radiation Risk and Ethics," "the fear of small doses, such as those absorbed from the Chernobyl fallout by the inhabitants of central and western Europe, is about as justified as ... the fear that sipping a glass of claret is harmful because gulping down a gallon of grain alcohol is fatal."¹¹

To date, a specific mechanism that is induced by low-level radiation has not been defined. This lack of knowledge should not immediately refute the possibility of hormesis; in fact, it should drive researchers to identify the mechanism. Radiation consisting of energy as low as 1 eV causes changes on the subcellular level. These altered molecules could be the very agents of hormesis.

Easily repaired damage to DNA may also induce the transcription of DNA repair proteins, temporarily halt DNA synthesis until the cell can recover, produce radical scavengers, and stimulate the immune system.

At the very least, hormesis is a theory that is worth investigating in a reliable, controlled setting. Studies performed by Wolff, Vaiserman, Mitchel, and Yonezawa all point to the beneficial effects of low doses of radiation. On the other hand, the side effects of radiation exposure might outweigh the good. A series of meticulous laboratory studies would help to settle the debate between LNT and hormesis. The program initiated by the Department of Energy has already cost about \$100 million and has focused mainly on cellular studies. Most of the studies done thus far do not provide conclusive evidence about humans. However, the theory of hormesis has already been sold to a small segment of people around the world. For example, the Misasa Springs claim to heal rheumatism, gout, atherosclerosis, high blood pressure, diabetes, digestive organs diseases, asthma, and skin diseases through inhalation of radon. According to the directors of the spa, the radon stimulates the body's cells, revitalizing them and developing capillaries. It also claims to improve antioxidant functions, which eliminate active oxygen, the suggested source of many diseases.

On a personal note, after having researched the topic of radiation hormesis for low-level doses, we are intrigued by its possibility. Simply put, we believe that the right dose of radiation is healthy. Small amounts of radiation stimulate DNA repair, better equipping the human body to guard against DNA damage. Repairing DNA more effectively increases both tolerance to high doses of radiation and the body's ability to defend against cancer. Radiation just might be a good thing. ■

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