

## Chapter 5

# RADIATION HORMESIS

“We do not know a millionth of 1 percent about anything.”  
Thomas Edison

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## 5.1 INTRODUCTION

The word “hormesis” is derived from the Greek word “hormaein” meaning: “to excite,” which in itself is again the origin of the word “hormone.” In 1902, the English physiologist E. Starling discovered that an acid extract from the human duodenum contained a substance designated as secretin that, when discharged into the bloodstream, stimulated the pancreas to release its secretions when food has passed through the stomach. In 1904, E. Starling coined out the word “hormone” to designate any substance that is produced by the body in small amounts and carried in the bloodstream to affect the function of other organs.

Biochemistry during the 1920’s was called “physiological chemistry” and developed around the study of vitamins and hormones, both low dose substances. C. Southam and J. Erlich noticed that large concentrations of oak bark extract inhibited fungal growth, but in low doses they lead to the paradoxical effect of stimulating fungal growth. Publishing their results in the journal *Phytopathology* in 1943, they modified Starling's word to “hormesis” which describes stimulation by low doses of agents that are harmful or lethal at high doses.

Hormesis came to refer to any stimulatory or beneficial effect induced by low doses of an agent that cannot be predicted from extrapolation of its detrimental or lethal effects when administered at high doses. When considered from the perspective of ionizing radiation, the topic raises heated debates from a majority of health physicists that vehemently opposes the concept calling it a pseudo-science, and a vocal minority of radiation biologists supporting it, leading to an unsettled controversy.

## 5.2 PHARMACOLOGICAL HISTORY

A pharmaceutical principle practiced by the ancient physicians was that: “A weak stimulus might stimulate what the same, but stronger, stimulus inhibits.” Modern physicians adopted the principle in the manufacture of vaccines. There are accounts of medieval criminals who would taste their poison before offering it in large doses to kill their victims. Alchemists apparently knew that a poison taken in a small dosage was not dangerous. Early physicians carried the drug “strychnine” in their bags and prescribed it as a stimulating tonic to their elderly patients. Only in high doses was strychnine considered as a harmful poison.

The Russian monk Rasputin is rumored to not being affected by arsenic given to him in a large dose by his enemies after intentionally conditioning himself, in anticipation of assassination attempts, to arsenic in low doses.

Any substance can exhibit toxic effects if used at an improper dose. For instance a severe lack of oxygen adversely affects the body at too low a concentration below 5 percent. A moderate oxygen deficiency however, stimulates Red Blood Cells (RBCs) production. The body at high altitudes compensates for the low oxygen concentration by providing a large surface area containing hemoglobin to absorb the lower oxygen concentration. Long distance marathon athletes living at high altitudes such as Kenya, excel at races conducted at lower altitudes such as Boston, Chicago or New York. Visiting athletic teams playing at high altitudes such as Denver, Colorado, at a one mile elevation above sea level, on the other hand, are conditioned by their teams to the higher altitude for a period of time before their games.

Common substances, such as nicotine, caffeine, alcohol, and water, have mild effects in low doses, but become toxic and even deadly at large dosages. Nicotine, for instance, is extracted from the tobacco or “nicotiana” plant and is also used as an insecticide.

Pharmacologists tested the toxicity of drugs by giving groups of test subjects, such as bacteria or mice, different doses and plotted the percent killed against the dosage given. The amount of a drug that killed 50 percent of the animals became the drug's Lethal Dose for 50 percent of the population abbreviated as: LD<sub>50</sub>. The complete curve takes the shape of a sigmoid. An LD<sub>90</sub> dose would be statistically significant in a very small population. Generating the graph for low doses was a difficult task, since only a few test animals died with low doses. For the LD<sub>10</sub> value, it took a large number of test subjects and a significant amount of time to reach statistical significance. Thus, the low end of the curve was often approximated or fudged. Because of this statistical difficulty, few pharmacologists paid attention to the very low dose effects.

### **5.3 RADIATION HORMESIS**

Antibiotics were available to agricultural chemists just after the World War II. T. Luckey and other colleagues in the 1950's added antibiotics to the food rations of livestock. They expected that the suppression of intestinal flora would decrease their growth. Instead, they discovered that the low dose dietary antibiotics caused a surge in animal growth. Since then, feeding antibiotics has become a standard practice for poultry, pigs and cattle and livestock husbandry in general. Experiments in germ free birds suggested a chemical hormesis effect.

Incidentally, livestock feeding with antibiotics is causing a controversy since some of these antibiotics such as Terramycin are also used in humans, and there is a suggestion that this is leading to the selection of surviving strains of bacteria that are resistant to these antibiotics limiting their efficacy in treating human disease. This has encouraged some European countries to ban their use in animal feed.

In surveying the literature, T. Luckey in the 1950's found that the hormesis effect was common, particularly when the dose was not of antibiotics but of ionizing radiation. A radiobiology study in 1898 had suggested that algae subjected to x-rays grew faster than unirradiated control groups. A stimulated growth was reported in trees in 1908 and

an increased life span in invertebrates in 1918 and in insects in 1919. X-rays stimulated seedlings growth was observed in 1927, plant growth in 1937, together with guinea pigs, rabbits and mice in the 1940's. Increased life span was the main reported effect in low dose irradiated rats, dogs, and even house flies in the 1950's. In a CRC Press 1980 monograph, T. Luckey revived the term "hormesis," this time with ionizing radiation and backed it up with a review of about 1,250 articles from the field of experimental biology.

H. Martland in 1925 described 18 female radium dial painters who after tipping brushes with their lips for five years, were exposed to high radiation doses and developed necrosis of the jaw bones and pernicious anemia. Other high-dose patients developed possible osteosarcomas. However, a thirty-year follow up of 1,155 low dose radium dial painters showed they had a lower cancer incidence than the general population and had a longer life span.



Figure 1. "Radium girls" luminous clock dial painters.

H. Muller in 1926 published his work on genetic damage and the inducement of mutations from x-ray irradiation of fruit flies. In the 1930's radiation became associated among geneticists, with chromosome damage. Significant chromosome defects occur after high doses, but mutations after low doses are just mathematical extrapolations from high dose data on fruit flies and mice.

Robert Stone during the Manhattan Project conducted experiments, raising mice in an atmosphere of uranium dust, and showed that the exposed mice lived longer than their unexposed controls. At this time the concept of Maximum Permissible Dose (MPD) was introduced.

In 1957, the nuclear accident at Windscale, England occurred, where a fire in a graphite reactor core released 20 curies of Iodine<sup>131</sup> into the atmosphere. Predictions of thousands of thyroid cancers were never realized.

In 1963, the Atomic Energy Commission (AEC) confirmed lower mortality in guinea pigs, rats and mice irradiated at low doses. In 1964, cows were exposed to a

radiation absorbed dose of about 150 centigrays (cGy) or rads after the first atomic bomb Trinity test in 1946 to test the effects of such a high dose. They were long afterwards quietly euthanized because of old age.

The concept of radiation hormesis is currently applied to the physiological effects of low Linear Energy Transfer (LET) radiation in the range of 1 to 50 cGys or rads of total absorbed dose. If it is determined that hormesis has merit as a real effect, it may affect radiation biology in the future by emphasizing its biomolecular and genetic implications, as well as the problems of damage and repair and radio adaptive responses.

## **5.4 EXPERIENCES WITH RADIATION**

In the early years of the discovery of x-rays, the general belief was that ionizing radiation had beneficial effects. An outrageous claim was made that blindness could be cured by exposure to x-rays. Radium was placed in ladies corsets. Mineral water containing radium from uranium ore minerals was popular as shown in the device called a “Revigator Dispenser” in Fig. 2.

During the period 1918-1930 about 400,000 bottles of Radithor and other tonic bottles containing one microcurie of Radium <sup>226</sup> and Radium <sup>228</sup> in “triple” distilled water were sold as shown in Fig. 3.

Some mixtures claimed that they could treat up to 150 diseases such as lassitude and impotence such as the Radione energy pills in Fig. 4; the forerunners to Viagra and its sister medications.

A radium Emanator shown in Fig. 5, and a box of Radioactive Earth as shown in Fig. 6 could be purchased by the health conscious consumers.

Radium solutions for drinking, compress pads containing radium, and even intravenous injections as shown in Fig. 7, were sold to the public.

Kerosene lamps used thorium dioxide ThO<sub>2</sub> mantles as shown in Fig. 8.

Ceramic ware of a brand name: Fiestaware used uranium salts as glazing materials (Fig. 9), and colored glassware collected by collectors as “depression glass” used radioactive substances such as uranium as coloring agents, and are consequently radioactive (Fig. 10).

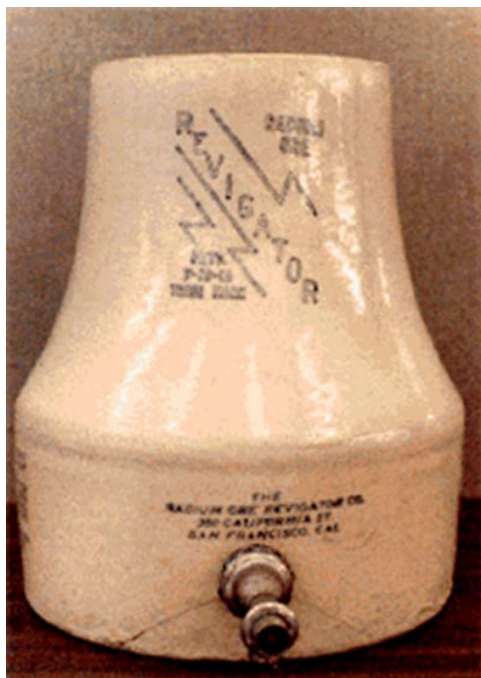


Figure 2. Revigator dispenser for water from a Thomas cone containing uranium ore.



Figure 3. Radithor tonic bottle available around 1918 contained one microcurie of Radium<sup>226</sup> and Radium<sup>228</sup>.

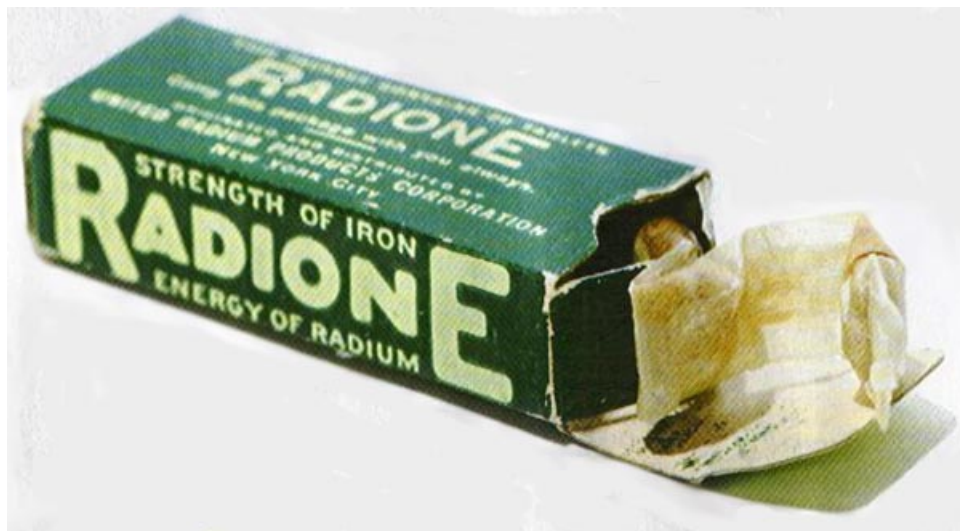


Figure 4. Radione energy pills.



Figure 5. Radium Emanator.



Figure 6. Box of radium-containing soil: Radioactive Earth.

It has been estimated by Macklis that the total collective skeletal radiation dose of each one of the victims of these snake oil medicines may have exceeded an effective dose of 35,000 centiSieverts (cSvs) or rads by the time of their death.

People still spend their vacations swimming in spas and drink mineral water containing radioactive substances. A whole industry was built around selling bottled mineral water containing thorium and uranium decay chain products. Sit-ups in closed uranium mine shafts are still being organized for its purported health effects irrespective of the hazard of the radon gas inhalation. Swimmers in Brazil sit on the beach and smear their bodies with thorium-containing black sands in the form of the Monazite rare-earths ore for their purported medicinal benefits.

Eventually people came to the realization that radiation was being misused leading to complications and harmful effects. The carcinogenicity of x-rays was first discovered as early as 1902. Once it was accepted that the excessive use of radiation can lead to deleterious effects, health regulations on the use of radiation were introduced in 1925 and for 30 years were based on the concept of a tolerance dose.

A Nobel Prize winner, Herman J. Muller in 1927, found out that x-rays are mutagenic and there exists a linear relationship between the dose and mutagenesis. His proposition was that all mutations caused by radiation and all other causes are detrimental.

Until World War II, radiation was admired and was considered as a great scientific miracle. The development of nuclear weapons and their use at the end of the war turned the admiration and curiosity into a fear of even small exposures to radiation and lead to an addition to the long list of phobias as “radiophobia.”



“STANDARD”

# RADIUM PREPARATIONS



“Standard” Radium Solution for Drinking

Each bottle contains two micrograms radium element in 60 cc. aqua dist.

Maximum-equilibrium constant of radium emanation, 5400 mache units.

PERMANENT

“Standard” Radium Compress

A means of applying radium locally for the relief of pain.

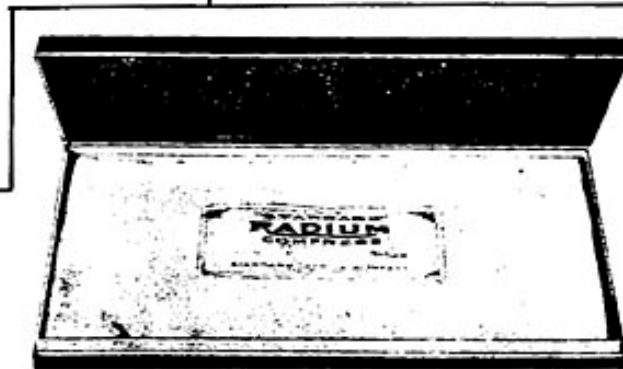
A flexible pad of standardized, guaranteed radium element content.



“Standard” Radium Solution for Intravenous Use.

In Ampulles of 2 cc. N. P. S. S. containing 5, 10, 25, 50, or 100 micrograms radium element.

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PERMANENT RADIO-ACTIVITY

## INDICATIONS

Subacute and Chronic Joint and Muscular Conditions.  
High Blood Pressure. Nephritis.  
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“The value of radium is unquestionably established in chronic and subacute arthritis of all kinds (luetetic and tuberculous excepted) acute, subacute and chronic joint and muscular rheumatism (so called) in gout, sciatica, neuralgia, polyneuritis, lumbago and the lancinating pain of tabes.”—Rowntree and Baetjer, Journal A. M. A. Oct. 18, 1913.

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Biologic Depot  
508 Butler Bldg

Figure 7. Radium solution for drinking and for intravenous injection is advocated as a medication.





Figure 8. Aladin kerosene lamps thorium mantle.



Figure 9. Fiestaware ceramics used uranium salt glazings.



Figure 10. Collectible “depression glass” used radioactive salts as coloring agents.



Figure 11. Glow in the dark radium alarm clock dials.



Figure 12. Radium glow spotter buttons.

## 5.5 LINEAR NO THRESHOLD (LNT) RISK DOSE RELATIONSHIP

Studies on the survivors of the bombings of Hiroshima and Nagasaki established the Linear No Threshold (LNT) relationship between their survivability and the large dose of radiation received by them.

Table 1. Observed and expected solid cancer death over the period 1950-2000 in Atomic Bomb survivors. Data: Preston et. al., 2004.

Weighted colon effective dose category [Sv]	Subjects	Integrated Population [Person.years]	Solid cancer deaths	Expected background	Fitted Excess
< 0.005	38,507	1,415,830	4,270	4,282	2
0.005-0.1	29,960	1,105,215	3,387	3,313	44
0.1-0.2	5,949	218,670	732	691	41

0.2-0.5	6,380	232,407	815	736	99
0.5-1.0	3,426	125,243	483	378	116
1.0-2.0	1,764	64,689	326	191	113
> 2.0	625	22,302	114	56	64
Total	86,611	3,184,356	10,127	9,647	479

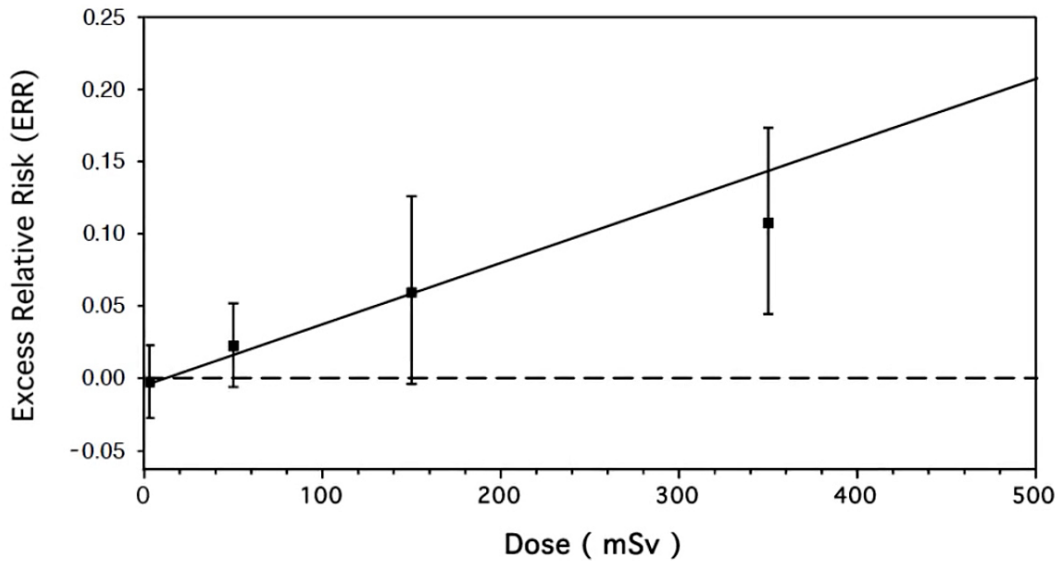


Figure 13. The cancer mortality Excess Relative Risk (ERR) in Atomic Bomb survivors cohort over the period 1950-1960 displays a linear fit to the data over the 0-50 cSv (rem) effective dose range. The vertical bars represent the 90 percent confidence interval.

Source: Preston et. al., 2004.

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) proposed the Linear No Threshold (LNT) theory in 1958. According to this theory:

1. The effects of low doses of ionizing radiation can be estimated by a linear extrapolation from the effects observed at high doses.
2. There is no safe radiation dose because even very low doses produce some biological effect.

The International Commission on Radiation Protection (ICRP) adopted the LNT theory in 1959.

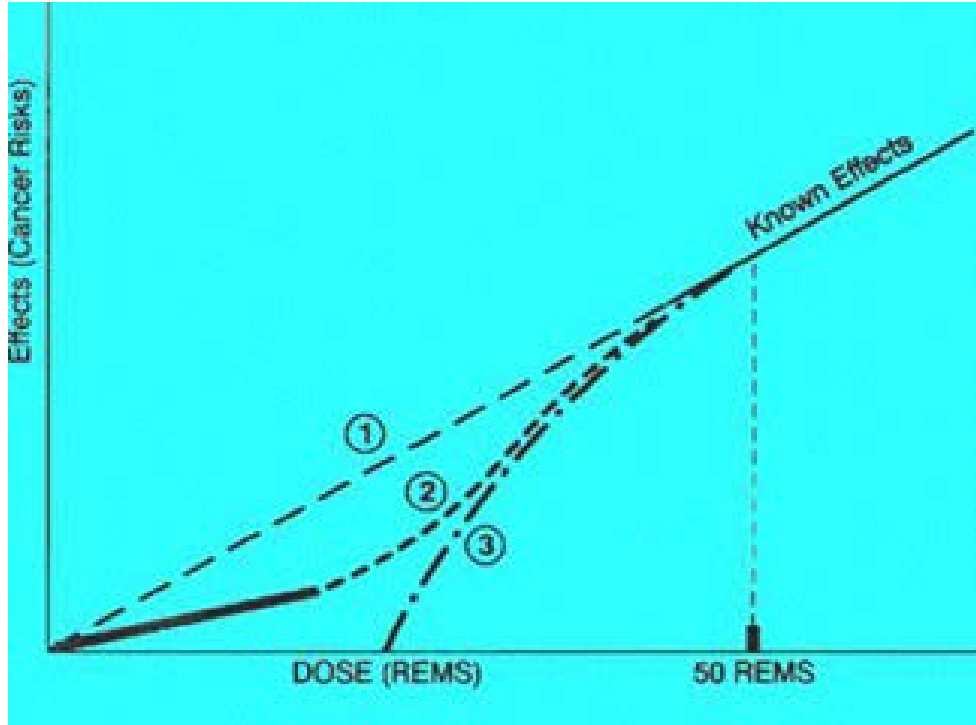


Figure 14. Dose Effect curves for nuclear radiation dose. Curve 3 represents the threshold hypothesis while curve 1 represents the Linear No Threshold (LNT) relationship.

According to the latest Biological Effects of Ionizing Radiation (BEIR) report there is a 0.79 percent probability of the occurrence of a latent cancer death risk for every 10 cSvs or rems of acute effective dose or dose equivalent. This implies that the risk  $R$  from radiation exposure is represented by the slope of the linear part of the curve in Fig. 14 is:

$$R = \tan \theta = \frac{0.79}{100} \times \frac{1}{10} = 7.9 \times 10^{-4} \left[ \frac{\text{cancer deaths}}{\text{cSv (rem)}} \right] \quad (1)$$

For comparison, there exists a probability of 18.33 percent for an individual of contracting cancer from all other environmental factors. The knowledge about the linear part is based on data from human exposure to high radiation doses, particularly among the Hiroshima and Nagasaki atomic bomb survivors. Below a dose equivalent of 50 cSvs or rems the unavailability of statistically significant data suggests an extrapolation of the high dose line to the origin of the y and x axes as curve 1. This is the conservative and prudent assumption to make in the absence of data for the low doses. In fact it is nowadays the accepted and followed norm for radiation protection.

The BEIR value is based on the concept that a single radiation hit could cause a cell to become cancerous; it does not recognize four protective responses that the cell possesses:

1. The body may be stimulated to produce detoxifying agents reducing the damage done by the chemical reactions induced by the free radicals generated by ionizing radiation.
2. The body may be stimulated to initiate damage repair mechanisms.
3. The cells may die removing the possibility of future abnormal subdivision. This process of programmed cell death is called “apoptosis,” occurring when the cell determines that conditions are no more optimal for its continued survival.
4. The body may be induced to produce an immune response that entails searching for the defective cells and targeting them for destruction, an ongoing process whether the damage is caused by radiation or any other causes such as heat or chemicals exposure.

Accounting for these repair mechanisms suggests the modification of the conservative linear hypothesis to a curve shown as curve 2 in Fig. 14 that is lower than the straight line hypothesis.

Another model suggests that the radiation damage at low radiation doses does not occur unless the radiation dose exceeds a certain threshold value as shown in curve 3 in Fig. 14.

Based on an analogy to vaccines: a less dangerous infection of a weakened or dead bacterium builds up the body defenses, and the need for trace minerals in the human body: none is bad, a little is good, a lot is a lot worse. A hormesis model can provide a curve for low doses that is not shown, where the curve would dip to negative values on the y axis.

## **5.6 HORMETIC DATA**

Yonezawa et. al. in 1996 showed that 21-ICR mice exposed to 8 Grays or 800 rads of x-rays absorbed dose had a survival rate 30 percent at 30 days after the irradiation, whereas when they were irradiated with 0.05 Grays or 5 rads of x-rays absorbed dose their survival rate increased to 70 percent at 30 days. He suggested the presence of two types of x-ray induced radio-resistance in mice, and the presence of three dose ranges with distinct biological effects. This does not convey any information unless compared to unirradiated controls. However other studies convey some possibility of a hormetic effect.

### **Epimediological Studies**

Some epidemiological investigations do not support the LNT theory. Studies by Cohen on the relationship between environmental radon gas concentrations and lung cancer contradict the theory at low doses of radiation and may even suggest a hormetic effect in that the total cancer mortality is negatively correlated with the background radiation dose instead of being positively correlated as expected by the linear hypothesis theory.

Mine, in studies among the Nagasaki bomb survivors, noticed in some age groups that the annual rate of death is less than what is statistically expected.

Kumatori reported that according to a 25-year follow up of the fishermen who were contaminated by the thermonuclear devices testing in 1954 at the Bikini Atoll at the Marshall Islands in the Pacific Ocean, reports that none of them died of cancer.

The epidemiological studies on the survivors of the Hiroshima and Nagasaki bombings who received less than 299 cSv (rem) in effective dose had no increase in the total number of cancer deaths, according to the UNSCEAR report in 1994. The mortality caused by Leukemia was also lower in this population at doses below 10 cSv (rem), than the age-matched control groups.

Mifune studied a spa area at Misasa, Japan where the average indoor radon activity density level is 35 [Becquerel / m<sup>3</sup>] and reports that the lung cancer incidence is 50 percent that in a low level radon region. He also suggests that in this high radon level area, the mortality rate caused by all types of cancer is 37 percent lower than the surrounding area.

### **Nuclear Workers studies**

In a Canadian survey of the mortality caused by cancer at nuclear power plants it was found by Abbat to be 58 percent lower than the national average.

In England, Kendall reports that the cancer frequency among nuclear power plant workers was lower than the national average. This could be a reflection of better working conditions and health screening and care among these workers rather than a hormetic effect.

### **Environmental Radiation studies**

Nambi and Soman observed that in Indian areas with high background radiation levels the incidence and the mortality rates from cancer was less than similar areas with a low background radiation level.

In the USA, Frigero reports that the mortality rate due to all malignancies was lower in states with a higher annual radiation dose. Cohen in the USA also suggests that the total mortality is negatively correlated with the background radiation dose.

In a Chinese study by Wei the mortality rate due to cancer among 74,000 people living in an area with high background radiation was lower than the mortality rate among a control group of 78,000 people living in an area with low background radiation level.

## **5.7 POSSIBLE HORMESIS MECHANISMS**

With new information from the new fields of proteomics and molecular and genomic phenomena the mechanisms of radiation hormesis wait for an adequate exploration and explanation. Three theories have been suggested to explain it:

### **1. Cellular Stimulation of the immune system**

It is recognized that large doses of radiation do suppress the immune system. However there are suggestions that low doses of radiation may stimulate the function of the immune system. Russ in 1909 showed that mice treated with low doses of radiation were more resistant than controls to bacterial disease.

### **2. Molecular DNA Repair**

As suggested by Ikushima, low doses of ionizing radiation are assumed to induce the production of special proteins that are involved in the DNA repair processes. Studies that used two-dimensional gel-electrophoresis, suggested the presence of new proteins in cells irradiated with low radiation doses. Cycloheximide, a protein synthesis inhibitor, was shown to block the hormetic effect. The importance and function of these radiation induced proteins remains unclear. In a review by Wolff, the inhibitors of poly ADP-ribose polymerase, an enzyme involved in DNA strand break rejoining, were found to possibly inhibit the induction of adaptive processes (Fig. 15).

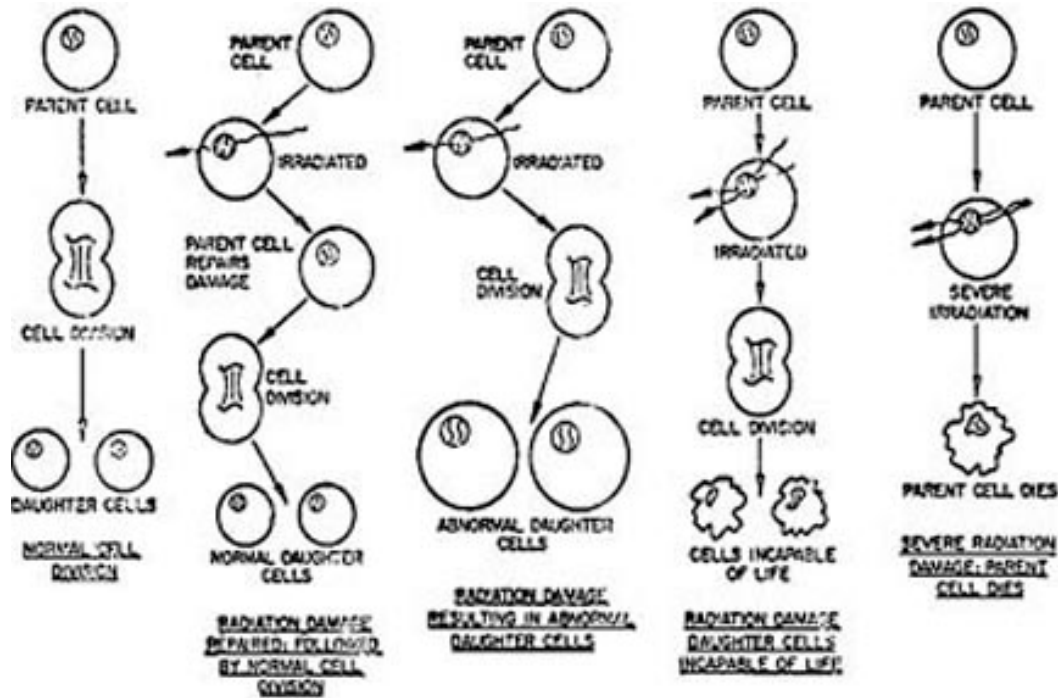
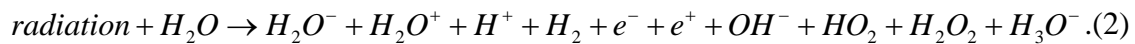


Figure 15. Different fates of cells exposed to radiation.

### 3. Molecular free radical detoxification

Human cells contain a substantial amount of water. Radiation interaction with water can generate a large number of free radicals:



Feinendengen et. al. discussed how low doses of ionizing radiation would cause a temporary inhibition of DNA synthesis with the maximum inhibition at 5 hours after irradiation. This temporary inhibition would provide a longer time for the irradiated cells to recover. Such inhibition may also induce the production of free radicals scavengers so that the irradiated cells would become more resistant to any further exposure.

### 5.8 RADIATION PRECONDITIONING



Azzam et al. reported that a single exposure of C3H 10T1/2 cells in vitro to low doses of 0.1 cGy or rad, which is at the background per capita yearly dose level of 100 [mrem / (capita.year)], reduces the risk of neoplastic transformations to below the spontaneous inducement level.

Redpath et al. confirmed their results. They used the Hela-x skin fibroblast human hybrid cell to magnify their results. Using a similar experimental protocol, they also demonstrated a statistically significant transformation frequency for the adapted cells by low level radiation compared with unirradiated cells in a four experiments pool set.

Similarly, Bhattacharjee showed that when mice were pre-irradiated with adapting doses of 1 cGy or 1 rad for five days without a challenge dose, thymic lymphoma was induced in 16 percent of the mice. Now, when the preirradiated mice were exposed to 2 Gy or 200 rads of a challenge dose, thymic lymphoma was induced again in 16 percent of the mice. However, with the challenge dose alone without preconditioning, the induction of thymic lymphoma was in 46 percent of the mice. It could thus be concluded that the low dose pre-irradiation may possibly cancel the induction of thymic lymphoma in the 2 Gy challenge dose. Another explanation is that the most genetically predisposed mice got the thymic lymphoma in the first irradiation and that what was left for the second experiment was the genetically radiation resistant individuals. A better experimental design based on Bayesian statistics and conditional probabilities may be needed to gain better confidence in the preconditioning conclusion.

Mitchell et al. in Canada have also demonstrated that a low dose preconditioning at 10 cGy or 10 rad administered at the rate of 0.5 [Gy / hour] modifies the latency for radiation induced Acute myeloid Leukemia (AML) in CBA/H mice after an exposure to 1 Gy or 100 rad chronic radiation. The latent period for development of AML was increased by the prior low level dose.

## **5.9 DISCUSSION**

If radiation hormesis can be better understood on the basis of the new knowledge in Genomics and Proteomics and considered as a real phenomenon, a great benefit can be derived from it in the fight against cancer. According to Luckey, a third of all cancer deaths may be premature and could be preventable by low level radiation preconditioning.

However, radiation hormesis is as yet not considered by many people as a valid scientific reality since ionizing radiation is harmful to some degree. Nevertheless, low levels of radiation have been essential for the process of evolution, which would have been much slower if the levels of ionizing radiation would have been much lower on the planet Earth. Radiation has been essential for the successful mutations favoring the adaptation of life to new circumstances and to biological diversity.

The implication is that even though radiation may be harmful to a single individual, it favors a whole species on the evolutionary scale.

While incremental radiation exposure increases the probability of occurrence of some harm, the marginal cost at low doses may be small and then becomes larger at high doses. A marginal cost against benefit model that considers both effects may be needed to adequately describe the effects of radiation at low and high dose levels.

Yet, the consensus from the Atomic Bomb survivors' studies is that:

“ ... in the presence of available data, it is neither sound statistical interpretation nor prudent risk evaluation to take the view that the risk should be considered as zero in some low-dose range due to lack of statistical significance when restricting attention to this range.”

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## **EXERCISES**

1. Calculate the expected Risk of yearly cancer deaths in the USA population of 285 million people from:

a) The natural radiation exposure at about 100 [mrem / (person.year)].

b) The natural and man-made sources of radiation at about 228 [mrem / (person.year)]