Radiation Hormesis: Historical and Current Perspectives

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ABSTRACT

The purpose of this article is to provide the reader with a better understanding of radiation hormesis, the investigational research which supports and does not support the theory and the relationship of the theory with current radiation safety guidelines and practices. The concept of radiation hormesis is known to nuclear medicine technologists but understanding its complexities and the historical development of the theory may be pertinent in better understanding radiation safety and regulations.

INTRODUCTION

Hormesis is the concept that biological systems can respond in a positive way, or be stimulated by, low doses of a physical or biological exposure. (1) Additionally, hormesis is defined as any physiological effect that occurs at low doses which cannot be anticipated by extrapolating from toxic effects noted at high doses. (2) Therefore, radiation hormesis is the theory that biological systems can respond positively with exposure from low doses of ionizing radiation.

In contrast to the hormesis theory, much of the radiation safety we as nuclear medicine technologists practice follows a different model. A brief discussion of the dose response models is required to provide the reader an understanding of the differences between a linear no threshold, threshold, and hormetic model which will be discussed in this article. A linear no threshold model states that the biological effects increase as the exposure to the physical or biological agent increases. (Figure 1) Threshold models state that no significant
biological response is observed until the exposure to the physical or biological agent reaches a threshold dose. (Figure 2) Hormetic models state that low dose exposure to a physical or biological agent helps the body, and as the exposure dose increases the benevolent effects decrease. At higher exposure doses, the hormetic model then takes on a linear appearance and biological damage is determined by increasing dose. (Figure 3)

In the United States the Nuclear Regulatory Commission is the governing body that sets limits and enforces laws concerning the safe use of radiation. (3) These regulations in radiation safety assume that radiation follows a linear no threshold model, and the biological effects of radiation are related linearly with the dose. (2) Radiation protection is based on a linear no threshold model, and dose effects at low levels are extrapolated from high level dose information observed from atomic bomb survivors, Chernobyl disaster survivors, and other populations with documented high exposure rates. (4) The hormesis theory is the subject of substantial research to evaluate the ongoing question if radiation continues this linear relationship at low doses or has a different effect. An analysis of the literature demonstrates that radiation science and toxicology may be related with hormetic effects, with numerous epidemiological studies supporting a theory of radiation hormesis; however the theory has not found mainstream success. The overall goal of this article is to provide the reader a better understanding of the concept of radiation hormesis and the literature supporting and not supporting the theory.

HISTORY

In the late 1800’s the discovery of x-rays by Wilhelm Roentgen, radioactivity by Henri Becquerel, and radium by Pierre and Marie Curie birthed the study of radiation effects on living things. (3) Radiation was first seen as benign and not dangerous, and was used for many personal applications. Radioactive sources, radium especially, could be found in multiple
everyday products. (5) There were different radioactive creams that promised skin rejuvenation, and radioactive elixirs that promised to rid the body of toxins and disease. (5) Following observed effects of radiation, the perception of radiation changed with the evidence that radiation could be harmful. Becquerel and Pierre Curie both sustained radiation burns from their own experiments, and it is thought that Marie Curie, as well as her daughter, died of leukemia from exposure to radiation in their experiments. (3) Also, the death of Eben M. Byers, a wealthy Pennsylvania industrialist, caught public attention. Byers had been taking radioactive elixirs for “rejuvenation,” and these were linked with his death. (6) The evident dangers of radiation were observed, and public opinion began to inquire to what levels of radiation are safe.

The bombings of Hiroshima and Nagasaki, in August of 1945 caused a great impact in the perception of radiation. Many of the studies that focused on beneficial use of radiation stopped, and the focus of investigations shifted to the effects of radiation exposure, and determining safe levels of radiation. Investigators focused on building a radiation dose response curve, which demonstrates the relationship between the biological effects of radiation as dose increases. (6) Data used to describe the effects of radiation on an individual was primarily collected from the survivors of the atomic bombings and other nuclear industrial workers. (6) Studies were conducted to determine a dose of radiation that was safe or had no effect, also called a threshold dose. (6) Scientists and officials could not prove, using the high dose atomic bombing data, that such a relationship existed so the affective response at high doses was extrapolated to low doses, and the linear no threshold model was accepted. (6) The linear no threshold model assumes there is not a safe level of radiation, or that all radiation is damaging. (7) Radiation regulatory agencies adopted this model for which many of the regulations and guidelines were based. Around the same time, threshold and hormetic models were studied in
other professional fields. In fact, toxicological studies discovered the interesting relationships between the dose of a toxicant, and the biological response to that toxicant. (8) These studies are important to radiation hormesis, because the data demonstrates most environmental exposures do not normally produce a linear response in the body, like the linear no threshold model assumes. (8)

Years before the discovery of radiation, and through the early 1900’s, advances in the toxicology field demonstrated that variable doses of toxic substances showed no effect, or in some cases beneficial effect. (9) Professor Hugo Schulz worked at the University of Greifswald in Germany in the late 1800’s, and made observations that various chemical and biological toxicants appeared to stimulate metabolism at low dosages. (9) His work became known as the Arndt-Shultz law, that stated ‘Weak stimuli accelerate vital activity, medium ones promote it, strong ones inhibit it, and very strong ones snuff it out.” (8) This relationship was also seen in the work of Ferdinand Hueppe, and became known as Hueppe’s Rule. (9) Because of scrutiny of their research, governmental concern of high dose effects, and the fact that low dose effects are hard to prove, the idea of hormesis began to fade, and threshold models became better accepted in toxicology. (9) The main difference in hormetic models and threshold models is, in a threshold model, doses below the threshold show no toxic effect, but in a hormetic model, doses below a certain amount may actually stimulate and promote a physiologic response. (9) Many pharmaceuticals, vitamins, and even toxicants were shown to have hormetic effects at low levels, but toxic effects at high levels. (8,10) These results in the toxicology field sparked research into the possibility of hormetic or threshold effects with radiation.

RADIATION HORMESIS INVESTIGATIONS

From the discovery of the x-ray to the mid 1940’s, the idea of hormetic effects of
radiation was supported in scientific literature, and for the most part, public opinion of radiation was positive. (1,6) Various plant studies showed hormetic responses to low doses of x-rays. (1) Plant seeds were exposed to radiation, and many of those plants responded with increased yields of soy, wheat, and flux. (1) Also, radiation demonstrated therapeutic effects with different types of skin diseases. (6) With the implementation of the linear no-threshold model a great deal of the research into radiation hormesis stopped, and divided radiation scientists into two divisions, those who supported linear no-threshold and those who supported different models. (6) Scientists who favor the horneric response at low doses, are also divided as to why these effects may occur. Some of the theories assessed include: radiation stimulates DNA repair; free radical detoxification; and immune system stimulation. (6) Advocates of both sides have theories as to what really happens to biological tissue at low doses of radiation. There has been multiple studies through the years on the effects of radiation at lower doses, and many of these studies can be explored in the works of Calabrese and Baldwin. (1,10) This article will further describe the following areas of investigation of radiation hormesis: 1. modern research into the possibility of hormetic effects from low dose radiation, 2. modern research that shows no horneretic effects, and 3. investigation into reasons why the hormesis model has not been widely accepted.

**SUPPORTING INVESTIGATION OF RADIATION HORMESIS**

As technology has progressed the ability to study effects at the cellular level has increased. Modern interest in the theory of radiation hormesis gained momentum again during the 1980’s. One investigation studied the reproduction of protozoans under the effects of low dose ionizing radiation. (11) In this study, the reproduction and growth rates of *T. pyriformis* were examined at below background radiation, background radiation, and different low radiation
rates (7.3 and 45 mrad/day). (11) The results indicated that the reproduction rates of *T. pyriformis* in radiation rates below background were lower (P<0.01) than in background levels, and both cultures at the low levels of radiation reproduced faster (P<0.01) than the background control. (11) More recent studies into the effects of low levels of radiation have been conducted, many with similar results.

During the mid-1990’s, Cohen analyzed the lung cancer mortality rates in 1,601 counties across the United States, and compared these rates to Radon exposure levels. (12) After controlling for smoking prevalence and many other confounders he found that as the low level Radon dose increased, lung cancer mortality decreased. (12) These results were opposite to what was expected, which was an increase in lung cancer mortality with increased Radon exposure. (12) Also, in a 2002 review of hormesis literature, Cohen made the statement “The evidence in this review leads to the conclusion that the linear no-threshold theory fails badly in the low dose region…” (13) The literature in the Cohen review demonstrated evidence that low (less than 50 cGy) radiation levels increase immune response, which helps the body fight DNA strand breaks due to radiation or other causes. (13) Also, the literature in the review indicated that there is a 20% probability that the slope of the dose response curve could be negative at lower doses. (13) These points were again supported by a study involving mice in 2004.

In 2004, Li et al. demonstrated low doses (75mGy) of radiation stimulated the bone marrow hematopoietic progenitor cells in mice. (14) These cells help the body regulate the number of different blood cells in the body; and stimulation of these cells could increase blood cell counts in patients experiencing therapeutic regimes. (14) Another 2005 study contrasts the similarities in toxicological response radiation response at low dose levels. (15) This study concludes that doses below 200 mGy stimulate DNA repair mechanisms and cells respond
positively to radiation. (15) Therefore, the linear no-threshold model does not describe the relationship at low levels, but possibly a combination curvilinear models should be used. (15) Yu et al. studied the effects of low dose radiation on mice implanted with sarcoma. (16) This study found that irradiated mice had a lower tumor occurrence rate than mice not exposed. (P<0.05). (16) Also, the growth of sarcoma was slower in the mice exposed to the low radiation dose. (16) The overall results indicated that low dose radiation has the potential to decrease tumor formation and increase immune function overall. (16)

In addition to the mentioned investigations, there have also been studies conducted within the past year that have interesting results. In early 2015 a review was conducted by N.S. Kudryasheva and T.V. Rozhko investigating the effect low dose particulate (alpha and beta) radiation has on luminous marine bacteria. (17) This review included multiple studies that investigated the effects of tritrium, americium-241, and Uranium 235,238 on bioluminescent bacteria. (17) The review concluded that in the presence of the low dose radiation, the bacteria showed adaptive characteristics, which was attributed to radiation hormesis. (17) In another study, the U.S. population was grouped into high impact states based on where nuclear weapon testing occurred. (18) Lung cancer incidence was studied in these states, and the results indicated that lung cancer incidence was lower (p<0.001) in men and women in these states as compared to others. (18) This correlated with the Argonne national lab report from 1973, that also reported a decrease in cancer rates in states with higher background radiation. (19)

**NON SUPPORTING INVESTIGATIONS OF RADITION HORMESIS**

Not all data in the above studies favor the theory of radiation hormesis. In the previously mentioned article by Calabrese and Baldwin, their review of the history of radiation hormesis showed multiple studies which supported the theory of hormesis, but also included data that
contradicted the theory. (1) There were multiple plant studies that showed negative or inhibitory effects in the presence of low dose radiation. (1) The authors did comment that this early research may not have accounted well for different ways plant species respond to variable doses of radiation. (1) There has also been more modern investigations that shed doubt on the theory of hormesis.

Many of the modern investigations which demonstrate contradiction to the radiation hormesis theory assess DNA breakage and repair. In a 2003 study, DNA double strand breaks after exposure to X-ray radiation were investigated. (20) This study was conducted on human lung cells at variable doses up to 200mGy. (20) The results demonstrated that there was not a stimulatory response when it came to the repair of DNA double strand breaks in these cells, and these findings could indicate that the linear no-threshold model is underestimating the effects at low doses. (20) Another study by Spencer et al., focused on the effects of low levels of radiation on the DNA repair mechanisms in human cells. (21) Ataxia-telangiectasia mutated (ATM) and histone H2A, which are active in the DNA damage recognition and repair sequence, were studied under low dose radiation. (21) The results showed that ATM activation was lowered by 40-50% and histone H2A levels were lower in the cells that received the low dose radiation. (21) A more recent study from 2014, further reinforces the findings from the previous literature. (22) The DNA double strand breaks in mice were found to be repaired at the same rate in cells that received low dose radiation as compared to ones that did not. (22) These studies are a few investigations demonstrating a possible flaw in the theory of radiation hormesis.

**ADDITIONAL REASONS AGAINST RADIATION HORMESIS**
There are also many thoughts as to why radiation hormesis has been suppressed politically, and the linear no-threshold model has been considered the norm. The history presented earlier will give a foundation as to the political and social reasons why the theory of hormesis is not widely accepted. Calabrese and Baldwin indicate challenges of experimentation, unawareness of toxicological hormesis research, scientific criticisms, and economic implications as reasons why radiation hormesis has not been given much consideration. (23) Assessing differences between background radiation and low dose radiation is very difficult, because the stimulatory response dose is very close to background levels. (21) In the time that the linear no-threshold model was adapted (1940s) the measuring devices used to discriminate these small differences made it very challenging. (23) Toxicological research going on at the same time showed hormetic relationships between different known toxicants at low levels, but the radiation scientists failed to realize this, and did not relate radiation to what was being published in the toxicological literature. (23) As stated above, many of the early studies showed inconsistent results. Some studies showed a stimulatory response, while some show inhibitory responses to low dose radiation. (1) This caused much critique from scientists at the time, and this criticism followed into documents to the Nuclear Regulatory Commission. (23) Lastly, many companies took advantage of the discovery of radiation to make products that promised rejuvenation or agricultural increases. (23) These companies profited from selling these products to the general public, and as noted above, with the death of Byers, this became widely controversial. (6,23) Also, the linear no threshold model may have sparked financial interest by radiation physicists, according to Brucer, “As soon as Health Physicists saw the money in radiation hysteria, the maximum permissible dose came down to background.” (24) Public fear of radiation led to multiple radioactive shielding legislative decisions. Companies began to sell, and still do today,
radioactive protective equipment such as lead aprons, portable shielding, and other radiation absorbing devices. (24) Another possible reason the hormesis theory lost support was, during much of the crucial years, the country was focused on fighting World War II. (23) Radiation hormesis really began to lose momentum in the late 1930’s and early 1940’s. (23) During this time attention to research in many scientific fields shifted to research that would help the war efforts, like the atom bomb. (23) Also the post war era had large groups of soviet scientists studying low dose effects of radiation, but with the cold war between the U.S. and the Soviet Union, the availability of this research was limited. (23) From the end of the Second World War until the late 1980’s the relationship between the western countries and the Soviet Union was very tense. (23) Information from both sides was not shared, including research into the effects of radiant at low levels, so much of the work of the Soviet scientists went unknown until long after radiation protection programs were implemented in the United States. (23)

The timing of all these combined factors affected scientific opinion of radiation hormesis, which consequently determined the theory’s fate in the regulations. (23) Many of the scientists at the time who helped form the Nuclear Regulatory Commission (NRC) and determine the linear no-threshold model, were not convinced that the hormesis theory was valid. (23) So, the NRC was founded, and the linear no-threshold model was accepted for all doses of radiation. (7) The idea that there is no safe dose of radiation has persisted since this time, even in the face of valid epidemiologic studies that demonstrate findings consistent with hormesis.

CONCLUSION

Radiation hormesis is the idea that low doses of radiation may stimulate or have positive outcomes on biological tissue. Ever since the discovery of x-rays, scientists have been trying to determine if there is a safe level of radiation, and the effects of radiation at different levels. In
the early years of research the theory of radiation hormesis had scientific and public support. During the same time many experiments in toxicology showed hormetic effects of various toxicants. Radiation scientists at the time failed to draw similarities between radiation and the toxicology research, and with the change of public opinion, scientific criticism, and other external factors, the theory of radiation hormesis lost momentum. The linear no-threshold model, based on high dose exposure, was accepted for applications of radiation safety and dose effects.

Even though the no-threshold model is widely accepted, there has been a resurgence of literature investigating the theory of radiation hormesis. Articles presented consist of valid epidemiological studies investigating the relevance of radiation hormesis in plants, bacteria, fungi, and mammalian cells. These studies demonstrate statistically significant differences when exposed to low doses of radiation for all of the different cell types investigated. On the other hand, there have been studies indicating low dose radiation has no effect or is inhibitory to DNA strand break repair. Conflicting results from both sides of the radiation hormesis argument demonstrate that effects at low radiation doses are not exactly known. As radiation science moves forward, more research is needed that investigates the theory of hormesis, and raises questions to the validity of the linear no-threshold model at lower doses of radiation.
REFERENCES


FIGURE 1: Example of Linear No Threshold Model

Increased biological effects

Increased exposure dose →
FIGURE 2: Example of Threshold Model
FIGURE 3: Example of Hormetic Model

Increased biological effects

Increased exposure dose
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