

**RADIATION HORMESIS;
POSSIBILITIES AND CHALLENGES.**

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TITLE PAGE

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DEDICATION

This is to my Father, God.

ACKNOWLEDGEMENT

A big thank you to my parents,again.

Chizu you are the best sister in the whole world!

**To all of you that have been here when it really really mattered,THANK
YOU!**

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CHAPTER ONE

1.1 INTRODUCTION

All living organisms evolved and live in a sea of ionizing radiation both internal and external but much of it is internal. It is a general belief that low doses of ionizing radiation produce detrimental effect proportional to the effect produced by high level radiation (S.M Javad, 2001). Despite the fact that high doses of ionizing radiation are detrimental, substantial data from both human and experimental animals show that biological functions are stimulated by low dose radiation (Luckey,1980). The word hormesis is derived from the Greek word “hormaein which means to “excite”. It has long been known that many popular substances such as alcohol and caffeine have mild stimulating effect in low doses but are detrimental or even lethal in high doses. In the early 1940’s,C.Southam and his co- worker J. Erlich found that despite the fact that high concentrations of Oak bark extract inhibited fungi growth, low doses of this

agent stimulated fungi growth. They modified Starling's word hormone to hormesis to describe stimulation induced by low doses of an agent that can not be predicted by the extrapolation of detrimental or lethal effect undivided by high doses of the same agent.

During the 1950's Luckey, a pioneer researcher in radiation hormesis, indicated that low doses dietary antibiotics caused a growth surge in livestock. Later he found that hormesis could be induced effectively by low doses of ionizing radiation. In 1980, the first complete report on radiation hormesis was published (Luckey TD 1980). In this report, he reviewed numerous articles regarding radiation hormesis. Since the first reports, 3000 papers have been published on the benefits of low doses of ionizing radiation.

1.2 BACKGROUND OF STUDY.

The concept of radiation hormesis is usually applied to physiological benefits from low LET radiation in the range of 1-50cGy total absorbed dose (Macklis 1991). It is widely believed that radiation biology in the future will be focused on biomolecular and genetic implications, problems of damage and repair and connected problems such as radiation hormesis and radioadaptive response (S.M Javad, 2001). A literature search revealed much information suggesting that large and small doses evoke opposite effects;

: Hippocrates, *Similia similibus curentur* or “likes are cured by likes”,

: Paracelsus, the father of infinitesimal doses, “the dose makes the poison”,

: Hahnemann, “Drugs have a dynamic effect when used in small doses”

: Cannon, “Adaptation to perturbations is the basis for homeostasis”

: Selye, “The General Adaptation Syndrome” and Arndt. Schultz, “poisons are

stimulants in small doses”. These were supported by the remarkable findings of Richet

(1906). He understood the oligodynamic action of metals as proposed by Nageli (1893): very dilute solutions of metallic ions are toxic. Richet quantified the toxic effect by using serial dilutions of several metallic ions. He found that each metal ion exhibited a threshold and was stimulatory at subharmful doses. They linked out antibiotic response to classic science. Nevertheless, the threshold dose response has become the key model in toxicology and pharmacology. Many physiologic functions show radiation hormesis: growth and visual acuity, learning and memory fecundity, immune competence, cancer mortality and average lifespan (luckey 1990: 1993). The effect of chronic, whole body exposure to low doses of ionizing radiation upon four physical function show radiation homesis.

CHAPTER TWO

2.1 POSSIBILITIES

In the early days of x-rays and radioactivity, it was generally believed that ionizing radiation has numerous beneficial effects. It was claimed that blindness might be cured by x-rays. Ladies corsets contained radium! Drinking mineral water containing radium was very popular. People went to spas to drink radioactive water or stayed for hours in caves to be irradiated by ionizing radiation. (For a review, see Wolff 1992).

Between 1925 and 1930, over 400,000 bottles of distilled water containing radium 226 and radium 228 were sold. It was advertised that some mixtures could treat over 150 diseases, especially lassitude and sexual impotence (Macklis 1990). It is estimated that the collective skeletal radiation dose of victims of such radioactive medicine may have exceeded 350Sv by the time the user died (Macklis 1991). Gradually people found that the improper use of ionizing radiation could lead to many complications and harmful effects. Later in 1927, Herman J. Muller a Nobel Prize winner, found that x-rays are mutagen and that there is a linear relationship between mutation rate and

dose. He proposed that mutations which are induced by radiations (or other mutagens) are mostly detrimental. When it was generally accepted that excessive radiation may be harmful, the first regulations for dose limits were introduced. Despite carcinogenicity of x-rays, was observed as early as 1902 (Kathren 1996) the first radiation protection limits suggested in 1925 and for three other decades, these limits were based on the concept of a tolerance dose (Muller 1928). Surprisingly, until the end of world war 11, ionizing radiation was considered a great scientific miracle. After the war, the development of nuclear power changed this great miracle into radiophobia. At that time, people became afraid of even very small doses of ionizing radiation. After the atomic bomb explosions in Hiroshima and Nagasaki, studies concerning life span of atomic bomb survivors showed a linear relationship between cancer mortality and high doses of radiation (Pollycove, 1998). The United Nation's Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), then proposed the linear no-threshold (LNT) theory in 1958 (UNSCEAR, 1958). According to LNT theory;

1. The effect of low doses of ionizing radiation can be estimated by linear extrapolation from effects observed by linear extrapolation from effects observed by high doses.
2. There is no safe dose because even very low doses of ionizing radiation produce some biological effect. In 1959 the international commission on radiation protection (ICRP) adopted the LNT theory. (ICRP 1959).

The results of many investigations do not support the LNT theory. Furthermore, several studies including Cohen's studies of the relationship between environmental radon concentrations and lung cancer even contradict this theory and clearly suggest a hormetic effect.

2.2 EXPERIMENTAL EVIDENCE

Cancer Prevention

Bhattacharjee in 1996 showed that when the mice preirradiated with just adapting doses of 1cGy/day for 5 days (without a challenge dose), thymic lymphoma was included in 16% of the animals (Bhattacharjee 1996). Interestingly when preirradiated mice were exposed to a 2cGy challenge dose, thymic lymphoma was included again in 16% of the animals. However, the challenge dose alone induced thymic lymphoma in 46% of the mice. From these results, it can be concluded that the low doses preirradiation possibly cancel the induction of thymic lymphoma by the 2Gy challenge doses. In 1996, Azzam and his colleagues showed that a single exposure of C3H 10T1/2 cells to doses as low as 0.1cGy reduces the risk of neoplastic transformations. They suggested that a single low dose at background or occupational exposure levels may reduce cancer risk. Recently, Redpath and his co-workers have confirmed the findings of Azzam and his co-workers (Azzam et al, 1996). To test the

generality of the observations of Azzam and his colleagues, they used the HeLa x skin fibroblast human hybrid cell. Using a similar experimental protocol, they demonstrated a significantly reduced transformation frequency for adapted to unirradiated cells (pooled data from four separate experiments). In addition, recently Mitchel and his co-workers in Canada have indicated that a low dose preirradiation (10cGy, 0.5Gy/h) modifies latency for radiation induced myeloid leukemia in CBA/H mice after exposure (Mitchel et al 1999). They showed that the latent period for development of acute myeloid leukemia (AML) was significantly increased by the prior low radiation dose. Interestingly, according to T.D Luckey, one third of all cancer deaths are preventable by low-level ionizing radiation (Luckey 1994, 1997).

Survival Rate

In 1996, Yonezawa and his colleagues indicate that when 21-ICR mice were exposed to 8GY of X-rays, about 30% of the animals survived 30 days the irradiation.

However, when mice preirradiated with 5 cGy of X-rays, the survival rate increased to about 70% (Yonezawa et al. 1996)

2.3 EPIDEMIOLOGICAL EVIDENCE

Although radiation hormesis data are still incomplete, extensive epidemiological studies have indicated that radiation hormesis really exist. A brief review on this irrefutable evidence is as follows:

Japanese studies

1-According to UNSCEAR report (1994), among A-bomb survivors from Hiroshima and Nagasaki who received doses lower than 200mSv, there was no increase in the number of total cancer death. Mortality caused by leukemia was even lower in this population at doses below 100 msv than age-matched control cohorts.

2-Mifune (1992) (Mifune et al. 1992) and his co-workers indicated that in a spa area (Misasa), with an average indoor radon level of 35 Bq/m³, the lung cancer incidence was about 50% of that in a low-level radon region. Their result also showed that in the

above mentioned high background radiation area; the mortality rate caused by all types of cancer was 37% lower.

3-According to Mine et al (1981), among A-bomb survivors from Nagasaki, in some age categories, the observed annual rate of death is less than what is statistically expected.

4-Kumatori and his colleagues (Kumatori et al. 1980) report that according to their 25 year follow up study of Japanese fishermen who were heavily contaminated by plutonium (hydrogen bomb test at Bikini), no one died from cancer.

Background Radiation Studies

1-In an Indian study, it was observed that in areas with a high-background radiation level, the incidence of cancer and also the mortality rate due to cancer was significantly lesser than similar areas with a low background radiation level (Nambi and Soman 1987).

2-In a very large scale study in U.S.A, it was found that the mortality rate due to all malignancies was lower in states with higher annual radiation dose (Frigerio 1976).

3-In a large scale Chinese study, it was showed that the mortality rate due to cancer was lower in an area with a relatively high background radiation (74,000 people), while the control group (78,000 people) who lived in an area with low background radiation had a higher rate of mortality (Wei L1990).

4-In the U.S.A., it was indicated that significantly, the total cancer mortality is inversely correlated with background radiation dose (Cohen BL 1993).

Nuclear Power Plant studies

1-In a Canadian survey the mortality caused by cancer at nuclear power plants was 58% lower than the national average (Abbat et al. 1983).

2-In U.K also it was indicated that cancer frequency among nuclear power plant workers was lower than the national average (Kendal et al. 1992).

CHAPTER THREE

CHALLENGES

During the last decade, there has been a concerted effort to determine whether the concept of hormesis is real and generalizable as well as toxicologically and biologically significant. To this end, there has been developed a rigorous a priori process to assess and quantitatively evaluate possible hormetic dose-response relationships, estimate the frequency of hormetic dose responses in the toxicological literature and estimate which toxicological model occurred more frequently in the peer reviewed literature. (Calabrese, 2002, 2003; Calabrese & Baldwin 2001a, 2003b). Our activities have shown that hormetic dose responses are more common than the traditional toxicological threshold model, can be generalized well by model, endpoint and chemical class, and display a predictable set of quantitative dose-response features in terms of magnitude and width of the stimulatory response. In short, the hormesis

model clearly outperforms either of the other two competitive models in fair head-to-head competition (Calabrese & Baldwin, 2001b, 2003a)

But despite the obvious superiority of the hormetic model over the linear model at low dose and the threshold model, toxicological thinking has so far been hesitant to accept and apply it. The reasons for this reluctance to change are complex but can be traced in large part to the fact that toxicology has been, primarily, an applied discipline with the laudable goal of protecting health. Faced with a huge number of compounds to be tested, toxicologists therefore streamlined their processes to reduce the number of animals used per dose and the number of doses per experiment. A typical toxicological examination derives study-specific LOAELs (lowest observed adverse effect levels) and NOAELs (no observed adverse effect levels) from experimental data using animal models in which only 2-4 different doses of the compound under scrutiny are used- plus control groups of course. With the goal of deriving a NOAEL with the fewest doses possible, it becomes immediately obvious that any insights into what is

happening in the domain below the NOAEL cannot be obtained by such studies. Furthermore, it takes many more doses-and, accordingly, animals and time-to get a clear picture of the domain in which hormesis takes place.

It is important to recognize that the dose-response relationship is the most important aspect in toxicology, around which all research and teaching is centred. It is therefore both troubling and of great concern that this field could have accepted a flawed toxicological dose-response model but also built an entire education and regulatory edifice on it with serious repercussions for academia, industry and the public. A detailed re-examination of this historical blind spot in toxicology reveals a complicated web of interacting factors that led to the demise of the hormesis hypothesis: first and foremost the principle concern with high-doses affects limited study designs and difficulties in assessing the typically modest hormetic responses especially within the framework of weak study designs. The field also saw bitter historical rivalries between traditional and homeopathic medicine, the latter regarding

