RADIATION HORMESIS; POSSIBILITIES AND CHALLENGES.

BY
OGBONNA CHIAGOZIE ADAOMA
2001/111312

SUBMITTED TO DEPARTMENT OF MEDICAL RADIOGRAPHY AND RADIOLOGICAL SCIENCES,FACULTY OF HEALTH SCIENCES,COLLEGE OF MEDICINE,UNIVERSITY OF NIGERIA,ENUGU CAMPUS.

IN PARTIAL FULFILLMENT OF THE COURSE
RG 592.

SUPERVISOR:MRS NWOGU .U
SEPTEMBER 2008

TITLE PAGE

RADIATION HORMESIS;
POSSIBILITIES AND CHALLENGES

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!

TABLE OF CONTENT

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. Erlish 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 closed (Macklis 1991). It is widely believed that radiation biology in the future will be focused on bimolecular 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 homeostatis"

: Selye, "The General Adaptation Syndrone"and Ardnt. 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 became 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 had exceeded 350Sv by the time the user died (M`acklis 1991). Gradually people find 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). Surprisinly, 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 liner 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

Bhattarchargee in 1996 showed that when the mice preirradiated with just adapting doses of IcGylday for 5days (without a challenge dose),thymic lymphoma was includes in 16% of the animals (Bhattarachargee 1996). Interestingly when preirradiated mice were exposed to a 2cGy challenge dose, thymic Iymphona 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 O.IcGy 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 (IOcGy, 0.5GyIh) modifies latency for radiation induced myeloid levkamia in CBA/H mice after exposure (mitehel et al 1999). They showed that the latent period for development of acute myeloid leukamia (AML) was significantly increased by the prior low radiation dose. Interestingly, according to T.D Luckey, one third of all cancer deaths are premature one 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 Nagazaki 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/m^3, 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 deat 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 plutunium (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 morality 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 mortalityis 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 a 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 predicable 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 scruity 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-does affects limited study designs and difficulties in assessing the typically modest hormetic reponses especially within the framework of weak study designs. The field also saw bitter historical rivalries between traditional and homeopathic medicine, the latter regarding

hormesis-that is, the Arndt-Schulz Law-as a central explanatory feature. This has resulted in a lack of intellectual leadership by those supporting a "hormetic perspective and a lack of governmental funding of the hormesis concept during the formative years of toxicological development from the 1930s onwards (Calabrese & Baldwin,, 2000a-e). All these factor contributed to today's situation, in which hormesis, despite growing supportive evidence mainly from biomedical research, has only a spotty and peripheral role in toxicology.

But, if accepted, the hormetic dose-response model could have a large impact on risk assessment in many significant ways. It would not even require a complete rethinking in toxicology as the hormetic response is a normal component of the traditional dose-response relationship. And because hormetic dose response are similar for carcinogenic and non-carcinogenic agents, it has the potential to harmonize risk assessment procedures for carcinogen and non-carcinogens alike, which have so far been treated differently.

But what is particularly important is the fact that the hormetic dose response occurs in the observable zone of the experimental data. This means that we would not need to extrapolate experimental data far into the realm of the uncertain as is done at present in cancer risk assessment, which relies on the animal-derived LNT prediction. Thus, we could replace this scientifically questionable practice with a verifiable procedure. In fact, as the hormesis hypothesis can actually be tested with the available data, for the first time in the modern history of cancer risk assessment, we would be able to rely on a verifiable dose-response model and not depend on unverifiable extrapolations of animals' data to estimates actual risk to humans.

The most fundamental change in the disk assessment process would be the adoption of the hormetic model as the default risk assessment tool replace the outdated LNT model for carcinogens and the threshold model for non-carcinogens. Because the number of dosages used in most bioassays, especially those used by government agencies such as the US National Toxicology program, is modest (3-4 dosages), there

is little like hood that the respective models sufficiently differ from each other in their predictive power. Thus, regardless of which dose-response model is selected as the default, it will be used in most cases. Typically, the selection of a default model has been driven by concern of the regulatory agencies to err on the side of safety, given all the uncertainties associated with extrapolating over many magnitudes.In addition to being guided by a protectionist public health philosophy, the selection of a default model also assumes objective superiority over its competitors both theoretically and based on experimental or empirical data. Substantial evidence now exists to support the scientific advantage of the hormetic model over its competitors. Given the situation, it would seem that the time has come to re-examine which model should be selected as the default in environmental risk assessment.

Perhaps the most exciting aspect of adopting the hormetic hypothesis in environmental risk assessment is that it would allow the field to move forward scientifically. It would replace the present status of compelling society by acting on

the basis of assumptions that cannot be adequately tested by a new risk assessment procedure that can be realistically evaluated with its results displayed visibly in the observable zone. This would be a major first step in placing "modern" environmental risk assessment on similar level with other type of "health insurance", where risk estimates are based on data that do not require extraordinary extrapolations and where the findings create a heightened sense of confidence.

CHAPTER FOUR

CONCLUSION

Finally, radiation hormesis is in a special class of hormetics. The very concept of hormesis has important implications for the field of clinical medicine. The dose-response relationships for medical agents commonly display the same hormetic dose-response relationships as their toxic counterparts. Many agents such as antibacterial, antifungals, antivirals and tumour. Fighting drugs display hormetic dose responses. The clinical significance of this has only recently begun to dawn on the medical community although it was recognized as early as the mid 40's for antibiotics such as streptomycin The consequences for human health are quite serious. An excess is harmful. Small amounts are needed for essential physiologic functions. Supplementation is usual for populations living in a partial deficiency. Irradiation supplementation promises increased quality of life and a new plane of health for

people in the 21st century. A broader recognition of the hormetic dose response in the wider biomedical domain has the potential to usher in a vast array of new opportunities for understanding basic biological processes and to exploit such knowledge in the development of new product and the improved treatment of patients.

REFERENCES

Abbatt, J.D. Hamilton, T,R. and Weeks, J.L. (1983) Epidemiological studies in three corporations covering the nuclear fuel cycle.

Biological Effects of low-level Radiation, Proc. IAEA-STI/Pub/646, International Atomic Energy Agency, Vienna, 351-361.

Bogoljubov, W.M. (19788) Clinical aspects of radon therapy in the U.S.S.R.Z. Phys. Med. Balneol. Med. Klimatol. 17, 59-61.

Cohen, B, L. (1993) Test of the linear-no threshold theory of tradition carcinogenesis, ICSE Conference, Paris.

Darby, S.C. Kendall, G.M, Fell, T.P. et al. 1989) A summary of mortality and incidence of cancer in men from the United Kingdom who Participated in the United Kingdom atmospheric weapons tests and experimental programs, Br. Med. J. 296,332-240.

Gilbert, E,S, fry, S.A., Wiggs, L.D. et al. 1989) Analysis of combined mortality data on workers at the Hamfort site, Oak Ridge National Laboratory, and Rocky Flats Nuclear weapons Plant, Radiat. Res. 120, 19.

Gribbin, M.A. Weeks, J.L. and Howe, G.R.(1993) Cancer mortality (1956-1985) among male employees of Atomic Energy Limited with respect to occupational exposure to low-linear-energy-transfert ionizing radiation, Radiat Res 3, 375.

Haynes, R.M. (1988) The distribution of domestic radon concentrations and lung cancer mortality in England and Wales, Rad. Prof. Dosim. 93-4.

Kendla. G.M., Muirhead, C.R. Mac Gibbon, B.H. et al. (1992) Mortality and occupation exposure to radiation; first analysis of the National Rigistry for Radiation Workers, Brit Med J, 304,220.

Luckey, T.D (1959) Antibioties in Nutrition, in H,S,Doldberg (ed), Anitbiotics, their chemistry and Non-Medical Uses, D,Van Nostrand Publisher, Princeton, pp 174-321.
Luckey T.D.(1990) Hormesis with Ionizing Radiation, CRC Press, Boca Raton Publisher, in Japanese Soft Science Inc., Tokyo.

Luckey, T.D. (1993) Raiation Hormesis. CRC Press, Boca Rayton Publisher, 1991. in Japanese, Soft Science Inc., Tokyo.

Luckey, T.d., Gordon, H.A., Wagner, M and Reyniers, J.A. (1956) Growth of germfree birds fed antibiotics, Anitibiots Chemother, 6,36-40.

Matanoski, G.M. (1985) Health Effects of Low Level Radiation in Shipyard workers, DOE Final Report. E.I. 99 DOE/EV/10095-T 1 and 2. DOE, Washington.

Moore, P,R, Evension, A. Luckey, T.D. McCOY, E., EXlvehjem C.A. and Hart, E.B.(1946) The use of sulfasuxadine, streptothrytcin and streptomycin in nutritional studies with the chick, J. Biol. Chem. 165,437-441.

Nageli, U. (1893) Uebor oligodynamische Erscheinugen in Lebenden Zellen Gesellsch. f.b. Naturwissenschaft 33,1-4.

Richet, C. (1906) De I'action de doses minuscules de substance sur la Ferentation Lactique-troisieme memoire-perioed d'acceleration et de ralentissement, Arch. Intern. Physiologies 4, 18-50.

Southam, C.M. and Ehrlich, J. (1943) Effects of extract of western red-ceder heater wood on certain wood decaying fungi in culture, phytopathol. 35, 517-524