An Introduction to Radiation Hormesis

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Paracelsus (more than 400 years ago):

All substances are poisons, there is none which is not a poison. The right dose differentiates a poison from a remedy.

Abstract

All living organisms evolved and exist in a sea of ionizing radiation, much of which is internal. It is a general belief that low doses of ionizing radiation produce detrimental effects proportional to the effects produced by high-level radiation. In recent decades, however, some pioneer scientists have shown that low-dose ionizing radiation is not only a harmless agent but often has a beneficial or hormetic effect. That is, low-level ionizing radiation may be an essential trace energy for life, analogous to essential trace elements. It has been suggested that about one third of all cancer deaths are preventable by increasing our low dose radiation. New theories concerning radiation hormesis and possible mechanisms are discussed.

Introduction

The expression "beneficial effects of radiation"may be very surprisingnot only for common people but also for many highly educated people. Wehave heard many things about the biological hazards of ionizing radiationbut never hear anything concerning possible beneficial effects of low levelsof ionizing radiation. Indeed we have learnt that when considering ionizingradiation, unalterable scientific facts show that it is a completely harmfulagent.

If you conduct a simple opinion poll, it will be disclosed that many peopleconsider ionizing radiation as one of the most important life threateningfactors [Click here to see the results of our poll]. However, according to published risk estimates, the risk of malignanciesfrom low doses of ionizing radiation (e.g. doses in diagnostic radiology)is negligible in comparison with many other common health risks such asoverweight or alcohol consumption. Nowadays in many developed countriesindividuals are very reluctant to get X-rays even when they are told bytheir physician that this type of radiography is necessary for their health.Usually no one explain that the effective dose from common diagnostic X-rayprocedures are typically very low. For example the effective dose froma chest X-ray is about 1 mSv and it would take just 10 days to accumulatethe same effective dose from background radiation. So despite the safetyof diagnostic X-rays , there is a kind of illogical "Radiophobia" in theminds of many highly educated people. This phobia originated from manyfactors but the most important of those factors are as follows:

1-Lack of basic radiation knowledge among general public and even highly educated people[Click here to see the evidence].
2-Mysterious nature of X-rays and generally ionizing radiation and also psychologicalproblems caused by atomic bomb explosions in Japan.
3-Consideration of linear no-threshold model as a law and not as a theoriticalmodel.
4-Vast literature indicating the biological hazards of high levels of ionizingradiation.
5-Exaggeration of radiation risks by press reports caused by increased useof nuclear technology.

On the other hand during the last few decades some pioneer scientists havestudied numerous beneficial effects of low doses of ionizing radiation.It has been indicated by many studies that any reduction in the naturalradiation causes deficiency symptoms in protozoa and bacteria [Ref. 1]. Furthermore recentlymany epidemiological studies have indicated that low dose irradiation maylead to beneficial effects such as increase in growth and development rates,increase in mean life span, stimulation of immune reactions and even decreasein cancer mortality [Ref. 1].

Literature Review

The word "hormesis" is derived from the Greek word "hormaein" which means"to excite". It has long been known that many popular substances such asalcohol and caffeine have mild stimulating effects in low doses but aredetrimental or even lethal in high doses. In the early 1940s C. Southamand his coworker J. Erlish first found that despite the fact that highconcentrations of Oak bark extract inhibited fungi growth, low doses ofthis agent stimulated fungi growth. They modified starling's word "hormone to "hormesis"to describe stimulation induced by low doses of agents whichare harmful or even lethal at high doses. They published their findingsregarding the new term "hormesis"in 1943 [Ref. 5]. Generally, hormesis is anystimulatory or beneficial effect, induced by low doses of an agent, thatcan not be predicted by the extrapolation of detrimental or lethal effectsinduced by high doses of the same agent.

During the 1950`s Luckey, a pioneer researcher in radiation hormesis, indicatedthat low dose dietary antibiotics caused a growth surge in livestock. Laterhe found that hormesis could be induced effectively by low doses of ionizingradiation. In 1980 the first complete report on radiation hormesis waspublished [Ref. 6]. In this report he reviewed numerous articles regarding radiationhormesis. Since the first reports, over 1000 reports have been publishedconcerning radiation hormesis. The concept of radiation hormesis is usually applied to physiological benefits from low LET radiation in the range of 1-50 cGy total absorbed dose [Ref. 30].Undoubtedly radiobiology of the next decade,as some scientists mentioned, will be focused on biomolecular and geneticimplications, problems of damage and repair and connected problems suchas radiation hormesis and radioadaptive response.

Hormesisand LNT Model

In the early days of X-rays and radioactivity it was generally believedthat ionizing radiation has numerous beneficial effects. It was claimedthat blindness might be cured by X-rays. Ladies corsets contained radium!Drinking mineral water containing radium was very popular. People wentto spas to drink radioactive water or stayed for hours in caves to be irradiatedby ionizing radiation. Between 1925 and 1930 over 400,000 bottles of distilled water containing radium 226 and radium 228 were sold. It was advertised that this mixture can treat over 150 disease, especially lassitude and sexually impotence [Ref. 33]. It is stimated that the collective skeletal radiation dose of victims of such radioactive medicine may have exceeded 350 Sv by the time the user died [Ref. 34]. Gradually people found that the improper use ofionizing 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 there is a linear relationship between mutation rate and dose. He proposed that mutations which areinduced by radiation (or other mutagens) are mostly detrimental. When itwas generally accepted that excessive radiation may be harmful, the first regulations fordose limits were introduced. . Despite carcinogenicity of X-rays was observed as early as 1902 [Ref. 31], the first radiation protection limits suggested in 1925 and for three decades these limits were based on the concept of a tolerance dose [Ref. 32]. Surprisingly, until the end of World War II, ionizing radiation was considered agreat scientific miracle. After the war the development of nuclear weaponsand later increased use of nuclear power changed this great miracle intoradiophobia. At that time people became afraid of even very small dosesof ionizing radiation.

After the atomic bomb explosions in Hiroshimaand Nagasaki, studies concerning life span of atomic bomb survivors showeda linear relationship between cancer mortality and high doses of radiation [Ref. 7].The United Nations Scientific Committee on the Effects of Atomic Radiation(UNSCEAR), then proposed the linear no-threshold (LNT) theory in 1958 [Ref. 8].According to LNT theory:

1-The effects of low doses of ionizing radiation can be estimated by linearextrapolation from effects observed by linear extrapolation from effectsobserved by high doses.
2-There is not any safe dose because even very low doses of ionizing radiationproduce some biological effect.
In1959 the international commission on radiation protection (ICRP)adopted the LNT theory [Ref. 9].
The results of many investigations do not support the LNT theory [Ref. 10,11,12,13,14,15]. 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. This contradictory evidenceis discussed in the following section.

ExtensiveEvidence Suggesting Hormesis

1. Experimental Evidence

1.1. Cancer Prevention

Bhattarcharjee in 1996 showed that when the mice preirradiated with just adapting doses of 1 cGy/day for 5 days(without a challenge dose), thymic lymphoma was induced in 16% of the animals [Ref. 35]. Interstingly, when preirradiated mice were exposed to a 2 Gy challenge dose, thymic lymphoma was induced 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 dose preirradiation possibly cancel the induction of thymic lymphoma by the 2 Gy challenge dose. In 1996, Azzam and his colleagues showed that a single exposure of C3H 10T1/2 cells to doses as low as 0.1 cGy reduces the risk of neoplastic transformations.They suggested that a single low-dose at background or occupational exposurelevels, may reduce cancer risk [Ref. 2]. Recently, Redpath and his co-workers haveconfirmed the findings of Azzam [Ref. 36]. 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 (10 cGy, 0.5 Gy/h) modifies latency for radiation induced myeloid leukemia in CBA/H mice after exposure to a 1 Gy chronic radiation exposure [Ref. 37]. 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 premature and preventable by low-level ionizing radiation [Ref. 3,4]

1.2. Survival Rate

In 1996, Yonezawa and his colleagues indicated that when 21-ICR mice were exposed to a 8 Gy of X-rays, about 30% of the animals survived 30 days after the irradiation. However, when mice preirradiated with 5 cGy of X-rays, the survival rate increased to about 70% [Ref. 38].

2. Epidemiological Evidence

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

2.1. Japanese studies

1-According to UNSCEAR report (1994)[Ref. 1], among A-bomb survivors from Hiroshimaand Nagazaki who received doses lower than 200 mSv, there was no increasein the number of total cancer death. Mortality caused by leukemia was evenlower in this population at doses below 100 mSv than age-matched controlcohorts.
2-Mifune (1992) [Ref. 16] and his co-workers indicated that in a spa area (Misasa),with an average indoor radon level of 35 Bq/m3, the lung cancer incidencewas about 50% of that in a low-level radon region. Their results also showedthat in the above mentioned high background radiation area, the mortalityrate caused by all types of cancer was 37% lower.
3-According to Mine et al (1981) [Ref. 17], among A-bomb survivors from Nagasaki,in some age categories, the observed annual rate of death is less thanwhat is statistically expected.
4-Kumatori and his colleagues (1980) [Ref. 18] reported that according to their 25year follow up study of Japanese fisherman who were heavily contaminatedby plutunium (hydrogen bomb test at Bikini), no one died from cancer.

2.2. 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 dueto cancer was significantly lesser than similar areas with a low backgroundradiation level [Ref. 19]. KERALA, INDIA
2-In a very large scale study in U.S.A, it was found that the mortality ratedue to all malignancies was lower in states with higher annual radiationdose [Ref. 20].
3- In a large scale Chinese study, it was showed that the mortality rate dueto 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 anarea with low background radiation had a higher rate of mortality [Ref. 21].
4-In the U.S.A., it was indicated that significantly, the total cancer mortalityis inversely correlated with background radiation dose [Ref. 22].

2.3. Nuclear Power Plant studies

1-In a Canadian survey the mortality caused by cancer at nuclear power plantswas 58% lower than the national average [Ref. 23].

2-In U.K also it was indicated that cancer frequency among nuclear powerplant workers was lower than the national average [Ref. 24].

TheMechanism of Hormetic Processes

Although still we do not now the entire mechanisms of radiation hormesis, the following theories may explain this process:

1-DNA repair (Mollecular level)
According to this theory, low doses of ionizing radiation induce the production ofspecial proteins, that are involved in DNA repair processes [Ref. 25].Studies using two dimensional gel electrophoresis indicated new proteins in cells irradiated with low doses of radiation.Also, it was further shown that cycloheximide, a protein synthesis inhibitor blocks this hormetic effect.The function and importance of these radiation induced proteins is still unknown. Also it was foud that inhibitors of poly ADP-ribose polymerase, an enzyme implicated in DNA strand break rejoining could prevent th

2-Free radical detoxification (Molecular level)
In 1987 Feinendengen [Ref. 26] and his co-workers indicated that low doses of ionizingradiation cause a temporary inhibition in DNA synthesis (the maximum inhibitionat 5 hours after irradiation). This temporary inhibition of DNA synthesiswould provide a longer time for irradiated cells to recover. This inhibitionalso may induce the production of free radical scavengers, so irradiatedcells would be more resistant to any further exposures.

3-Stimulation of immune system (Cellular level)
Manystudies have indicated that in contrast with high doses of ionizing radiation,low doses cause stimulation of immune system.In 1909 Russ first showed that mice treated with low-level radiation were more resistant against bacterial disease [Ref. 27].Later in 1982 Luckey published a large collection of references supporting immunostimulatory effects of low doses of ionizing radiation [Ref. 28].

Conclusion

Our radiation protection policy is based on linear extrapolation from the dose-response data of high doses of ionizing radiation. According to the results of many worldwide studies, this assumption is not compatible with observed health effects of low levels of radiation. Obviously LNT and current radiation protection regulations exaggerate the risk of low level ionizing radiation (in the range of 1-50 cGy) and cause radiophobia [Ref. 29]. It is concluded that according to new findings, the existence of radiationhormesis and adaptive response are not deniable and abandoning the LNT theory in low dose risk estimations possibly would be a realnessecity in a near future.

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