REVIEW ARTICLE

Linear, no threshold response at low doses of ionizing radiation: ideology, prejudice and science*

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The linear, no threshold (LNT) response model assumes that there is no threshold dose for the radiation-induced genetic effects (heritable mutations and cancer), and it forms the current basis for radiation protection standards for radiation workers and the general public. The LNT model is, however, based more on ideology than valid radiobiological data. Further, phenomena such as 'radiation hormesis', 'radioadaptive response', 'bystander effects' and 'genomic instability' are now demonstrated to be radioprotective and beneficial. More importantly, the 'differential gene expression' reveals that qualitatively different proteins are induced by low and high doses. This finding negates the LNT model which assumes that qualitatively similar proteins are formed at all doses. Thus, all available scientific data challenge the LNT hypothesis.

Keywords: Genomic instability, hormesis, LNT hypothesis, radioadaptive response, stochastic effects.

THE linear, no threshold (LNT) hypothesis which states that the genetic effects observed following exposure of cells and organisms to moderate and high doses of ionizing radiation could be extrapolated backwards from the high dose to low dose region, provides a convenient pragmatic basis for the purposes of regulation in radiation protection. However, for a radiation geneticist to elucidate the biological defence mechanisms against 'oxidative stress', caused not only by ionizing radiation but also by several metabolic processes, there is need to know whether ionizing radiation really induces genetic damage even at very low doses of low LET external radiation. From an evolutionary perspective, living organisms evolved under conditions of even more intense radiation. Then with origin and evolution of unicellular photosynthetic organisms, the concentration of oxygen in the atmosphere became significant enough to cause oxidative stress to the anaerobic organisms which predominated the planet. Reactive oxygen species (ROS) such as hydroxyl radicals, superoxide anion ($O_2^{\bullet -}$), hydroperoxide ($^{\bullet}HO_2$), hydrogen peroxide (H_2O_2) and several organic peroxides were mainly responsible for causing oxidative stress. However, the tenacity of life is such that the successful aerobic organisms (i.e. those which managed to survive the oxidative stress) developed defence mechanisms against ROS. Ionizing radiation is an oxidizing agent by inducing free radicals in the cells which react with oxygen to form ROS. The defence mechanism in the cells and organisms normally copes with the damaging ROS up to a certain level of concentration. Beyond a threshold level, the defence mechanisms collapse and hence the cells and organisms suffer from deleterious effects. This is why Paracelsus (1493–1541), a Renaissance physician, naturalist, and father of modern toxicology posed a question, 'What is not a poison? All things are poison and none without poison. Only the dose determines that thing is not poison'.

Oxygen is a necessary evil in the sense that it is required for the very survival of all aerobic organisms, including humans, but these aerobic organisms also pay a price by developing with advancing age several degenerating diseases (cardiovascular, cancer, rheumatoid arthritis, senescence, etc.). And so far as radiation is concerned, varying levels of it are part of the human environment. There are millions of people living in high-level natural background radiation (HLNBR) areas in Kerala, parts of Tamil Nadu, Iran, China, Brazil and a few other places. India and China have carried out studies on biological and health effects in the HLNBR areas. The results of studies on these populations do not show increased morbidity and mortality.

The purpose of this review article is mainly to unravel the genesis of the LNT model, and its tenability in view of the tremendous knowledge explosion in radiobiology.

X-ray-induced sex-linked recessive lethal mutations in *Drosophila melanogaster*

A turning point in our understanding of radiation action on living cells occurred in 1927, when Hermann J. Muller at the University of Texas, Austin published an epoch-making paper, 'Artificial transmutation of the gene'[1]. In

*I dedicate this paper to Prof. M. S. Swaminathan, whose inspiring lectures and research guidance in radiation genetics at the postgraduate school, IARI, New Delhi five decades ago motivated me towards a research career in radiobiology.

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that paper he wrote, 'when the heaviest treatment was given to the sperm, about a seventh of the offspring that hatched from them and bred contained individually detectable mutations in their treated X-chromosome'. And he goes on, 'Comparison of the mutation rates under two sets of conditions showed that the heavy treatment had caused a rise of about fifteen thousand percent in the mutation rate over that in the untreated germ cells'. Muller[1] was studying X-ray-induced lethal mutation on the only one X-chromosome of the males. The doses employed were very high with over 90% of the treated flies dying without even emerging from pupae. This could have been due to induction of dominant lethal mutations. Secondly, another statement in the paper, 'In the experiments herein reported, several different dosages were made use of, and while the figures are not yet quite conclusive they make it probable that, within the limits used, number of recessive lethal does not vary directly with the X-ray absorbed, but more nearly directly with the square root of the latter.' With a better understanding today of radiation-induced double-strand breaks (dsbs) and more exactly that these often lead to the deletion of segments in the chromosomes, the sex-linked recessive lethals are mostly the 'deletions' and not 'point mutations' (base pair changes). Muller's studies involved almost lethal doses of X-rays and used recessive lethal and not visible mutations as the end-point.

At this juncture, it is clarified that radiation protection standards pre-existed Muller's discovery. The initial safety standards were prompted soon after the report of a skin cancer in 1902 and the first case of leukaemia in 1911. These observations led to the creation of the American X-ray and Radiation Protection Committee in 1928, to fix the safe dose limit for radiation workers. Two decades later, following World War II, the American X-ray and Radiation Protection Committee became the National Committee for Radiation Protection and Measurement (NCRPM). The first report of this Committee was published in 1931, and it did not contain exposure standard such as Roentgen unit, but rather standards in terms of lead-equivalent insulation. However, within the context of the radium evaluation, the Committee determined that the best indicators of high radiation exposures were skin changes within the tips of the fingers, with a reddening and shiny appearance of the skin around the finger nails. This is the 'erythema' found to be induced following an exposure in excess of 600 r (6 Gy). The dose 600 r was derived from a poll of radiotherapists who suggested 550 r, which was rounded up to 600 r to account for background scatter radiation. Further, a safety factor was introduced using 1/100 of the erythema dose (i.e. 600 r) spread over 30 days (one month). This amounts to 6 r spread over 30 days, or 0.2 r/day (in the present SI system, it is about 1.86 mGy/day or 680 mGy/year). In a nutshell, it denoted a safe whole-body exposure of 0.1 r/day for hard X-rays, and it was also used to guide radium protection standards. It should be noted that 0.1 r/day is suggestive of a 'threshold dose', thereby implying that daily exposures only in excess of 0.1 r for 30 days could cause damage to cells and organs. The tissue tolerance dose was later replaced with 'maximum permissible dose', since it was considered that genetic damage could occur at doses below the tissue tolerance dose. What this also implied was that a dose that could be 'permitted' could still injure, but to an 'acceptable' degree.

The mutagenic effects of ionizing radiation discovered in 1927 did not lead to the linearity concept until late 1946. The turning point for this was the detonation of atomic bombs (A-bombs) over Hiroshima and Nagasaki in August 1945. It triggered genetic concerns over the A-bomb survivors and their descendants. It was also atleast partly responsible for the award of the Nobel Prize in 1946 for the discovery Muller made in 1927. NCRPM, which had not placed a high priority on addressing concerns with genetic effects before August 1945, did so in 1947. In fact, the US Atomic Energy Commission (AEC) requested NCRPM to include the recent Nobel Prize winner, Hermann J. Muller in the committee. Just a few months earlier, Muller in his Nobel Prize lecture on 12 December 1946, had declared that the dose-dependence for radiation-induced germ cell mutations was linear and that there was 'no escape from the conclusion that there is no threshold'[2]. He also stated that the principle of simple and direct proportionality between dose and mutation frequency has been extended to total doses as low as 400 r and at rates as low as 0.01 r/min of gamma rays. But 400 r is not a low dose. In his two recent papers, Calabrese[3,4] concludes that Muller ignored the scientific papers which had indeed revealed a 'threshold' dose for the genetic effects and chose only those which supported his ideology. He points out that the correspondence between Muller and Curt Stern (an outstanding *Drosophila* geneticist of that time) one month prior to Muller's Nobel Prize lecture, reveals that Muller knew the results and implications of the studies by Ernst Caspari and Stern, since Stern had sent the manuscript to Muller in early November 1946 – about five weeks prior to the Nobel Prize lecture. Their results showed a 'threshold' for the radiation-induced sex-linked recessive lethal mutations in *Drosophila*. Muller's reply to Stern was that he had no comments to make on the results; yet he asked the authors to replicate the studies. Hence, it delayed the publication of the paper, which was subsequently published in 1948 (ref. 5). The findings were that the mutation rate in *Drosophila melanogaster* irradiated at low dose-rates and dosages revealed a 'threshold' dose. However, in the same year, a paper by Spencer and Stern[6] supported a linear dose–response within the context of an acute exposure to X-rays. The seemingly bizarre results were then explicable in terms of several major differences in the experimental designs (e.g. X-rays versus gamma rays with much lower Linear Energy Transfer (LET), exposure

duration 2 h versus 21 days, dose rate differences by 15,000-fold, etc.). More than half a century later, radiobiologists are now aware of how the low doses and low dose rates of external low LET ionizing radiations enable the cells and organisms to repair the damaged DNA or else induce either differentiation or death of the damaged cells (i.e. protection from genetic damage).

A criticism of Muller is that he made selective citations in his Nobel Prize lecture to buttress the LNT model. Just to provide an example, Muller had cited Oliver[7]; Hanson and Heys[8] and Timofeeff-Ressovsky *et al.*[9], who all had used high doses and dose rates and found linearity. He did not cite the papers of Hanson and Heys[10]; Weinstein[11]; Stadler[12] and Serebrowsky and Dubinin[13], which did not support linearity at low doses, and low dose rates. Had Muller cited both the supporting and opposing sets of papers, he could not have declared, 'no escape from the conclusion that there is no threshold'.

As against the ideology-based LNT hypothesis, the recent low dose radiation genetic studies by Koana *et al.*[14] involving the same organism (*D. melanogaster*) and same end-point (sex-linked recessive lethal on the male X-chromosome), have shown a reduction of background (spontaneous) mutation rates by low dose (0.2 Gy) X-rays. Their findings of mutation frequencies (%) are given in Table 1.

While the abovesaid paper deals with sex-linked recessive lethal mutations, Koana *et al.*[15] had earlier observed a threshold at 1.0 Gy (100 rads) for the somatic mutation rates in the same organism.

A point for consideration at this juncture is whether the 'deletions' on X-chromosome manifested as recessive lethal mutations are relevant for radiation protection standards. The lethal mutations which are induced at high doses result in the death of the organisms. Hence, they become inconsequential for both somatic (i.e. cancer) and germ cell (i.e. heritable) mutations. The doses far below those which do not adversely affect the viability and fecundity of the exposed organisms and which induce viable mutations, including morbidity are more important from the point of radiation protection.

Since mutations result from alterations in the DNA at the molecular level, it would be ideal to design experiments to detect DNA damage in organisms exposed to low doses delivered at very low dose rates. Olipitz *et al.*[16] have reported that integrated molecular analyses indicate undetectable change in DNA damage in mice after continuous irradiation at about 400-fold natural background radiation. The animals were exposed to 0.0002 cGy/min (i.e. about 400-fold natural background radiation) continuously for 5 weeks, with a total dose of 10.5 cGy. This challenges the existing paradigm in radiation genetics that dose of exposure is cumulative.

Table 1. X-ray induced mutations in *Drosophila melanogaster*

Dose	Mutation rate (%)
Unirradiated	0.33
0.2 Gy	0.07
10.0 Gy	0.79

Source: Koana *et al.*[14].

Low dose radiation effects at cellular and organismal level

There is no doubt that whatever happens at the DNA (genetic) level should ultimately reflect at the physiological (e.g. cell division, growth, lifespan) level. Hence, Jayashree *et al.*[17] have reviewed some of these. These authors have cited the book *Radiation Hormesis*[18], which has catalogued a large number of published reports on radiation hormesis. Radiation hormesis is the induction of stimulation of cell division and growth by low doses and inhibition of these by high doses. Lorenz *et al.*[19] were among the first to demonstrate a significant increase in the lifespan of the mice by daily whole-body irradiation at 0.11 rad/day. The lifespan of the males increased by about 100 days from 684 ± 14 (unirradiated) to 783 ± 14 (irradiated) days. The lifespan increase for females was not significant. With the increase in lifespan, there was also significant increase in the incidence of cancer. Later, Caratero *et al.*[20] demonstrated that the female C57Bl/6 mouse continuously irradiated for its whole life with dose rates as low as 7 or 14 cGy/year gamma rays, had significantly higher lifespan compared with controls living in the same room (549 ± 9 days for the control and 673 ± 13 days for the irradiated groups). In a subsequent paper, Courtade *et al.*[21] focused on cancer incidence in these two groups. At autopsy, cancer was found in 40.9% of control and 37.9% of irradiated mice. It was mainly represented by lymphomas (23.7% and 21.9%) and histiocytic sarcomas (12.6% and 8.7%) respectively, for controls and irradiated mice. They concluded that continuous 10 cGy/year of gamma irradiation had no adverse effect on malignant and non-malignant diseases. Lacoste-Collin *et al.*[22] have shown that continuous irradiation with low-dose gamma rays enhances the lifespan and stimulates the immune system in SJL mice prone to B-cell lymphoma. Zhang *et al.*[23] have shown that bone marrow cells exposed to low doses (6 and 8 cGy) and infused into heavily irradiated (7.5 Gy) mice, greatly facilitate haemopoietic reconstitution of the heavily irradiated recipient mice.

There are also several reports in plant and animals cells that sub-ambient levels of ionizing radiation reduce their proliferation rates. Planel *et al.*[24] first demonstrated this in protozoan *Paramecium tetraurelia.* Kawanishi *et al.*[25] repeated the studies and found that both the single-cell *Paramecia* and the mouse cells *in vitro* suffer from growth retardation when they are shielded from normal level of background radiation. So, some level of radiation is essential for normal growth of both unicellular and multicellular organisms.

Another phenomenon which negates the paradigm that radiation doses are cumulative is radioadaptive response. In this case, a small (i.e. priming) dose confers protection to cells subsequently exposed to much higher (i.e. challenging) doses of ionizing radiation, as described and discussed by Wolff[26] and Bonner[27]. Farooqui and Kesavan[28] were the first to demonstrate this phenomenon *in vivo* in whole-body irradiated mice. Rigaud and Moustacchi[29] showed radio-adaptation at gene mutation level in mammalian cells.

Radioadaptive response in terms of chromosomal aberrations and micronuclei formation has been demonstrated by Thierens *et al.*[30] in the lymphocytes of radiation workers after a short-term (about one month) occupational exposure. The authors suggest that short-term occupational exposure may act as an *in vivo* adaptive response and stimulate DNA repair in G_0-phase lymphocytes. Schollnberger *et al.*[31] showed that mammalian cells exposed to low dose (110,100 mGy) of gamma rays had a three-to-four fold reduction of the transformation frequency per surviving cell (TF/SC). They also observed that linear extrapolation from moderate (or high) to low doses may not be justified.

From the point of radiation carcinogenesis, Portess *et al.*[32] found that low-dose irradiation on non-transformed cells stimulates the selective removal of precancerous cells via intercellular induction of apoptosis.

Two other phenomena, viz. 'bystander effects' and 'genomic instability' also challenge the LNT hypothesis. The bystander effect is the unexpected biological response in cells that are not themselves traversed by ionizing radiation but are located in the neighbourhood of irradiated cells. That is, unirradiated cells behave as if they have been irradiated. During the last two decades, evidence has accumulated to indicate that genetic changes such as increased levels of sister-chromatid exchanges[33], micronuclei[34], DNA-damage inducible proteins[35] and mutations[36] occur in greater than expected number of cells in culture exposed to very low fluencies in which only a fraction of the cells are actually traversed by an α-particle track, and thus directly exposed to radiation. There is direct evidence for the involvement of protein, connexin-43 in mediating intercellular communication, in the transmission of damage signals to non-irradiated cells[37].

The bystander effect is related to another phenomenon called 'genomic instability' in which the descendants (unirradiated) of the irradiated cells and experimental animals display an abnormally high frequency of genome modifications, sometimes persisting for several generations of cells *in vitro*[38]. Current studies highlight similarities between the adaptive response, the bystander effect and genetic instability[27,39]. Yang *et al.*[40] suggest that in most cases the genetic instability appears to be the prelude to cell death, and certain proteins such as clusterin are known to induce the death of such genetically unstable cells.

What is now evident is that bystander effect, genomic instability and radio-adaptive responses are all phenomena to protect the system by eliminating cells with potential genetic damage[41–46]. These are not the deleterious effects.

Differential gene expression induced by low and high doses

Jayashree *et al.*[17] have discussed the 'differential gene expression' (table 1 of their review paper) at low and high doses. They also brought out how it negates the LNT hypothesis. Since then, there has been an impressive increase in the number of publications on differential gene expression at low, moderate and high doses. Tubiana *et al.*[47] have provided references to some of the significant papers on differential gene expression and these are not repeated here. However, it is important to cite in this review two noteworthy papers, one by Yin *et al.*[48] and another by Mezentsev and Amundson[49]. Yin *et al.*[48] have characterized the cellular functions associated with the altered transcript profiles of mouse brain exposed to low (0.1 Gy) and high (2 Gy) dose *in vivo* gamma irradiation. Brain irradiation modulated the expression patterns of 1574 genes, of which 855 showed more than 1.5-fold variation. About 30% of genes showed dose-dependent variations, including genes exclusively affected by 0.1 Gy. About 60% of the genes showed time-dependent variation, with more genes affected at 30 min than at 4 h. Early changes involved signal transduction, ion regulation and synaptic signalling. Low-dose irradiation also modulated the expression of genes involved in stress response, cell-cycle control and DNA synthesis/repair. The conclusion drawn by Yin *et al.*[48], which challenges the LNT model, is that the doses of 0.1-Gy-induced changes in gene expression are qualitatively different from those at 2 Gy. The low dose irradiation of the brain induces expression of the genes involved in protection and reparative functions, while down-regulating the genes involved in neural signalling activity. The paper by Mezentsev and Amundson[49] is epoch-making. In order to gain insight into low doses in tissues, the authors have profiled global gene expression in a three-dimensional tissue model that imitates the structure and function of human epidermis at 4, 16 and 24 h after exposure to high (2.5 Gy) and low (0.1 Gy) doses of low LET radiation. The most significant gene ontology groups among genes altered in expression were consistent with effects observed at the tissue level, where low dose was associated with recovery and tissue repair, while the high dose resulted in loss of structural integrity and terminal differentiation. The literature in this field is rapidly growing and it is now necessary to acknowledge that cellular responses induced by low and high doses of radiation are qualitatively different. The LNT hypothesis rests on the assumption that the cellular

response at low and high doses is qualitatively the same and varies only quantitatively. The UNSCEAR 2012 report[50] (para 52) has cited this paper among others and concludes: 'Despite these caveats, there are reasonably sound indications that gene expression changes are radiation dose and dose-rate dependent. Most changes observed cannot be specifically linked to disease and are generally measured very soon after irradiation'. This statement is untenable for the following two reasons:

(i) There is no disease known that is specifically ascribable to exposure to ionizing radiation. Ionizing radiation induces 'oxidative stress' like most other dietary and environmental genotoxins. And oxidative stress in turn, contributes to an increase in the frequency of spontaneous occurrence of cancer, cataract, cardiovascular diseases, arthritis, etc. Therefore, it is not scientifically appropriate to expect that changes induced in gene expression should be specifically linked to a disease.

(ii) The fact that 'most changes are generally measured very soon after irradiation' is not something that would disqualify the differential gene expression at low and high doses. It is well-established that physical stage (i.e. absorption of radiant energy) with the formation of free radicals occurs in a time-span of nano- to microseconds and then the formation of ROS, alterations in molecular signalling, gene expression, DNA repair or apoptosis, etc. may take minutes to hours or even days depending upon the nature of the organisms (unicellular or multicellular, etc.) and their innate capacity for radiation tolerance. The point is that the radiation-induced cellular events proceed sequentially in time-span of nanoseconds to minutes, hours, days and even generations.

The UNSCEAR statement gives an erroneous impression that it is not yet the right time to accept the differential gene expression as a challenge to LNT hypothesis.

Tubiana *et al.*[47] refer to several of the above-said papers on differential gene expression and conclude that (a) the sets of genes that are activated or repressed are not the same after low or high dose, dose rate and (b) temporal gene expressions are also not the same after high doses (3 h after a 2 Gy dose) and low doses (only after 48 h for a mGy dose).

More specifically, the studies of Ding *et al.*[51] suggest that at high doses the responding genes tend to be involved in cell proliferation and mitotic death, etc. while low dose exposures tend to affect genes involved in signal transduction, intercellular signalling and development of response to DNA damage. Manning *et al.*[52] also confirm that genes involved in apoptosis and cell-cycle regulation can be affected by doses of 0.1 Gy X-rays. More work would be necessary to understand and define the molecular signal transduction for gene expression at low and high doses, but what is clearly evident is that differential gene expression is rather universal than unique in the biological world.

In a nutshell, the radiobiological observations of hormesis, radio-adaptive response, bystander effects genomic instability and the differential gene expression do not support the LNT model. In fact, studies by Koana *et al.*[14] reveal that exposure of *Drosophila* spermatocytes to low dose X-irradiation reduces the frequency of mutations significantly below the spontaneous background mutations, which is really the radiation hormesis at the level of mutations.

Epidemiological studies

Taubes[53] has described how epidemiology has serious limitations. Yet, there seems to be much reliance on epidemiological than on unequivocal radiobiological data in arriving at the low dose biological effects, especially by the 2006 report[54], BEIR VII. On the contrary, the French Academy of Sciences–French National Academy of Medicine[55] has used a wide range or radiobiological data to discuss the carcinogenic effects of low doses of ionizing radiation. It is therefore to be expected that the conclusions drawn by the French Academy of Sciences–French National Academy of Medicine are more veracious and acceptable.

Further, the BEIR VII report[54] does not seem to have done a thorough job of analysing the inherently weak epidemiological data on cancer incidence among the A-bomb survivors in Hiroshima and Nagasaki. Luckey[56] has analysed all the seven BEIR reports. Of these, only those directly relevant to the genetic effects (i.e. heritable mutations, somatic cell mutation or cancer) are discussed below:

(1) The 1990 BEIR V report[57] states (p. 252) 'The risks of acute leukemia and chronic myeloid leukemia are increased by irradiation of the haemopoietic cells, the magnitude of the increase depending on the dose of irradiation.' This concept is not supported by the data of Shimuzu *et al.*[58,59] on the cancer risk and mortality among the A-bomb survivors. Also, the relative risk of colon cancer was significantly lower in the dose range of 10–19 rad than at 0 rad.

Regarding the discrepancies between actual data on the health effects of ionizing radiation among the A-bombs survivors in Hiroshima and Nagasaki and the conclusions drawn by the 1996 BEIR VII report[54], Luckey[56] brings out discrepancies between actual data of Shimizu *et al.*[58,59] and the conclusions in the BEIR VII report. Luckey[56] also observes that the statement in the BEIR VII report[54], 'The committee concludes that the current scientific evidence is consistent with the hypothesis that there is linear, no-threshold dose-response relationship between exposure to ionizing radiation and the development of

human cancers in humans' ignores the paper by Miller *et al.*[60], who show radiation hormesis (reduced cancers) among 31,700 Canadian women who were monitored with multiple fluoroscopic examinations during treatment for tuberculosis. In contrast to the BEIR VII report[54], the French Academy of Sciences–French National Academy of Medicine[55] questions the validity of the LNT hypothesis with the support of the results of several low-dose radiobiological studies. Its statement in section 3.3.1 that 'oxidative stress induces transcription of many genes implicated in signaling that activates cell defenses. The efficacy of the defenses against reactive oxygen species decreases at high dose rates', is scientifically appropriate. This report describes LNT hypothesis as a useful tool for regulatory purposes and that it should not, however, be used to cause trauma in the exposed survivors in the case of nuclear accidents as in Chernobyl and Fukushima. The psychological trauma of the exposed survivors, in turn, promotes nuclear phobia or radio phobia among people living in developing countries like India, which urgently need nuclear energy to augment their energy production.

(2) The other analysis by Luckey[56] involves a study by Cardis *et al.*[61]. This study presents the results of internationally combined analyses of mortality data on 95,673 workers (85.4% men) monitored for external exposure to ionizing radiation during their employment for 6 months or longer in the nuclear industry in any of the three countries. Cardis *et al.*[61] conclude (p. 117), 'Although they are lower than the linear estimates obtained from studies of atomic bomb survivors, they are compatible with a range of possibilities, from a reduction of risk at low doses, to risks twice those on which current radiation protection recommendations are based. Overall, the results of this study do not suggest that current radiation risk estimates for cancer at low level exposures are appreciably in error.' A prejudice against radiation hormesis at low doses is evident from the statement (p. 119), 'As there was no reason to suspect that exposure to radiation would be associated with a decrease in risk of any type of cancer, one-sided tests are presented throughout.' Luckey[56] has reworked on the data of Cardis *et al.*[61] and shown reduced cancer mortality rates (radiation hormesis) for the 32,000 exposed nuclear workers as compared to 45,825 unexposed (control) nuclear workers. The cancer mortality was found substantially reduced for those exposed in the range of about 1 to 7 cGy. Cardis *et al.*[61] conclude (p. 129) 'Combining data from seven cohorts in three countries has provided the opportunity to obtain the most comprehensive and precise direct estimates to date of the carcinogenic effect of low-LET radiation at low doses and low dose-rates. Overall, the estimates resulting from these analyses were consistent across studies, as well as with those derived from high-dose, high dose-rate studies.' The observations and interpretations are at variance with each other. Prejudice in favour of LNT model is revealed.

Studies on the genetic effects in the inhabitants in HLNBRAs

There are several areas in India, China, Brazil and Iran, where the inhabitants are exposed to radiation doses that are similar to, or even above those doses that occupational nuclear workers receive[62]. The estimated background radiation doses in the densely populated monazite-bearing sands in Kerala vary from about 1.0 to over 35.0 mGy/year. Large-scale studies involving newly born population from the control (average 1.15 mGy/year) and high background radiation (1.50 Gy/year to about 35 mGy/year) have shown no increased incidence of cytogenetic abnormalities and micronuclei in the blood cells[63–65]. The studies by Nair *et al.*[66] in India, and Tao *et al.*[67] in China show that cancer incidence and cancer mortality among the inhabitants in the normal level and high level natural radiation areas do not vary significantly.

In a nutshell, the elaborate studies for over four to five decades in India and China suggest that high level natural background radiation has not increased the incidence of cancer morbidity and mortality among the inhabitants. Some of the families have been living in these areas for several generations.

Concluding remarks

Sophisticated cellular and molecular studies reveal that low and high doses of low LET ionizing radiations induce entirely different pathways of response. In particular, the phenomenon of differential gene expression shows that low and high doses result in qualitatively different functional proteins. Further, cellular protective mechanisms such as radioadaptive response, bystander effect and genomic instability with intercellular communication from radiation-damaged cells to undamaged cells so as to prepare them for cell death or cell differentiation (either by apoptosis, or necrosis or mitotic death) seem effective in averting genetic damage. Cell death is essential to prevent transmission of deleterious mutations to progeny, as well as neoplasmic transformation in somatic cells. Thus, the radiobiological data unequivocally support a distinction between the biological effects of low and high doses of low LET radiation.

A few noteworthy epidemiological studies, despite confounding factors, have been carefully analysed. It is noted that the results from these studies do not lend unequivocal support to the LNT hypothesis.

The regulatory agencies would however, want reliable advice on the threshold doses for inducing genetic effects. It is certainly needed but requires a much wider discussion among radiation biologists, radiation protection agencies, regulators and health physicists. In the meantime, the International Commission on Radiological Protection (ICRP) might like to rethink on the statement of Lauriston Taylor[68] (co-founder of ICRP) in his Sievert Lecture

1980: 'No one has been identifiably injured by radiation while working within the first numerical standards (0.2 r/day) set by the NCRP and then the ICRP in 1934.' 'An equally mischievous use of the number game is that of calculating the number of people who will die as a result of having been subjected to diagnostic X-ray procedures. An example of such calculations are those based on a linear, non-threshold, dose-effect relationship, treating the concept as a fact rather than a theory…. These are deeply immoral uses of our scientific knowledge.' A brainstorming discussion on this statement is highly desirable.

Finally, India needs nuclear power, and the moral responsibility of all those concerned in the regulatory agency is not only the protection of radiation workers and the general public, but also avoidance of unnecessary scare and radiophobia. The UNSCEAR 2013 report[69] states that no radiation-related deaths or acute diseases have been noted among the workers and general public exposed to radiation from Fukushima nuclear accident, but the most important health effects are on mental and social well-being, related to the enormous impact of the earthquake, tsunami and nuclear accident, and the fear of stigma related to perceived risk of exposure to ionizing radiation.

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