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Different aspects of hormesis and radiation hormesis†

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Abstract : Hormesis is adopted by seeds, plants, micro-organisms, mice, guineapigs and human beings. It is induced by chemicals, pharmaceuticals, heavy metals and toxicological compounds of varied types. Physical inducing agents are temperature and different types of ionizing radiations.

Hormesis follows biphasic time-response and dose-response relationships which can be quantitated. The hormetic response is controlled by summation of informations, effectors and sensors. It has been reported in erythropoetic tissue, lymphokine cascade in antibody formation and thymidine reuse in mammals etc.

Radiation hormesis is connected with radiation dose, LET, dose rate, size and mass of cells, types of radiation, probability of interaction of radiation with target, time lag between dose and response etc.

At its preliminary stage the concept of hormesis was dismissed but later a large number of authors have supported this concept.

Mechanistically radiation hormesis can be attributed to different causes namely : (i) cellular damage of DNA and its repair, (ii) mutagenesis and its repair, (iii) micronuclei formation and its repair, (iv) different types of chromosomal aberrations and their repair etc. These repairs are done by antioxidants, different types of enzymes and immune responses and cell cycle control etc.

Low dose hormesis has been reported under various conditions namely : (i) environmental and epistemological problems, (ii) background radiation dose estimation, (iii) dose estimation in nuclear installations, (iv) estimation of dose for atomic survivors, (v) accidental dose estimation in Chernobyl etc. In the above cases hormesis depends on internal factors like – lighting condition, intensity and duration of radiation, measurement time of exposure etc.

Societal aspects of hormesis e.g. application in biogerontology, radiation protection aspect, increase in life span for cancer – induced patients applying hormetic principles, environmental and toxicological aspects have been mentioned.

Future prospects of hormesis (both theoretical and practical) are given below :

Theoretical : (i) Low level effects, (ii) linear extrapolation from high level exposure, (iii) shape of dose-response curve and mechanism of radiation effects at low dose, (iv) molecular and cellular studies on mechanism of hormesis, (v) pharmacological hormesis mechanism, (vi) role of hormesis in environmental risk and hazard assessment methods and their evaluation, (vii) role of hormesis in the improvement of harmonization of cancer and non-cancer cases.

Practical : (i) Predictive assay of clinical and therapeutic measures using hormetic principles, (ii) toxicological, agricultural, behavioral, societal, biogerontological and economic aspects of hormesis.

Keywords : Hormesis, radiation hormesis, physical and chemical inducing agents, factors that influence radiation hormesis, detection of hormetic dose by tissue-equivalent dosimeters, maximum limit of exposure, mechanism of radiation hormesis, theoretical and practical aspects of hormesis, future recommendations.

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Introduction

The aim of this review is to bring out the importance of this topic in a comprehensive manner giving importance to its salient features though there are books available in this broad field of research[1,2]. Dosimetric aspects, mechanistic aspects, societal aspects and future theoretical and practical aspects of hormesis – are the objectives of this review.

Definition :

The term hormesis has been coined in 1942. It is the beneficial response of an organism to a low dose of a physical or chemical agent[3]. This low dose refers to ionizing or non-ionizing radiation for a physical agent and concentration or amount when applied to chemical agent. If the dose exceeds a certain limit the effect is no longer beneficial but it becomes detrimental. So, hormesis is a biphasic dose-response relationship[4].

Physical and chemical induction of hormesis :

(a) Physical agents for inducing hormesis are temperature and low LET ionizing radiations like beta, gamma and X-rays. (b) Chemical agents for inducing hormesis are aliphatic or aromatic hydrocarbons, pesticides, heavy metals, polychlorinated phenyls, antibiotics, alcohols, essential trace elements, vitamins, pharmacological compounds etc.

Normally in a chemically induced hormetic response, the response increases with time initially but afterwards it starts decreasing even if time increases. This is known as response – time inversion. Similarly hormetic response increases with increase of dose initially but with further increase in dose there is no more increase in response, but a decrease in it. This is known as response – dose inversion. Inversion of action with time following administration of dose[4] has been depicted in Fig. 1(a) and inversion of action as more of the same agent is administered[4] has been depicted in Fig. 1(b). Example for response – time inversion is salicylates which at toxic doses stimulates the central nervous system but in a short time, with no additional drug a marked depression sets in.

Example for response – dose inversion is that of vitamins. At low doses of many vitamins, the result is depression of growth, but at optimal dose growth is stimulated. But again at much higher doses toxic manifestation occurs and growth is once again depressed.

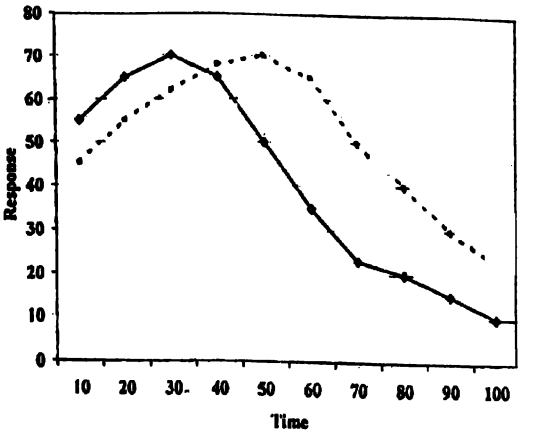

Fig. 1(a). Inversion of action with time following administration of a single dose : (•) practical curve and (...) theoretical curve.

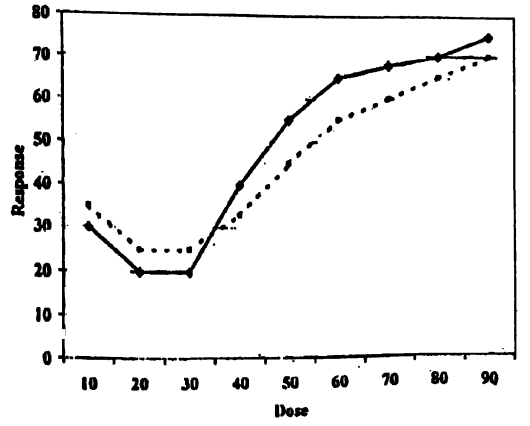

Fig. 1(b). Inversion of action as more of the same agent is administered : (•) practical curve and (...) theoretical curve.

In classical pharmacology or toxicology a sigmoid curve is used to describe the relationship of a biological response to a given dose. This is called quantal response[5]. Theoretical and practical quantal response curves for pharmacological/toxicological compounds[3] have been depicted in Fig. 1(c). As an example chick can not grow without trace amounts of Ni in its food, yet at higher doses Ni is toxic.

Hormesis induced by physical agents are dependent on temperature range and its rate of increase, radiation

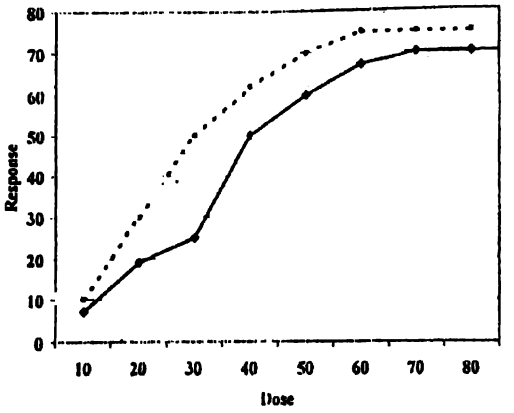

Fig. 1(c). Classical pharmacological/toxicological curves : (•) practical curve and (...) theoretical curve.

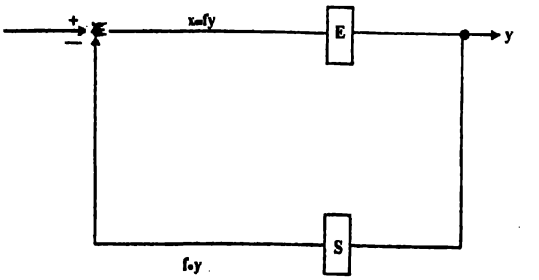

Fig. 2. Schematic model diagram for growth hormesis the elements of a minimal feedback mechanism : Σ = summation of information; E = effector; S = sensor; x = preferred state; y = state of a system; f.y = information of the state.

dose range and its rate, type of radiation and its LET etc. All these come under radiation hormesis.

End-points for detection of hormesis :

End points can be many depending upon exposure medium and biological model. The physical and chemical exposure media have been mentioned. The biological models can be cell systems, tissues (either normal or tumorous), organs, flowers, plants, vegetables, bacteria, fungi, algae, hydra, larvae, different types of animals etc. The end-point is chosen as specific exposure oriented response in suitable biological models and these can be many e.g. life span, growth, dry weight, survival, growth regeneration time and growth inhibition, photosynthesis, cell-division, enzyme activation or deactivation, heamolysis, erythropoesis and tumor induction etc.

Versatility of hormetic response :

Hormesis is adopted by seeds[6] and plants[7], insects, micro-organisms[8], mice[9], guineapigs[9] and human beings[8].

Homeorhesis and hormesis :

In the simplest form these are essentially devices for continuously sensing the state (Y) of a system and relating that information (f.Y) from a sensor (S) to some preferred state (X). The difference between them is (e = X - f.Y) is reduced by effector E whose action is expressed as a transfer function. The kind of oscillatory behaviour observed following a steep input depends on how well the information passes round the control loop. Fig. 2 depicts the elements of a minimal feedback mechanism[10]. As there are delays in the passage of information and in effecting any reduction in E, the output of such systems is inevitably oscillatory, following perturbation. This has been demonstrated in hydroids and yeasts[10].

Radiation hormesis :

Definition : The occasional observation that a small dose of radiation can enhance immunity and/or elicit a proliferative response under certain circumstances has generally been interpreted as evidence of a compensatory or reparative reaction to injury, rather than a stimulatory or hormetic effect per se. Only more recently has the possibility that such a reaction to radiation may represent a hormetic effect began to receive the attention it deserves. Only scattered references show non-hormetic effect in risk management[11]. The early literature on stimulatory or hormetic effects of ionizing radiation has been reviewed[12,1,13,14].

Radiation hormesis, is also versatile and shows its stimulatory effects when plants, bacteria, insects and mammals are exposed to low to intermediate doses of ionizing radiation, contrasting markedly with the inhibitory or cytotoxic effects that characteristically predominate at higher dose levels. The stimulatory or hormetic effects include enhancement of growth and survival, augmentation of immune response and increased resistance to mutagenic and clastogenic effects of further irradiation. This implies that the dose-response relationship for genetic and carcinogenic effects may be also biphasic which means far reaching implication for radiation protection. The extent to which such responses may actually reduce the risk attributable to low level of irradiation needs determination[8].

Radiation-induced hormetic effects :

These are manifested in various ways. Some of these

are : cell systems and their renewal, growth kinetics, physiological processes, cell proliferation, immune functions, enzyme inactivation etc. These are explained with diagrams below. Combined together they also illustrate the mechanism of radiation hormesis.

(a) Cell and tissue-kinetics will have a considerable effect on radiation response under the stress of continuous low dose rate irradiation. The factors for this response are cellular sensitivity i.e. cell cycle effects - which determine rate of cell sterilization and death and compensatory cell proliferation and capacity for regeneration. In rapidly dividing cell renewal systems there is an effective elimination of damaged cells with almost complete repair of cellular non-lethal damage. In slowly dividing cells, renewal or repair of tissues or elimination of cellular radiation damage takes place. The pattern of cell proliferation during regeneration is relatively little disrupted by prior continuous irradiation. Experimental data on intestinal epithelium, immuno-heamatopoetic tissues, seminiferrous epithelium and regenerating liver showed differences in adaptation to continuous low dose rate irradiation involving intra-cellular and extra-cellular control mechanisms which regulate cellular proliferation and differentiation and thereby control cell population levels and physiological function[15].

(b) Cell renewal depends on type of tissue, dose rate and time elapsed after irradiation. Examples are as follows :

(i) For arriving at steady state cell population, small intestine of rat required a dose rate of 4 Gy per day and a period of 2 days. (ii) Testis of dog required 2-5 mGy per day for 15 days. A dose rate of 100 mGy per day or less was near the threshold for recovery processes.

A cell renewal system under continuous irradiation will contain four physiological compartments namely stem cell compartment (S), proliferative compartment (P), differentiation compartment (D) and functional compartment (F).

Normally under irradiated state there is an unidirectional flow like S-P-D-F. But the nutrients like oxygen, external controls from other systems like humoral factors will have their influence also. Upon gamma irradiation back flow of cells from P to S, D to P and D to S take place. The steady state of cell population is dependent upon physological system under study, dose of irradiation, dose rate, nutritional status, oxygen tension, transfer coefficients from one compartment to the other, rate limiting step etc. For example in erythropoetic tissue, cell population sequence is as follows : Pro-erythroblasts - Basophilic erythroblasts (B) - Polychromatic erythroblasts (P) - Orthochromatic erythroblasts (O) - Reticulocytes (R) - Erythrocytes. The schematic representation has been shown in Fig. 3. This figure shows schematic representation of erythropoetic tissue as a cell renewal system[16]. Reserve capacity for proliferation and repopulation ability appears characteristic of the very slowly proliferating renewal tissues. The examples are liver cells and slow seminiferrous epithelium.

Here the hormetic responses are slow. But for blood forming cells like stem cells, lymphocytes and reticular cells - the hormetic response is fast[16].

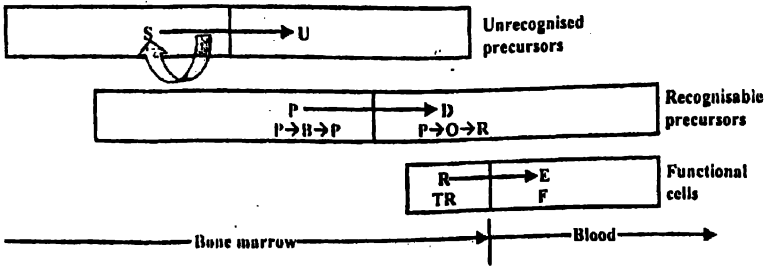

Fig. 3. Schematic representation of erythropoetic tissue as a cell renewal system. S : Unrecognised precursor stem cells, U : Immediate precursor stem cells, P : Proliferation compartment, D : Differentiation compartment, Tr : Transitional forms in bone marrow, F : Functional end cell compartment, P→B→P : Procythroblasts→ Baseophilic erythroblasts→Polychromatic erythroblasts, R→E : Reticulocytes→Erythrocytes and P→O→R : Polychromatic erythroblasts→Orthochromatic erythroblasts→Reticulocytes.

(c) Immune system function :

The effect of low dose single and continuous whole body irradiation on immune function namely placque forming cell reaction (PKC) of spleen and reactivity of thymocytes to IL1 were undertaken[17]. The PKC of spleen was found to be stimulated by single dose of X-rays in the dose range of 0.025–0.075 Gy and by continuous exposure to gamma rays with a cumulative dose of 0.65 Gy. The PKC values were more for exposed cells at a dose rate of 0.0054 Gy/s for 6 h by about 18%. The reactivity of thymocytes to 25% IL1 is between 0.025 and 0.10 Gy which continuously increased implicating an increased reaction of whole organ. PKC is a standard technique in assessing the capacity of antibody formation. Antibody formation has the D_0 value of less than 1 Gy. The lymphokine cascade in antibody formation[18] is shown in Fig. 4. All these explain radiation hormesis and its expression in the immune system[18].

0.001 Gy per 8 h day until death of experimental mice and guineapigs had a slightly greater mean life span compared to control animals. There was a marked weight gain during the growth phase in both species. Increased tumor incidence in mice at 0.001 Gy was observed. This is probably due to regenerative hyperplasia during early part of exposure. In presence of continuous injury there is physiological enhancement of defence mechanisms against infection[9].

(e) Hormetic response in seeds and plants :

Hormetic effect is observed in the growth of organisms at very low doses. Irradiation of seed[6] before planting can stimulate early plant growth, leading to advanced maturity and increased yield[7]. The reported effects include increased height, weight, growth rate, flowering and yield. The magnitude of the effect is usually small, being about 10% of control values and the effects often

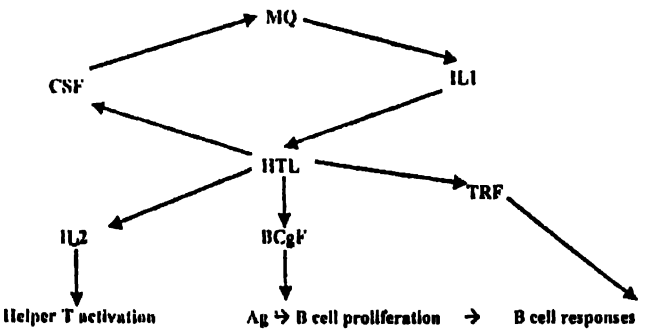

Fig. 4. Lymphokine cascade in antibody formation. MQ : Macrophage, IL1 : Interleukin 1, IL2 : Interleukin 2, Ag : Antigen, CSF : Cell signal factor, TRF : Transforming factor, BCgF : B cell growing factor and HTL : Highly transformed cell lines.

(d) The table below will show (Table 1) the dose ranges at which different types of cells show variation in response.

Table 1

Dose range (Gy)	Tissue	Effect
0.025–0.075	Spleen	Placque forming cell reaction increased
0.025–0.250	Thymocytes	Reactivity to interleukin 1 showed dose dependent depression
0.025–0.100	Thymus	Increase in cell number
0.05 Gy (single)	Spleen cells	Unscheduled DNA synthesis was stimulated

are not reproducible. The exposure level was reported to induce such effects is about an order of magnitude greater than that reported for similar hormetic responses in animals. There is no understanding of the mechanisms of such responses of the cellular and physical factors pertinent to the induction of such effects but observations are there that certain low level exposures result in increased yield. This is consistent with known mechanisms of cellular damage and known responses of plants to a compromise to apical dominance. Storage time after irradiation must be minimized to gain the greatest response. Hormesis in seeds is not manifested reliably in advanced maturity or yield increases because of environmental effects. Here photon energy and dose rate are important factors.

Dosimetric concepts in relation to radiation hormesis :

With radiation, unlike chemicals, a small absorbed organ dose can deliver a large amount of energy to macromolecular cell targets. If the relevant target is hit, even the best efforts of any repair processes probably can not prevent cell transformation. The smallest average organ dose can be effective particularly for high LET radiation. Hormesis enhanced protection processes may render ineffective marginally large amounts of energy deposition per cell target and thus perhaps reduce the incidences of carcinogenesis. For high LET radiation zero incidence is unlikely[19]. Estimates have been given for the critical values of linear energy transfer (LET), dose rate and dose below which radiation hormesis is likely to occur but above which it is unlikely to occur. The critical value of LET is estimated to be 15-20 keV/μm and hence radiation hormesis may occur with β, γ or X-rays. But it is unlikely to occur with α-particles. The critical value of dose rate is estimated to be 1-10 mGy per day for the life-time exposure. But this could be higher for the short period exposure. A comparison between plants and animals for critical dose rate response showed that dry seeds and bulbs require a dose rate which is 1000 times more than animals. The salient features regarding dosimetric aspects are given below :

(i) Critical value of LET : This is denoted as Lc and

$$Lc \approx 15\text{-}20 \text{ keV}/\mu m \quad (1)$$

This LET corresponds to protons or neutrons of few MeV. Radiation hormesis can occur by β or γ radiation of about 1 MeV (LET≈ 0.3 keV/μm) or X-rays (0.1 to 0.3 MeV).

(ii) Dose rate : Dose rate at which radiation hormesis occurs,

$$Dci \approx 1\text{-}120 \text{ mGy per day (life time exposure)} \quad (2)$$

For short period exposure,

$$Dc = > Dci \quad (3)$$

where Dc = critical dose rate below which radiation hormesis could occur. Dci = dose rate at which radiation hormesis occurs.

A model predicts that there is no limit for the critical value of dose, Dc, when the dose rate D is below Dci, because then the beneficial effect will always exceed the harmful effect. This is when Dc is greater than Dci it is natural to expect that Dc decreases. Therefore denoting T as the average life if an animal Dc ≈ Dci T for

$$D = < Dci = Dci\ T\ (D/Dci)^{-n} \quad (4)$$

where n is a positive constant to be determined by experiment[20]. The dose rate response curve corresponding to radiation hormesis[19] has been shown in Fig. 5.

(iii) Low doses and low dose rates : At low dose and low dose rates the amount of energy deposited in an individual cell organelle (i.e. hit size) is highly variable from one cell to another.

(iv) Distribution of hit sizes in the individual cell nuclei and to fractional number of exposed area cells that experience a hit at an exposure level should be known. The crucial relationship between hit size and probability of cellular response[20] have been depicted in Figs. 5(a), 5(b) and 5(c).

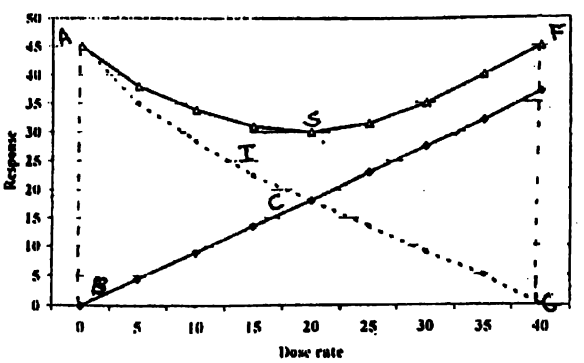

Fig. 5. Dose rate response curve corresponding to radiation hormesis. C : Conventional response due to the direct effects of ionising radiation such as DNA damage, I : Response corresponding to indirect effects, E : Environmental level and S : Total sum of I and C. (•) BC; (...) AIG, (Δ) ASF.

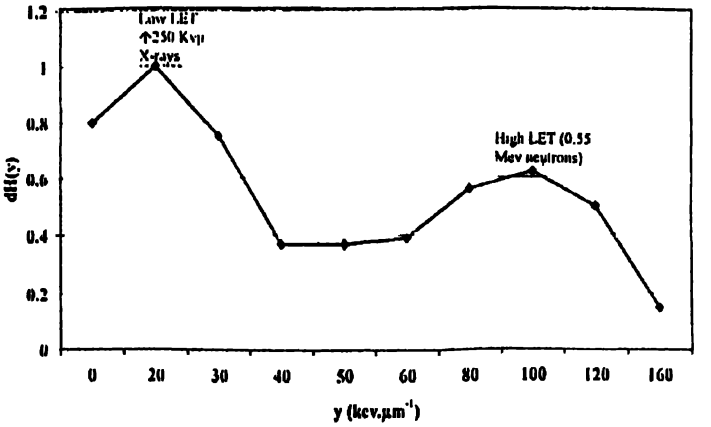

Fig. 5(a). Hit sizes as functions of energy deposition per unit cell. dH(y) : Hit size and y (keV.μm^{-1}) : Energy deposition per unit cell.

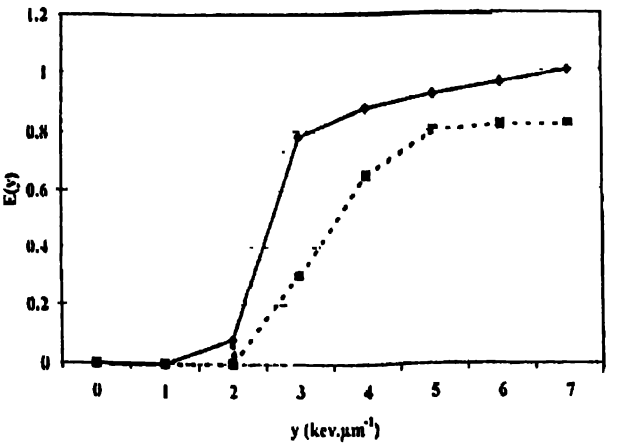

Fig. 5(b). Probability of a defined cellular response in cells of a given hit size. E(y) : Probability of hit and Y : Energy deposition per unit cell : (•) Curve 1, (▪) Curve 2.

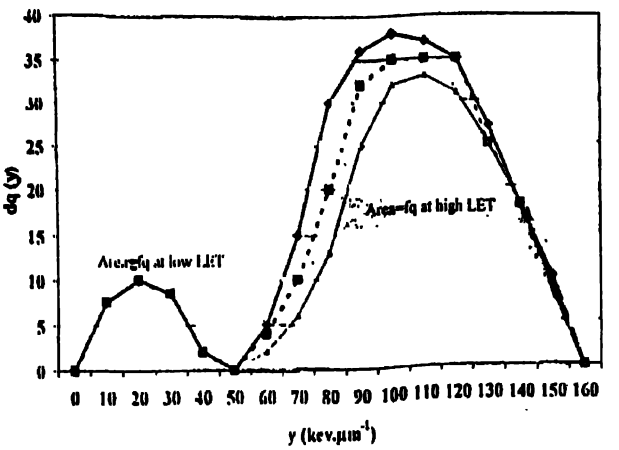

Fig. 5(c). The results of multiplying the curves in panel a by that in panel b is panal c. The dotted lines refer to anticipated results using various assumptions about the mechanisms of hormesis : (•) Curve 1, (▪) Curve 2, (...) Curve 3.

Target hit size distributions :

The hit sizes [$d_H(y)$] are functions of energy deposition per unit cell [y (keV/μm)]. This is also controlled by probability of hit E(y). The hit size has been expressed arbitrarily within a tissue sphere of 1 μm diameter. Panel 5(a) shows a plot of $d_H(y)$ against y (keV/μm). This is also controlled by probability of hit E(y). The hit size has been expressed arbitrarily as that in a tissue sphere of 1 μm diameter. It shows a peak for low LET i.e. 250 kVp X-rays and a peak for high LET i.e. 0.55 MeV neutrons. Panel 5(b) shows a plot of E(y) versus y (keV/μm). The solid line shows probability E(y) of a defined cellular response in cells of a given hit size. Mutation is a function of hit size empirically done. Panel 5(c) shows the plot of dq(y) versus y (keV/μm). The results of multiplying the curves in "Panel 5a" by that in "Panel 5(b)" is "Panel 5(c)". The dotted lines refer to anticipated results using various assumptions about the mechanisms of hormesis. The types of changes observed suggested that growth size, rate and curve shape may respond independently and in some cases in opposite directions. Thus while one aspect of growth may change by hormesis other aspects of same growth function may be changing in a way which is suggestive of a stress response. So the mathematical model is dependent upon a particular aspect of growth response, species chosen, stressor type and intensity, growing time etc. For Cypress seedlings and two species of waterfowl following mathematical model holds good[21].

$$W_{i+1} - W_i = \frac{2(m+1)}{T(1-m)} [(W\alpha^{1-m} \times W_i^m) - W_i] + e_i \quad (5)$$

where W_i = body weight or size at time t_i; $W\alpha$ = asymptotic weight or size; T = overall growing time indicative of growth rate; m = Richards shape parameter and e_i = Stochastic error at time t_i.

Dose estimation for nuclear workers :

Nuclear radiation or power plant workers are susceptible to get exposure of ionizing radiations. Their work performance does not decrease to any considerable extent by the dose received during about 1 month. This occupational exposure is determined accurately. Measurement of blood lymphocytes related chromosomal radiosensitivity give an indication of hormetic response. Chromosomal radiosensitivity was assessed *in vitro* by G_0 – assay and G_0 – micronucleus assay (MN). For MN assay a low dose rate (LDR) *in vitro* irradiation protocol was applied in addition to high dose rate (HDR) irradiation of blood samples in order to determine dose rate sparing effect (DRS). The dose rate sparing effect of low dose rate (LDR) irradiation compared to high dose rate irradiation was calculated by :

$$DRS = [1 - (\gamma_{LDR}/\gamma_{HDR})] \times 100 \quad (6)$$

where γ_{LDR} = micronucleus yield of LDR; γ_{HDR} = micronucleus yield for HDR. Pre- and post-irradiation exposure did not show variation in chromosomal aberration. Micronucleus assay was done *in vitro*. The G_0-MN assay with LDR irradiation protocol reveals systematic reduction in chromosomal radiosensitivity with increasing dose. For workers receiving 4–10 mSv (highest dose) decrease of MN yield and increase of dose rate sparing was observed. Short term exposures may have induced hormetic responses depending upon situation. Based on these types of studies, the occupational exposure dose limit in nuclear industry has been restricted to 10 mSv per year for radiation workers[22].

Linear-no-threshold (LNT) model – its significance and implications :

According to linear-no-threshold (LNT) model for a low LET radiation, in radiation-induced stochastic effects (e.g. neoplastic transformation and cancer) the risk increases linearly without a threshold. Any radiation exposure is predicted to increase the number of cancer cases among a large population of people. Cancer risk extrapolation from high to low doses based on this model is widespread. Indirect evidence is provided, suggesting that for brief exposures to low LET radiation doses of the order of 1 mGy, that a decrease below the spontaneous level is many orders of magnitude more probable than for any increase in risk as would be predicted by extrapolating from high to low doses using the LNT model. The risk reduction has been largely due to a protective apoptosis mediated process (PAM) that selectively eliminates cells that contain genomic instability. The minimum exposure is 0.01 mGy for X-rays and gamma rays. But if the dose is above 250 mGy for brief exposure at a high rate, the PAM process is not expected to be activated. For protracted exposure doses as high as 400 mGy may activate the PAM process[23]. LNT model has undergone test for health care patients with benefit in which effective dose ranged from few μSv to a few mSv[24].

International Commission on Radiological Protection

(ICRP) has recommended the LNT model above a few mSv per year[25]. A few reports (ICRP 2004; Report from French Academy of Sciences and Medicine 2005 and American Academy of Sciences) have appeared on low doses of radiation. These reports indicate the importance of biological effects of low doses, yet the conclusions differ[26]. Each element within the reaction chain that is affected by ionizing radiation contributes in a specific way to the final biological end point of interest. The resulting dose-response relationship represents the superposition of all these effects. For doses below 10 mSv there is neither a closed or clear picture of the entirety of radiation action. Moreover, no clear evidence (epidemiological) exist for increase of risk for stochastic effects in this dose range. So LNT concept is preferred against any alternative concept[27]. Recent reports from National Research Council (BEIR VII) and International Commission on Radiological Protection (ICRP) have considered the appropriateness of the use of LNT for purposes of radiation protection standard setting. The overall conclusion was that current scientific evidence remains consistent with LNT hypothesis. The dose and dose rate effectiveness factor is used for adjustment in the extrapolation from high to low doses and from high to low dose rates[28].

Development of tissue-equivalent dosimeters :

For radiation hormesis accurate and sensitive tissue-equivalent dosimeters are required. For this low dose range we have developed some chemical, biochemical and biopolymeric dosimeters capable of measuring tissue-equivalent low dose, Table 2 will give the dosimeter, its composition dose range, dose rate, lowest dose mea-

Table 2. Characteristics of some chemical, biochemical and bio-polymeric dosimeters

Dosimeter	Composition	Dose range, dose rate, type of radiation, lowest dose	Applicable tissue/ type of application	Reference
FBX	0.20 mM Ferrous ammonium sulphate + 0.20 mM xylenol orange + 5 mM benzoic acid in 0.05 *N* H_2SO_4	Linear up to 10 Gy; 0.017 Gy/s; γ-radiation; 0.05 Gy	On body surface and inside body cavities	29
Modified FBX	Same as FBX + 5 mM ammonium nitrate	Linear up to 16 Gy; 0.017 to 0.17 Gy/s; γ-radiation and thermal neutrons; 0.05 Gy	Same as FBX; can be used in nuclear accident	30
Diltiazem	25 µg/ml Diltiazem, pH 2.13–2.27	Linear up to 10 Gy; 0.018 Gy/s; γ-radiation; 2 Gy	Can be used as *in vitro* dosimeter for cardiovascular epithelial cells	31
DNA and DNH	100 and 200 µg/ml respectively in 0.1 *M* phosphate buffer	Linear up to 100 Gy; 0.0156 Gy/s; γ-radiation; 20 Gy	Can be used as *in vitro* dosimeter for nucleated tissues	32
H_1 Histone	50 µg/ml in 2.5×10^{-4} (*M*) EDTA buffer; 200 µg/ml in 0.01 *N* HCl	Linear up to 100 Gy; dose rate 0.0135 Gy/s; γ-radiation; linear up to 12 Gy; dose rates 0.0135 and 0.0504 Gy/s	Can be used as *in vitro* dosimeter for nucleosomal aberration	33
DNA-H_1	25 : 25 µg/ml in 0.1 *M* phosphate buffer and in 0.15 *M* SSC buffer, pH 7.0	Linear up to 50 Gy; dose rate 1.50 Gy/min; γ-radiation; 10 Gy	Dose determination in chromosomal aberration	34
DNA-H_3	50 : 50 µg/ml in 0.9% HCl, pH 6.70–6.90	Linear up to 30 Gy; 0.0106 Gy/s; γ-radiation; 10 Gy	Chromosomal aberration nucleosomal organisation	35

surable, type of radiation etc., While chemical and biochemical dosimeters are tissue-equivalent, the biopolymeric dosimeters are ideal for all types of nucleolar tissues. This is a novel approach as because these dosimeters are closely approaching tissue composition, need not require correction factor for getting absorbed dose, the composition can be suitably changed simulating a particular tissue, can be given any desired shape and size and after encapsulation can be put inside body cavities or outside on the surface of body for measuring dose.

Biochemical mechanistic aspect of radiation hormesis :

Non-specific generation of intra-cellular free radicals in excess of normal levels (due to acute radiation absorption by cells) leads to a delayed production and temporary inhibition of thymidine kinase. The enzyme activity reaches a minimum at 4 h even after a low level exposure with full recovery soon thereafter. This process appears to represent a biochemical response to an initial physical event which must be distinguished from the response of the DNA repair enzyme system. A reduction of cellular thymidine kinase activity is expected to cause a temporary reduction of DNA synthesis and thus may be of advantage to the cell. It is suggested that this response of thymidine kinase activity to free radicals generated by radiation or by other means and the probable consequences of DNA synthesis may represent an example of radiation hormesis[36]. A simplified scheme of the pathways for it is depicted in Fig. 6. Here in this scheme thymidine reuse in mammals has been depicted. Thymidine is liberated by dead cells and eventually released by proliferating cells.

Physiological aspects of qualitative and quantitative DNA damages connected to radiation hormesis :

Steady state of non-radiation induced DNA damage far outweighs DNA damage from low doses of low LET radiation, both qualitatively and quantitatively. Because tissue effects are predominantly the consequence of individual cellular responses, the doses to micro-masses of cells in tissues appear primarily more relevant. Low cell doses are correlated by intra-cellularly operating factors which unequivocally cause a dual effect depending upon cell types and species. These dual effects are : (i) a rise in DNA damage above background as a function of dose and (ii) a simulation of the physiological DNA damage control system in terms of reactive oxygen species detoxification, DNA repair and removal of damaged cells. This stimulation lasts from hours to weeks after irradiation and except during apoptosis, vanishes at higher cell doses.

Low dose induced stimulation of the DNA damage control system appears as a physiological stress response. This operates on endogenous ROS and non-radiation induced DNA alterations over prolonged duration. Non-radiation induced DNA damage apparently far exceeds corresponding effects from low dose and low dose rate of low LET radiation. Thus the radiation-induced hormesis is expected to affect predominantly the non-radiation DNA damage for prolonged period of time after individual cells experience energy deposition events.

The physiological DNA damage control system oper-

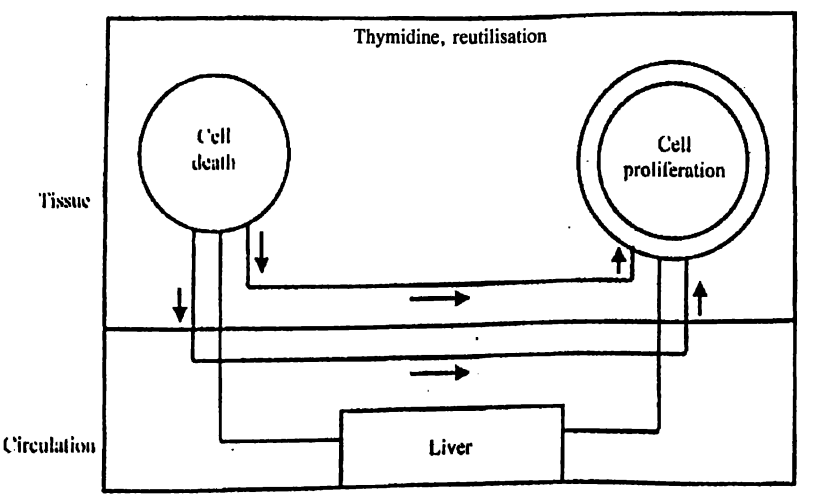

Fig. 6. A simplified scheme of the pathways of thymidine reuse in mammals. Thymidine is liberated by dead cells and eventually released by proliferation.

ates as an anti-mutagenic bio-system. So gene mutations caused by non-radiation sources are expected to be reduced by low doses of low LET radiation.

So, cell doses are high but the formation of hit cells is low because of intra-cellular operating factors. These factors are anti-oxidants like GSH, SOD, catalase, peroxidase and enzymes connected to cell cycle control factors pertaining to cell differentiation and immune response etc. The anti-mutagenic DNA damage control bio-system under normal control condition and when exposed to high background radiation have been depicted in Figs. 7 and 8 respectively. Fig. 7 depicts the anti-mutagenic DNA damage control bio-system. Estimations are based on data in literature. Fig. 8 depicts the anti-mutagenic-DNA damage control bio-system response to high background radiation[37].

Environmental, epistemological and toxicological problems in assessing cancer risks at low radiation doses in relation to radiation hormesis :

Radiation hormesis should be emphasized from sociological point of view as well. It is associated with low dose of radiation release to the environment from nuclear energy. The hormetic hypothesis suggests that ecologically realistic low levels of ionizing radiations may be beneficial to humans. This is supported by the fact that the annual cancer incidence rate seems to decrease by 0.03/μSV increase in external background radiation dose from 79 per 100000 corresponding to zero environmental radiation[38].

The following epistemological problems arise in assessing cancer risk at low dose of radiation :

(i) Prediction as to radiogenic cancer seem often if not always neglected the response variability in individuals (i.e. prediction on radiation dose but not radio-sensitivity).

(ii) In the effect of the conditionally possible agent the exposed individual or population must be considered as an open statistical system.

(iii) On epistemological grounds we can not gain knowledge about carcinogenic capacity of radiation doses.

(iv) Based on some principles, cancer risks can not be predicted at very low radiation doses merely on the basis of models[39].

Normal distribution pattern with three different standard deviations illustrates how dose-effect curves change when the variation in radio-sensitivity increases in irradiated populations (Fig. 9). This figure shows cancer incidence plotted against relative dose. Normal distribution functions with three different standard deviations illustrating how dose effect curves change when the variation in radio-sensitivity increases in irradiated populations[40].

Recent advances in procedures for the analysis of sigmoidal curves have provided some sensitive methods of detecting and evaluating hormesis in the growth responses

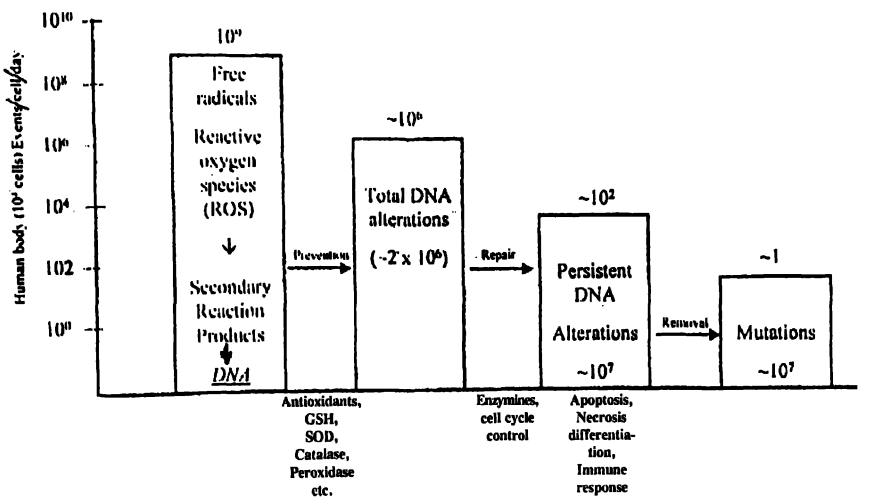

Fig. 7. The antimutagenic DNA damage control biosystem. Estimates based on data in literature.

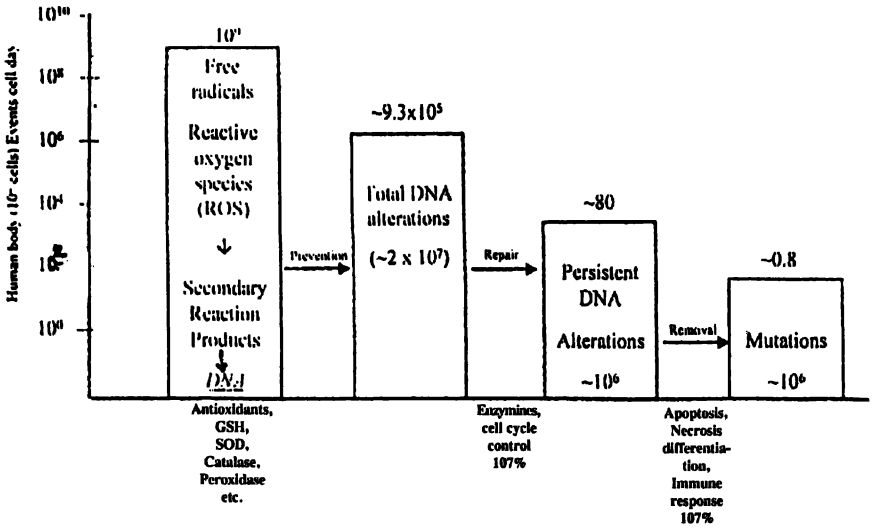

Fig. 8. Antimutagenic DNA damage control biosystem response to high background radiation = 120%. Estimates based on data in literature.

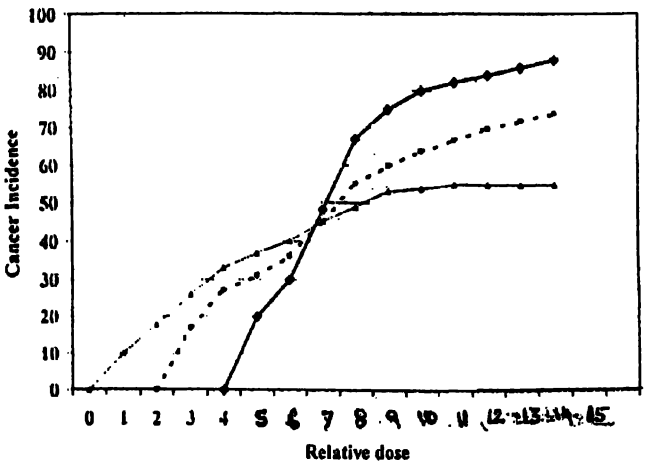

Fig. 9. Normal distribution functions with three standard deviations illustrating how dose effect curves change when the variation in radiosensitivity increases in irradiated populations : (•) Sigma 1, (...) Sigma 2, (▲) Sigma 3.

of organisms exposed to a variety of stressors. These processes allow quantification and independent evaluation of the following three major properties of a sigmoid growth curve.

(i) Size - a measure of the asymptotic approach by the growth processes.

(ii) Rate - a measure of the approximate amount of time required to complete growth.

(iii) Shape - a quantity which indicates the specific path taken by the growth process to approach the asymptote within the time constraint of growth potential.

Background radiation can simulate the proliferation of single cell organisms like protozoa and cyanobacteria. But this low dose induced (mostly gamma and beta) hormesis depends on internal factors like age of starting single cells and external factors like lighting conditions. The stimulatory effect was observed below 50 mGy in a limited range of doses. This is an unique way to find out

background radiation induced hormesis[17]. Cancer incidence and mortality data from cohort of Japanese atomic bomb survivors showed uncertainty in dose estimation. Leukemia data agree threshold model but solid tumor data does not suggest improvement with a threshold[40].

Environmental aspect :

Hormesis is an extreme version of the non-linear fitness gradients for general environmental stresses, such as temperature fluctuations. Some metabolic reserves should occur under moderate temperature stresses because of the need for pre-adaptation. Because heat shock proteins are induced by all stresses, adaptation to extreme temperature should translate into adaptation to other stresses. Evolutionary and ecological considerations suggest two components of hormesis in relation to ionizing radiation : background radiation hormesis and stress derived radiation hormesis. Exposure under stress derived radiation hormesis is considerably larger than background radiation hormesis[41].

Toxicological aspect :

In order to analytical evaluation of risk assessment, risk management and risk communication for human health and ecological risk and for occupational health risk specific applications were reviewed and summarized taking into consideration the following factors : (i) contaminated sites, (ii) contaminants, (iii) priority substances, (iv) standards development, (v) food safety, (vi) medical devices, (vii) prescription drug use, (viii) emergency response, (ix) transportation and (x) risk communication[42].

Risk assessment from radionucleides : The Royal Free Hospital has set up a project to examine the whole procedure and approach the risk assessment for ionizing radiations and has produced a standardized approach using matched risk assessment forms for both general risks and ionizing radiation risks[43].

Future aspects :

As the phenomenon of hormesis has been studied in its totality, especially in foreign countries, future prospects of it needs evaluation in India as well.

(i) Theoretical aspects : For in depth understanding and dissemination among scientists. (ii) Practical aspects : For sustenance and beneficial effects to all species in different fields.

The different issues that should be given importance in theoretical aspects are : (i) low level effects, (ii) linear extrapolation from high level exposure, (iii) shape of dose-response curve and mechanisms of effects of radiation at low doses, (iv) molecular and cellular studies for understanding radiogenic effects and provide information about likely shape of dose-response curve at low doses of radiation and (v) mechanistic explanations of pharmacological systems. The impact of multiple chemical interactions on the occurrence of hormesis in different systems should be undertaken.

Practical aspects : Epidemiological studies include the following : (i) influence of development/ageing processes, gender, diet and various disease states on the occurrence of hormesis and (ii) the possible occurrence of inter-individual variation in hormetic responses and how this may impact regularly on medical practices.

Environmental issues : This includes (i) risk assessment methods, (ii) hazard assessment methods and (iii) improvement in harmonization of cancer and non-cancer.

The salient features of some practical aspects e.g. predictive, clinical, therapeutic, toxicological, agricultural, modification of behavioural systems, societal and economic aspects of hormesis are mentioned below.

(i) Proper choice of chemo-therapeutic agent and radiation dose, dose rate and fractionation as shown by adaptive responses may markedly reduce cost of cancer treatment. This gives economic benefit.

(ii) The selection of animal models for research as predictive of human responses and public health importance is of societal value.

(iii) Agricultural productivity may be increased by optimizing proper hormesis inducing treatments.

(iv) Behavioural performance, especially memory stimulation, may be enhanced by proper choice of a hormesis inducing agent. Neuro-protective effect of one ultra-low exposure level of glutamate in an *in vivo* rat stroke model has been found to reduce brain injury by 40% and significantly improve EEG recovery and performance. Protective effects of low level exposure have been expressed in CNS injury. GABA channel blocker picrotoxin (10^{-13} *M*) reversed impairment of optokinetic and vestibule-ocular reflex produced by high dose GABA ergic activity. Neuron viability is consistently 10% higher

in spinal and cortical neurons pre-exposed to glutamate concentrations of 10^{-18} to 10^{-30} *M*.

(v) Toxicological : Cd exposure well below toxic dose showed no adverse effect level induced gene expression of protective proteins (e.g. metallothionine etc.). 40% reduction in mortality to acute Cd toxicity *in vitro* and *in vivo* show protective effects of ultra-low exposure of Cd. In renal and immune T cells ultra low Cd levels produce higher levels of metallothionine.

Future recommendations :

(i) Individual level consequences of sub-organism hormesis, (ii) Processes - both biotic and abiotic, regulating population size and health, (iii) Demonstration of hormesis in the dose-response curve of carcinogenesis, (iv) Potential alteration in traditional bio-assays for carcinogenesis, (v) Whether physical and biological stressors can also cause hormesis? This is important because of population health than are chemical stressors, (vi) No radiation dose is below regulatory concern and appropriate dose levels should be established, (vii) New and/or improved therapies by hormetic induction should be looked into and (viii) Factors of hormetic origin that can improve public health on a long term basis should be worked out[44].

Hormesis in biotechnology :

This is still another area which has got research element in it and also has practical utility. Ageing has many facets like : (i) it differs with species, (ii) intra-species individual variation, (iii) it varies with organs, systems and tissues within an individual, (iv) varies with different organelles within a cell and (v) varies with bio-macromolecules.

Different diseases that are connected with ageing are arthritis, muscular dystrophy, multiple sclerosis, encephalo-myography, some cancers, atherosclerosis, Alzheimer's disease, Parkinsons disease etc. During mild repeated stresses hormetic cellular responses get up-regulated to constant internal and external stresses and thereby the maintenance and repair pathways are rejuvenated[44]. Gerantogenes (i.e. longevity assurance genes) involved in heamo-dynamic repair pathways may play important roles for hormesis. The pathways include DNA repair, free radical scavenging, heat shock response etc. Normally mild stress can be stimulatory without becoming too costly but severe stress up-regulation may become energetically too costly. So severe stress may invariably cause biological collapse completely. The phenomenon has been observed in Drosophilla, Nematodes and Yeast cells also. Some inexpensive techniques that are beneficial are : exercise, caloric restriction. Repeated mild heat shocks (RMHS) show hormetic effects by prevention of age related cell enlargement. This is due to accumulation of abnormal and inactivated proteins. It has been observed now that RMHS stimulates heat shock response of human cells and prevents the accumulation of glycated and glyoxidated abnormal proteins by stimulating the proteasome pathway of protein degradation[45,46].

Conclusion : Hormesis, if properly understood and applied, can alleviate many difficulties faced by human beings. So, its short/long term benefits in quantitative terms should be evaluated.

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References

1. T. D. Luckey, "Hormesis with Ionizing Radiation", CRC Press, Boca Raton, Florida, 1980.
2. T. D. Luckey, "Radiation Hormesis", CRC Press, Boca Raton, Florida, 1991; A. Furst, *Health Physics*, 1987, **52**, 527.
3. E. J. Calabrese, M. E. Mc Carthy and E. Kenyon, *Health Physics*, 1987, **52**, 531.
5. I. L. O. Buxton, "The Pharmacological Basis of Therapeutics", ed. L. L. Buxton, McGraw Hill Medical Publishing Division, New York, 2006, 11th ed., pp. 1-39.
6. S. C. Shepherd and P. J. Regitting, *Health Physics*, 1987, **52**, 599.
7. M. W. Millier and W. M. Miller, *Health Physics*, 1987, **52**, 607.
8. A. C. Upton, *Critical Reviews in Toxicology*, 2001, **31**, 681.
9. C. C. Congdon, *Health Physics*, 1987, **52**, 593.
10. A. R. D. Stebbing, *Health Physics*, 1987, **52**, 543.
11. C. J. Paperellio, *J. Appl. Toxicol.*, 2000, **20**, 147.
12. E. J. Calabrese and C. A. Baldwin, *Belle News Letter*, 1999, **8**, 38.
13. E. J. Calabrese and L. A. Baldwin, *Belle News Letter*, 1999, **8**, 2.

14. E. J. Calabrese and L. A. Baldwin, *Belle News Letter*, 1999, **8**, 47.

15. J. R. Totter, *Health Physics*, 1987, **52**, 549.

16. J. I. Fabricant, *Health Physics*, 1987, **52**, 561.

17. H. Plannel, J. P. Soleihavoup, R. Tixador, G. Richolley, A. Conter, F. Cronte, C. Caratero and Y. Glaubin, *Health Physics*, 1987, **52**, 572.

18. S. Z. Liu, W. H. Liu and J. B. Suit, *Health Physics*, 1987, **52**, 593.

19. V. P. Bond, L. E. Feinendigen and C. A. Sondhans, *Health Physics*, 1987, **52**, 658.

20. K. Okamoto, *Health Physics*, 1987, **52**, 671.

21. I. Lehr Brisbain, K. W. Mc Leod and G. C. While, *Health Physics*, 1987, **52**, 552.

22. H. Thirens, A. Vral, M. Barbe, M. Meijlayers, A. Bayens and L. D. Ridder, *Int. J. Radiat. Biol.*, 2002, **78**, **12**, 1117.

23. B. R. Scott, *Human Experimental Toxicology*, 2008, **27**, 163.

24. B. F. Wall, G. M. Kendall, A. A. Edwards, S. Bouffer, C. R. Muirhead and J. R. Meara, *Brit. J. Radiol.*, 2006, **79**, 285.

25. D. J. Higson, *Health Physics*, 2004, **87**, 547.

26. M. Tubiana, A. Aurengo, D. Averback and R. Masse, *J. Radiol. Prot.*, 2006, **26**, 317.

27. J. Breckow, *Radiat. Environ. Biophysics*, 2006, **44**, 241, 257.

28. R. J. Preston, *Health Physics*, 2008, **95**, 541.

29. S. N. Upadhyay, Jasbir Singh and A. R. Reddy, *Indian J. Radiol.*, 1982, **36**, 141.

30. S. N. Upadhyay, M. M. Gupta, A. R. Reddy and A. Nagaratnam, *Int. J. Appl. Radiat. Isot.*, 1982, **33**, 47.

31. S. N. Upadhyay, *J. Surface Sci. Technol.*, 2001, **17**, 157.

32. S. N. Upadhyay and T. L. Mathew, *Indian J. Biochem. Biophys.*, 2000, **37**, 178.

33. S. N. Upadhyay, *J. Indian Chem. Soc.*, 2001, **78**, 424.

34. S. N. Upadhyay, R. Bhardwaj and N. K. Chaudhuri, *J. Indian Chem. Soc.*, 2005, **82**, 310.

35. S. N. Upadhyay, *Indian J. Biochem. Biophys.*, 2001, **38**, 406.

36. E. Feinendigen, O. Muhlensippen, V. P. Bond and C. A. Sondhans, *Health Physics*, 1987, **52**, 664.

37. M. Pollycove and L. E. Feinendigen, *Human and Experimental Toxicology*, 2003, **22**, 290.

38. K. S. V. Nambi and S. D. Soman, *Health Physics*, 1987, **52**, 675.

39. G. Walinder, *Health Physics*, 1987, **52**, 675.

40. G. S. Baker and D. G. Hoel, *Health Physics*, 2003, **85**, 709.

41. P. A. Parsons, *J. Appl. Toxicology*, 2000, **20**, 103.

42. C. Jardine, S. Hrudev, J. Shortreed, L. Craig, D. Krewski, C. Furgal and S. Mc. Coil, *J. Toxicol. Environ. Health, Critical Review*, 2003, **6**, 569.

43. C. H. Green, J. E. Agnew and I. A. Fife, *Nuclear Medicine Communication*, 2003, **24**, 1017.

44. E. J. Calabrese, *Critical Review in Toxicology*, 2001, **31**, 637.

45 S. I. S. Rattan, *Current Reviews in Toxicology*, 2002, **31**, 663.

46. E. I. Masoro, *Experimental Gerontology*, 2000, **35**, 299.