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EDITORIAL

Hormesis – an exciting field in genetic toxicology and evolutionary biology

The term 'hormesis' describes the beneficial effects at low concentrations/doses of substances/agents which at higher doses are toxic/lethal. Hormesis means 'to excite in small amounts': Greek 'Hormoligosis'. The effects seem to be largely physiological in nature at low concentrations/doses; at higher doses the agents cause genotoxicity expressed as chromosomal aberrations, mutations, cancer and lethality. However, toxic effects noted at high doses cannot be anticipated by extrapolation of dosage. Agathokleous *et al*. (*Environ. Res.*, 2018, **165**, 274–278) observe that hormesis rewrites the history of toxicology. Hormesis was invariably encountered by genetic toxicologists working with physical and chemical genotoxic agents since 1974 when research on environmental mutagens gained momentum in several scientifically advanced countries including India. As early as 1975, scientists at the Bhabha Atomic Research Centre (BARC), Mumbai not only pioneered research in environmental mutagenesis, but also, supported initiation of research in this field in several universities. Many scientists recorded that several genotoxins at low doses/concentrations reduced the spontaneous level of adverse effects.

When an adverse biological effect is plotted against concentration/dose of a chemical or physical agent, the shape of the dose-effect curve is not linear, but 'J'-hockey stick shaped, suggesting that at very low doses the adverse effects are below those observed in untreated control (normal population). Unable to comprehend as to how a genotoxic agent at low levels of exposures could reduce observed damage below the spontaneous level in the untreated cells and organisms, the research papers mostly omitted it from discussion. Hormesis has been most frequently observed in organisms exposed to low doses of radiation. When a given harmful biological effect is plotted against a series of doses from very low to high doses, it is commonly observed that the adverse effects are greatly reduced in comparison with spontaneous rates and at high doses the adverse effects are increased. It is observed, that in the past, several papers dealing with hormetic effects at low doses were mostly rejected. However, T. D. Luckey in his book *Radiation Hormesis* (CRC Press, Boca Raton, FL, 1991, p. 239) has compiled several of the earlier observations on hormesis by various authors. Among them is a study by Lorenz *et al*. (*J. Natl. Cancer Inst.*, 1955, **15**, 1049–1058) which showed a significant increase in life-span of mice daily irradiated with 0.11cGy gamma-rays. Many years later, Courtade *et al*. (*Int. J. Radiat. Biol*., 2002, **78**, 845–855) confirmed these findings.

The general reluctance to publish reports on hormesis in the early years suggests that it is difficult to introduce strikingly novel observations which contradict the well-established paradigms. In his epoch-making book *The Structure of Scientific Revolutions* (University of Chicago Press, 1962, p. 264), Thomas Kuhn draws a distinction between progress in 'normal science' which is viewed as 'development-by-accumulation' of accepted theories and the discovery of 'anomalies' during revolutions in science which lead to new paradigms. The new paradigms challenge the existing data/concepts and therefore these are resisted and even rejected. It takes time for the new paradigm to get wider acceptance and happens only after a large proportion of the scientific community realizes that it provides effective solutions to overcome existing roadblocks with the earlier ones.

The problem with radiation hormesis has been that it effectively challenged two hitherto unsubstantiated assumptions in basic radiation biology. These are: (i) radiation exposures even at very low doses are harmful; and (ii) radiation doses are cumulative. These two unscientific assumptions form the foundation of the 'linear, no threshold' (LNT) hypothesis put forth by H. J. Muller.

These assumptions were essential in order to buttress the LNT hypothesis put forth by Muller in his Nobel Prize Lecture in December 1946. LNT proposes that for genetic effects induced by ionizing radiation, a 'threshold dose' does not exist as for 'deterministic effects'; even minute addition of dose to the background level would result in an increase in the harmful genetic consequences. Until today, there has been no scientific support to LNT; instead hundreds of papers based on well-designed experimental studies negate the LNT model. Presently well-established 'radioadaptive response' (i.e. a low priming dose to cells and organisms significantly reduces the

adverse effects following their subsequent exposure to near lethal challenging high doses) rejects the fallacy that radiation doses are cumulative. The notion of cumulative dose effect ignores well-known DNA repair mechanisms. In two editorials (*Curr. Sci*., 2014, **106**, 7–8 and *Radiation Prot. Environ*., 2017, **40**, 51–58), Kesavan has pointed out that LNT model lacks scientific evidence. Several scores of papers published before and after his papers (e.g. Calabrese, E. J., *Environ. Res*., 2015, **142**, 432–442; Koana *et al*., *Radiat. Res.*, 2007, **167**, 217–221) have recognized 'hormesis' at low doses and refuted the LNT hypothesis. Credit goes to L. A. Sagan (*Health Phys*., 1987, **52**, 521–525) for calling the attention of radiation researchers to focus on hormesis, which is often encountered, but overlooked!

While formal science is yet to accord recognition to hormesis, the traditional knowledge in India has utilized it in the indigenous systems of medicines over hundreds of years. For example, arsenic and strychnine which are lethal at high doses are used as curative agents at low concentrations. In pest control by the chemical pesticide – imidacloprid, multi-generational exposures to low concentrations result in an enhanced insecticide tolerance (Rix, R. R. and Cutler, G. C., *Pest. Manage. Sci*., 2018, **74**(2), 314–322).

In the recent years, it is beginning to be realized that hormesis also plays a vital role in evolutionary biology. In fact, Costantini, D. (*Dose-Response*, April–June 2019, pp. 1–4, doi:10.1177/1559325819843376SAGE) says that 'hormesis can be an evolutionary expectation'. Environmental stress is one of the driving forces of evolution. Moderate amounts of stress are known to facilitate adaptation by inducing a number of phenotypic and genotypic responses (Badyaev, A. V., *Proc. Biol. Sci.*, 2005, **272**(1566), 877–886; doi:10.1098/rspb.2004.3045). It is known that genetic recombination generates variation required for adaptation of organisms to environmental perturbations. A pioneering finding is that in *Drosophila melanogaster*, the recombination frequency is increased in young flies exposed to either heat or cold stress, but at near lethal temperature extremes, it is decreased (Parsons, P. A., *Biol. J. Linn. Soc.*, 1988, **35**(1), 49–68). In this case, hormesis operates by increasing the recombination frequency and thereby genetic variation.

There is a general notion that oxidative stress is harmful to well-being of the organisms and several drugs and dietary additives are regularly advertised through print and electronic media to counteract it. It is now becoming clear that biological systems do need certain levels of oxidative stress that plays significant role in evolutionary ecology and physiology. The book *Oxidative Stress and Hormesis in Evolutionary Ecology and Physiology: A Marriage between Mechanistic and Evolutionary Approaches* (Springer, Berlin, 2014, p. 348) by D. Constantini illustrates how oxidative stress and hormesis have shaped diversity in organism life-histories, behavioural profiles, morphological phenotypes and ageing mechanisms. It also provides insight into how organisms work and how they evolve to sustain their physiological functions under a vast array of environmental conditions.

It is plausible that hormesis plays different roles in genetic and phenotypic responses to environmental stresses ('abiotic'). Hormesis operating via genetic responses possibly involves nonlethal mutations and/or induction of expression of genes for DNA repair, apoptosis to eliminate cells with unrepairable damage and enzymes which scavenge free radicals and eliminate/reduce reactive oxygen species. At higher doses, gene expressions comprise those governing mitotic catastrophe, necrosis and other forms of cell death. The aforementioned constitute the phenomenon of 'differential gene expression' in cells and organisms exposed to low and high doses. A brief account of differential gene expression (Kesavan, P. C., *Curr. Sci*., 2014, **107**(1), 46–53 and *Radiat. Prot. Environ*., 2017, **40**, 51–58) shows how it demolishes the LNT model.

Hormesis is also reported to induce what is called 'somatic memory' (Sani *et al*., *Genome Biol*., 2013, **14**(6), R. 59). Exposure of *Arabidopsis* seedlings to short mild salt stress resulted in reduced salt uptake and enhanced drought resistance after a second salt stress exposure compared to controls (i.e. the seedlings that were not given mild salt stress).

In basic biology, there are several more phenomena to be discovered. More importantly, the mechanisms need to be elucidated. Hormesis is an exciting field, as this phenomenon is involved in genetic toxicology on one hand, and evolutionary biology on the other. What seems to be the underlying factor is the 'mild stress' which influences gene expression and or epigenetic actions in different ways. So, we have a fertile field for intensification of research in near future.

Climate change exerts varying levels of abiotic stress on the entire marine and terrestrial flora and fauna. In this context, the possible roles of hormesis need to be studied. In order to motivate and initiate research in these unexplored areas, the Department of Science and Technology, Department of Biotechnology, Department of Atomic Energy and other such agencies should consider hormesis as one of the thrust areas for support. Towards the end of the 20th century, John Maddox, editor of *Nature* for over two decades, raised a question 'What remains to be discovered'. He might as well have rephrased the question as, 'What remains to be discovered and what essential corrections need to be made in certain existing discoveries'.

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