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GUEST EDITORIAL

Linear, no threshold model in low-dose radiobiology: ideology versus science

Within a decade after the discovery of X-rays in 1895 and ionizing radiations from the decay of radioactive elements in 1896, several cases of skin cancer among the radiation workers were noticed mainly where exposure of about 600 r (6 Gy) had caused erythema (reddening of skin). A 'threshold dose' was clearly evident. In USA, the National Committee for Radiation Protection and Measurement (NCRPM) fixed the tissue 'tolerance dose' as 1/100th of the erythema dose (600 r) spread over 30 days or 6 r spread over 30 days or 0.2 r/day (in the SI system about 1.86 mGy/day or 680 mGy/year).

The question is how the concept of tissue tolerance dose was abandoned in favour of a stringent 'linear, no threshold (LNT)' model that has no foundation in modern radiobiology. It is the fear of the mutagenic potential of ionizing radiation championed by the Nobel laureate Herman J. Muller that led to linearity at low doses in radiation risk assessment. In 1927, Muller demonstrated that X-rays induce sex-linked recessive lethal mutations in the fruit fly, *Drosophila melanogaster*. His paper (*Science*, 1927, **66**, 84–87; doi:10.1126/science.66.1699.84) won him the Nobel Prize. In his studies, Muller had used high doses of X-rays to irradiate the males (sperm cells). *A much debated question since then has been whether ionizing radiations at low doses and dose-rates are also mutagenic.* Muller's study was not designed to assess the mutagenic effects of X-rays at low doses and at low dose-rates; yet, he thought that there would be *no* threshold dose for genetic damage induced by ionizing radiation, and therefore, a backward extrapolation of the high dose data would provide a measure of genetic risk at low doses.

The 1940s are noted for dethroning 'tolerance dose' and enthroning the 'linear – no-threshold' dogma. Two major events facilitated this paradigm shift. One was the detonation of atomic bombs (A-bombs) over Hiroshima and Nagasaki in August 1945, which raised concerns over possible deleterious genetic effects in the survivors (cancer) and transmission of deleterious mutations to their children. The other was the Nobel Lecture by Muller on 12 December 1946, in which he declared that there is 'no escape from the conclusion that there is no threshold'. The question whether his statement represented merely an 'ideology' to set precautionary principle, or it was supported by unequivocal experimental data assumes considerable relevance today. Two recent papers by Edward J. Calabrese (*Arch. Toxicol*., 2011, **85**, 1495–1498; doi: 10.1007/s00204-011-0728-8; *Toxicol. Sci*., 2012, **126**, 1–4; doi: 10.1093/toxsci/kfr.338), provide evidence that Muller proposed the scientifically inappropriate ideology in spite of his having had knowledge of several papers in the 1930s and 1940s which did *not* support linearity at low doses for genetic damage. It is now known that he rather selectively cited the work of those scientists who reported that linearity best described how radiation affected germ cells of the fruit fly and omitted to refer to several other observations that did *not* support a linear dose-response. What, however, renders Muller's statement rather deceptive is that he had received a manuscript from Curt Stern (an outstanding *Drosophila* geneticist) in early November 1946, which demonstrated a threshold dose-response for mutations in the male *Drosophila* germ cells, exposed to low dose-rates of X-rays. Since Muller's Nobel Lecture was on 12 December 1946, he had about 5 weeks to have given thought to Stern's manuscript written jointly with Ernst Caspari. Further revelation was that Muller had critically reviewed the Caspari–Stern manuscript and asked for its replication while also making a comment ...'I have so little to suggest in regard to the manuscript'. Comments and recommendations were contradictory.

Immediately, after the A-bomb detonations over Hiroshima and Nagasaki in 1945, predictions of possible sharp increases in the incidence of cancers and deleterious mutations in the children to be born to the A-bomb survivors were made. In the 1940s, the structure of the DNA, the genetic material, was not known. Much less was known about its capacity for repair when damaged. Today, we know that when a physical or chemical agent induces DNA damage, there are several repair processes and mechanisms (i.e. apoptosis, necrosis, mitotic catastrophe, etc.) to eliminate the cells with irreparable DNA damage. The view that photons (like bullets) hit the vital targets of a cell for inactivating them (i.e. the 'hit theory') provided tacit support to the LNT hypothesis.

The LNT model enhanced the fear of radiation by predicting that a large proportion of the children born to A-bomb survivors would carry deleterious mutations. Wild imaginations of 'two-headed' babies and other birth defects haunted the exposed survivors and the general public. Social discrimination of the exposed survivors was an offshoot. The fear of ionizing radiation, however, received a jolt when the results of scientific studies carried out by outstanding American and Japanese geneticists conclusively showed that there were *no* deleterious genetic changes in the children of the A-bomb survivors. These studies supported by the Radiation Effects Research Foundation (RERF) included more than 50,000 children of Japanese bomb victims. These children had no chromosomal aberrations, no increased incidence of cancers, no mutations and no birth defects. They were all as normal as the children of the unexposed parents (Schull, W. J. *et al*., *Science*, 1981, **213**, 1220–1222; Neel, J. V. *et al*., *Am. J. Hum. Genet*., 1988, **42**, 663–676). A recent view being increasingly accepted is that ionizing radiations do not induce heritable mutation in humans. Possibly the damaged germ cells are eliminated by apoptosis. With the realization that ionizing radiation does not induce heritable mutations, the focus of stochastic effects was shifted to somatic mutations (cancer). In 1957, E. B. Lewis made a case of radiation-induced leukaemia being linear at low doses (*Science*, **125**, 965–972). Since then, the LNT model is sustained by making predictions of increased incidence of cancer mobidity and mortality among radiation workers, and general public exposed to nuclear accidents such as Chernobyl (1986), Fukushima (2011), etc. Strictly adhering to the dogma 'all radiation is harmful', the Committee of BEIR in its first (BEIR I, 1972) and third (BEIR III, 1980) reports has asserted that 'cancer induction is the only source of somatic risk that needs to be taken into account in setting radiation protection standards for the general population', and 'cancers arising in a variety of organs and tissues are the principle late somatic effects of radiation exposure' respectively. What is, however, unfair from a scientific point of view is that the BEIR reports have consistently omitted about 1000 publications reporting beneficial effects (including significant reduction in the cancer incidence below the spontaneous rates) in humans and experimental organisms exposed to low doses and chronic radiation. The term 'hormesis', describes the phenomenon of induction of stimulation at low doses and inhibition (lethal effect) at high doses. T. D. Luckey's epoch-making book, *Radiation Hormesis* (CRC Press, Boca Raton, 1991) cites several scientific papers on the subject and discusses the possible mechanisms, including stimulation of the immune system.

In a more recent paper, 'Nuclear law stands on thin ice' (*Int. J. Nucl. Law*, 2008, **2**(1), 33–65), Luckey has drawn attention to hormesis with regard to leukaemia (i.e. reduction in the incidence) in the A-bomb victims of Nagasaki. He has taken the data from the BEIR I report, which omits the fact of *reduction in leukaemia* in people exposed to radiation in the range 10 to 70 cGy. The threshold dose for induction of leukaemia is around 100 cGy. Instead, BEIR I report concludes. '…excess leukemia cases in Nagasaki amount to one per 10^6/year/rad'.

There is considerable interest among radiation workers and radiobiologists in the results of the study on total cancer mortality rates based on data from seven cohorts in three countries (Cardis, E. *et al*., *Radiat. Res*., 1995, **142**, 117–132). Luckey has reanalysed the data (*Int. J. Nucl. Law*, 2008, **2**(1), 33–65) and shown that cancer mortality among the nuclear workers is significantly *reduced* in the exposure dose range 0.5–100 cSv. This is in contrast to the statement of Cardis *et al*., 'As there is no reason to suspect that exposure to radiation would be associated with a decrease in any specific type of cancer, one sided tests are presented throughout'. This supports the view that ideology prevails over scientific truth. In their book *Radiation and Health* (Taylor and Francis, 2003), T. Henriksen and H. D. Maillie have analysed the health status of the survivors of A-bombs (Hiroshima and Nagasaki) and arrived at threshold doses for induction of solid cancers and leukaemia at 100 and 200 mSv respectively.

The United Nations Scientific Committee on the Effects of Atomic Radiations has recognized 'radio-adaptive response' in which a small priming dose enhances the tolerance of biological systems to much higher doses. Both hormesis and radio-adaptive response induced by low doses, challenge the LNT model. Currently, the exciting findings are that low and high doses induce differential gene expression. This emphatically dismisses the LNT hypothesis. Further, phenomena such as 'bystander effects' (i.e. unirradiated cells adjacent to irradiated cells behaving as if they were exposed) and 'genomic instability' (i.e. in which the cells several generations after irradiation exhibit DNA damage) also invalidate the LNT model. All these phenomena which represent a universal protection mechanism evolved over millions of years (Bauer, G., *Int. J. Radiat. Biol*., 2007, **83**, 873–878). Ogura, K. *et al*. (*Radiation. Res*., 2009, **171**, 1–8) have shown in *Drosophila* that mutation frequency at 0.5 mGy (0.09%) is significantly lower than that in the unirradiated group (0.32%). The mutation frequency shoots up to 0.77% following an exposure to 10 Gy.

The implications of science over ideology are important to nuclear industry.

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