

## POINT/COUNTERPOINT

*Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to Colin G. Orton, Professor Emeritus, Wayne State University, Detroit: ortonc@comcast.net. Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.*

### Point/Counterpoint: Low-dose radiation is beneficial, not harmful

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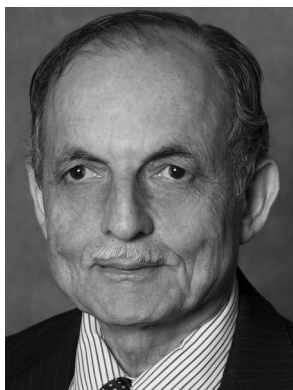
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#### OVERVIEW

The recent rush to embrace the concept that diagnostic x-ray procedures are being overused, or that doses are too high and need to be reduced, is based upon the assumption that low doses of radiation are harmful and should be avoided as much as possible. On the other hand, some believe that such low doses of radiation are not harmful and might even be beneficial. This is the premise debated in this month's Point/Counterpoint.



Arguing for the Proposition is Mohan Doss, Ph.D. Dr. Doss obtained his Ph.D. in Physics in 1980 from Carnegie-Mellon University, Pittsburgh, PA and then spent the next ten years in research positions at the University of Washington, Seattle, Lawrence Berkeley Laboratory, Berkeley, CA, and the Saskatchewan Accelerator Laboratory, Saskatoon, Canada. He then began his career as a Diagnostic Physicist at Regina General Hospital in Regina, Canada. In 2001 he joined Fox Chase Cancer Center Philadelphia, where he is now Associate Professor. He is certified in Nuclear Medicine Physics by the Canadian College of Physicists in Medicine. Dr. Doss's major research interests include biodistribution and dosimetry of new PET imaging agents, small animal PET imaging, and health effects of low dose radiation, and he has published over 50 papers. He is the recipient of the 2014 Outstanding Leadership Award in the field of dose-response by the International Dose-Response Society.



Arguing against the Proposition is Mark P. Little, D.Phil. Dr. Little obtained his D.Phil. in Mathematics from New College, Oxford in 1985. He then worked for the next six years at British Coal, Harrow, London, and Berkeley Nuclear Laboratories, Nuclear Electric, Berkeley, UK. He then continued with his career in epidemiology first as Principal Scientific Officer, Epidemiology Group,

NRPB, Chilton, UK, and then in the Department of Epidemiology and Biostatistics, Imperial College Faculty of Medicine, London, UK. In 2010 he moved to the USA as Senior Investigator at the Radiation Epidemiology Branch, National Cancer Institute, Rockville, MD. Dr. Little's major research interests have included models and epidemiological studies of cancer induction by radiation, risks associated with mobile phones, cancer risks of radiation exposure of children, and deleterious effects of occupational radiation exposures, on which he has published over 150 papers and supervised the work of 20 researchers and graduate students.

#### FOR THE PROPOSITION: Mohan Doss, Ph.D.

##### Opening Statement

The process of oxidative metabolism in living beings sometimes results in the production of free radicals which can cause oxidative damage. Our body has an elaborate system of antioxidants to neutralize these free radicals. This system is not perfect, and a small amount of damage does persist. There is evidence that accumulation of such damage contributes to causing many of the aging-related diseases.

When free radical production is increased, e.g., from low-dose radiation (LDR) exposure (or increased physical/mental activity), our body responds with increased defenses consisting of increased antioxidants, DNA repair enzymes, immune system response, etc. referred to as adaptive protection.<sup>1</sup> With enhanced protection, there would be reduced cumulative damage in the long term and reduced diseases. The disease-preventive effects of increased physical/mental activities are well known.

There is considerable evidence from animal studies supporting the hypothesis that LDR reduces the likelihood of cancer as well as nonmalignant diseases.<sup>2</sup> For humans, (i) epidemiological studies of irradiated populations exhibit reduced risk of cancer from LDR,<sup>3-5</sup> (ii) interspersed adjuvant LDR treatment has resulted in better tumor control and reduced metastases in radiation therapy of non-Hodgkin's lymphoma patients,<sup>4</sup> and (iii) tissues subjected to LDR have shown reduced second cancers per kg in radiation therapy patients.<sup>4</sup> For noncancer diseases in humans, LDR has been shown to control many such diseases.<sup>2,6</sup> Thus LDR is indeed beneficial, as it results in reducing cancer and noncancer diseases.

The present concerns over the carcinogenic potential of LDR are based on the concepts that LDR causes DNA damage resulting in increased mutations, and that the accumulation of mutations can transform a normal cell into an uncontrollably dividing cell, causing cancer.<sup>7</sup> This argument unjustifiably ignores LDR adaptive protective responses.<sup>1</sup> If the effect of LDR adaptive protection is included, there would be reduced DNA damage following LDR,<sup>1</sup> reducing the likelihood of transformation of normal cells into those with malignant phenotypes.

Also, the above mutation model of cancer cannot explain the more than 100% increase in cancers in organ transplant patients (and in AIDS patients), in whom the immune system is suppressed.<sup>8</sup> Hence there is little credibility in the prediction of a small percentage increase in cancer from LDR based on this model. On the other hand, using immune system deficiency as the cause of clinical cancer, many of the characteristics of cancer incidence can be explained.<sup>2</sup> Since LDR boosts the immune system, LDR would be expected to reduce rather than increase the risk of cancer.<sup>1,2</sup>

For both cancer and noncancer diseases, there is a threshold dose below which no increased risk of disease has been observed. The atomic bomb survivor data, considered to be the most important data for estimating radiation effects in humans, have traditionally been used to justify LDR carcinogenic concerns. Recent reanalysis has shown the data are more consistent with a threshold, or radiation hormesis, model than the linear nonthreshold (LNT) model.<sup>4,5</sup>

In view of the above, we can conclude confidently that low-dose radiation is beneficial, not harmful, from both mechanistic and epidemiological considerations.

## AGAINST THE PROPOSITION: Mark P. Little, D.Phil.

### Opening Statement

The detrimental tissue-reaction (deterministic) and stochastic effects associated with moderate and high dose

ionizing radiation exposure are well known.<sup>9</sup> In contrast to tissue-reaction effects, for stochastic effects scientific committees generally assume that at sufficiently low doses there is a positive linear component to the dose response, i.e., that there is no threshold, or beneficial effect.<sup>9</sup> Moreover, there is accumulating direct evidence of excess risk of cancer and various other health endpoints in a large number of populations exposed at moderate and low doses. I review some of this evidence below.

There is evidence of excess cancer incidence of most types associated with radiation exposures of the order of 10–20 mGy from diagnostic x-ray exposure in the Oxford Survey of Childhood Cancers and in various other groups exposed *in utero*.<sup>10</sup> These data remain somewhat controversial, but as Wakeford and Little note “the consistency of the childhood cancer risk coefficients derived from the Oxford Survey and from the Japanese cohort irradiated *in utero* supports a causal explanation of the association between childhood cancer and an antenatal x-ray examination found in case-control studies. This implies that doses to the foetus *in utero* of the order of 10 mSv discernibly increase the risk of childhood cancer.”<sup>10</sup> There is also evidence of excess risk of childhood leukemia associated with natural background radiation exposure, at doses above 5 mGy, in a large UK population-based case-control study.<sup>11</sup> At slightly higher doses, increased risks of leukemia and brain cancer have been observed in patients who were exposed as children to multiple computerized tomography examinations resulting in doses of about 60 mGy to the respective tissues (red bone marrow, brain).<sup>12</sup> The excess risks in all of these studies are consistent with those in the Japanese atomic bomb survivor data.<sup>10-12</sup>

The health risks of low-level exposure to ionizing radiation have been assumed to be related primarily to cancer.<sup>9</sup> Evidence has recently emerged of an association between lower doses (<0.5 Gy) and late circulatory disease. In particular, a recent systematic review and meta-analysis suggested an excess radiation-associated risk at occupational and environmental dose levels (<0.5 Gy).<sup>13</sup> However, the presence and magnitude of the excess circulatory disease risk at low doses is still relatively controversial, and much remains unknown as to the shape of the dose-response curve.<sup>13</sup> There is also accumulating evidence from the Japanese atomic bomb survivors and various other moderate- and low-dose exposed groups of excess risk of cataracts.<sup>14</sup>

There are data, reviewed in Ref. 15 suggesting an increase in stable chromosome aberrations and other markers of biological damage in the peripheral blood lymphocytes of nuclear workers and other groups with protracted radiation exposures. Chromosome changes play a major role in carcinogenesis and there is increasing evidence that the presence of increased frequencies of chromosome aberrations in peripheral blood lymphocytes in healthy individuals could be a surrogate for the specific changes associated with carcinogenesis and therefore indicative of risk.<sup>15</sup> Much other *in vitro* and *in vivo* radiobiological data suggest small adverse effects of moderate dose exposure—in particular there is little data to suggest a threshold in dose, or possible hormetic (beneficial) effects of low-dose radiation exposure.<sup>9, 15, 16</sup>

In summary, excess cancer risks have been seen in a number of (largely pediatrically- or *in utero*-exposed) groups. Excess risks of circulatory disease and cataracts have also been observed in a number of groups exposed to low or moderate doses. The available data on biological mechanisms do not provide general support for the idea of a low-dose threshold or hormesis for any of these endpoints. This large body of evidence does not suggest, indeed is not statistically compatible with, any large threshold in dose ( $>10$  mGy), or with possible beneficial effects.

### Rebuttal: Mohan Doss, Ph.D.

Dr. Little quotes the consistency of childhood cancer risk factors from Oxford and Japanese studies as evidence for carcinogenicity of *in utero* LDR.<sup>10</sup> However, for the Japanese cohort, leukemias were observed only following high dose radiation (HDR), and the risk coefficients were calculated using an assumed LNT model, creating the illusion of increased risk of leukemias from LDR whereas none was observed.<sup>10</sup> Also, cohort studies, which are superior to case-control studies, have not shown increased leukemia risk.<sup>17</sup>

The study of childhood leukemias correlated with background radiation<sup>11</sup> does not consider confounding factors such as breastfeeding. Small changes in the results from consideration of such factors could make the increased leukemias statistically insignificant. The study of childhood cancers following CT scans<sup>12</sup> has methodological issues including the lack of a control group, raising major doubts about its conclusion.<sup>18</sup>

With regard to heart disease, the meta-analysis<sup>13</sup> combined LDR and HDR data, effectively transferring HDR risk to LDR as described in a detailed critique.<sup>19</sup> Regarding cataracts, Chernobyl and atomic bomb survivor data do show a threshold dose for cataracts requiring surgery.<sup>14</sup>

Although Dr. Little expressed concerns regarding LDR-induced chromosome changes, mutation is not the primary determinant of clinical cancer, whereas deficiency in immune system is an important factor.<sup>2</sup> Since LDR *increases* immune system response,<sup>20</sup> it would *reduce* the cancer risk.<sup>2</sup>

Finally, Dr. Little quoted the UNSCEAR 1993 Report<sup>16</sup> as lack of evidence for the beneficial effects of LDR. However, Annex B of the UNSCEAR 1994 Report did discuss the beneficial effects of LDR. Also, many publications in recent years have demonstrated the disease-preventive effect of LDR for cancer and noncancer diseases.<sup>2,4,21</sup>

In conclusion, since the opposing arguments presented by Dr. Little are explainable as discussed above, considering the arguments and evidence presented in my Opening Statement, we can indeed conclude confidently that LDR is beneficial, not harmful.

### Rebuttal: Mark P. Little, D.Phil.

Dr. Doss discusses the well-known involvement of the immune system in cancer, and more generally the role of adaptive response. The critical issue is whether the up-regulation

of the immune system or other forms of adaptive response that may result from a radiation dose offsets the undoubted carcinogenic damage that is caused. The available evidence, summarized in my Opening Statement, is that it does not, and that, given the similarities in risks per unit dose following exposures to very low doses of radiation and with those after moderate dose radiation exposure,<sup>10–12,15</sup> the nonlinearities induced by any adaptive response cannot be substantial. While adaptive response modulating the effect of relatively high challenge doses of radiation (of several Gy) following a smaller priming dose (of usually at least several tens of mGy) is well known experimentally (mostly *in vitro*), it is not universally observed in all experimental systems, nor does it last more than a few days, and there is little or no evidence for its involvement at low priming and challenge doses.<sup>22,23</sup>

Responding to the points relating to existence of a possible dose threshold, or hormetic effect, there is no evidence for these either for cancer<sup>24,25</sup> or for noncancer disease<sup>26</sup> in the Japanese atomic-bomb survivors. Naturally, thresholds below a certain size cannot be ruled out by the Japanese data, but the evidence suggests that thresholds cannot be larger than about 60 mSv for cancer<sup>24,25</sup> or larger than about 0.9 Sv for noncancer disease.<sup>26</sup> Taken together with the other data discussed above,<sup>10–12</sup> thresholds or hormetic effects much above 10 mGy can be largely discounted for cancer.

<sup>1</sup>L. E. Feinendegen, M. Pollycove, and R. D. Neumann, "Hormesis by low dose radiation effects: Low-dose cancer risk modeling must recognize up-regulation of protection," in *Therapeutic Nuclear Medicine*, edited by R. P. Baum (Springer, Berlin, 2013).

<sup>2</sup>M. Doss, "Shifting the paradigm in radiation safety," *Dose-Response* **10**, 562–583 (2012).

<sup>3</sup>B. Cohen, "The cancer risk from low-level radiation," in *Radiation Dose from Adult and Pediatric Multidetector Computed Tomography*, edited by D. Tack and P. Gevenois (Springer-Verlag, Berlin, 2007), pp. 33–49.

<sup>4</sup>M. Doss, "Linear no-threshold model vs. radiation hormesis," *Dose Response* **11**, 480–497 (2013).

<sup>5</sup>M. S. Sasaki, A. Tachibana, and S. Takeda, "Cancer risk at low doses of ionizing radiation: artificial neural networks inference from atomic bomb survivors," *J. Radiat. Res.* **55**(3), 391–406 (2014).

<sup>6</sup>E. J. Calabrese and L. A. Baldwin, "Radiation hormesis: its historical foundations as a biological hypothesis," *Hum. Exp. Toxicol.* **19**, 41–75 (2000).

<sup>7</sup>E. J. Hall and A. J. Giaccia, *Radiobiology for the Radiologist*, 6th ed. (Lippincott Williams & Wilkins, Philadelphia, 2006).

<sup>8</sup>C. M. Vajdic and M. T. van Leeuwen, "Cancer incidence and risk factors after solid organ transplantation," *Int. J. Cancer* **125**, 1747–1754 (2009).

<sup>9</sup>United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), "UNSCEAR 2006 Report, Annex A: Epidemiological studies of radiation and cancer," (United Nations, New York, 2008), pp. 13–322.

<sup>10</sup>R. Wakeford and M. P. Little, "Risk coefficients for childhood cancer after intrauterine irradiation: a review," *Int. J. Radiat. Biol.* **79**(5), 293–309 (2003).

<sup>11</sup>G. M. Kendall *et al.*, "A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980–2006," *Leukemia* **27**(1), 3–9 (2013).

<sup>12</sup>M. S. Pearce *et al.*, "Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study," *Lancet* **380**, 499–505 (2012).

<sup>13</sup>M. P. Little *et al.*, "Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks," *Environ. Health Perspect.* **120**, 1503–1511 (2012).

<sup>14</sup>M. P. Little, "A review of non-cancer effects, especially circulatory and ocular diseases," *Radiat. Environ. Biophys.* **52**, 435–449 (2013).

- <sup>15</sup>M. P. Little *et al.*, "Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do," *Radiology* **251**, 6–12 (2009).
- <sup>16</sup>United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). "Sources and effects of ionizing radiation. UNSCEAR 1993 Report to the General Assembly, with scientific annexes" (United Nations, New York, 1993), pp. 1–922.
- <sup>17</sup>R. L. Brent, "Carcinogenic risks of prenatal ionizing radiation," *Semin. Fetal Neonatal Med.* **19**(3), 203–213 (2014).
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