From:	Carol Marcus
To:	CMRBurns Resource; CMRBARAN Resource; CHAIRMAN Resource
Subject:	[External_Sender] Fwd: Addendum 2 to Petition of 2/9/15
Date:	Tuesday, June 19, 2018 11:53:50 PM
Attachments:	Hormesis Petition to NRC Addendum 2 06-05-18.docx Hormesis Petition to NRC Addendum 2 Calabrese.pdf Hormesis Petition to NRC Addendum 2 Doss.pdf Hormesis Petition to NRC Addendum 2 Ducoff.pdf Hormesis Petition to NRC Addendum 2 Marcus LNT Lecture.pptx Hormesis Petition to NRC Addendum 2 Scott.pdf Hormesis Petition to NRC Addendum 2 Tanooka.pdf

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-------- Forwarded Message --------
Subject: Addendum 2 to Petition of 2/9/15
Date: Tue, 19 Jun 2018 15:44:03 -0700
From: Carol Marcus <csmarcus@ucla.edu>
To:vietti-cook annette NRC <SECY@nrc.gov>

June 19, 2018

Dear Ms. Vietti-Cook:

Attached is an addendum to my petition of 2/9/15. I am also sending a copy by snail mail with hard copies of all the references.

Thank you for your attention and consideration.

Sincerely,

Carol S. Marcus, Ph.D., M.D.

CAROL S. MARCUS, Ph.D., M.D.

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June 19, 2018

Annette L. Vietti-Cook
Secretary, USNRC
Attention: Rulemakings and Adjudications Staff
U.S. Nuclear Regulatory Commission
11555 Rockville Pike
Rockville, MD 20852

Re: Addendum #2 to my petition dated Feb. 9, 2015

Dear Ms. Vietti-Cook:

Some 40 months ago I submitted a petition to the NRC requesting that the linear no-threshold (LNT) theory no longer be used as the basis of radiation protection. With the appearance of a seriously flawed NCRP Commentary (No. 27) last month, I feel compelled to add a second addendum to my petition. One wonders whether the NRC contracted with the NCRP for this commentary in order to get ammunition to refute my and two other similar petitions.

NCRP Commentary No. 27 is dreadful science and pure propaganda, bought and paid for by NRC abusing User Fee money. I am referencing the comments of Dr. Mohan Doss to the draft document. The NCRP ignored his comments. The NRC should not. I am also referencing a paper by Dr. Bobby R. Scott criticizing the epidemiologic "tricks" used to force a linear response at low dose.

I am also referencing an excellent review paper by Dr. Edward J. Calabrese describing the birth and eventual acceptance of the LNT as the basis of radiation protection. The fraud involved is rather shocking.

The NRC should understand that epidemiological studies are not really necessary to prove or disprove LNT. One needs only to go back to the definition of LNT to understand why this myth is wrong. The LNT assumes that one mutation can cause a fatal cancer, and that there is no such thing as radiation repair. A corollary is that therefore it does not matter whether a radiation dose is delivered at low dose over a long time or instantaneously, the effect on carcinogenesis is the same. We know today that one mutation cannot cause a cancer, and that radiation repair is part of the adaptive response of organisms, including humans. We know that chronic doses of radiation are

much less hazardous than the same total dose delivered acutely. Low dose stimulated adaptive responses not only repair the radiation damage, but repair similar damage caused by other noxious agents, primarily oxygen metabolism. **This is what results in radiation hormesis.** For many years the NRC has given alpha radiation doses a relative biological effectiveness (RBE) factor of 20. Why? Because the dense radiation damage caused by the alpha particle's high linear energy transfer (LET) radiation relative to low LET radiation (x-rays, gamma rays, and beta particles) inflicts such concentrated damage that adaptive responses are largely inhibited by that damage. Acceptance of the RBE concept is basically an acceptance of the existence of radiation repair. **And once you accept the existence of radiation repair, LNT is dead.** I am including references from Dr. Howard Ducoff and Dr. Hiroshi Tanooka as well as a Power Point which I was invited to give at a conjoint meeting of the Los Angeles Radiological Society and the Western Regional Society of Nuclear Medicine and Molecular Imaging in January of 2018.

I urge the NRC to accept modern science.

Thank you for your attention and consideration.

Sincerely,

Carol S. Marcus, Ph.D., M.D.
Prof. of Radiation Oncology, of Molecular and Medical Pharmacology (Nuclear Medicine), and of Radiological Sciences (ret.); David Geffen School of Medicine at UCLA

References:

1. Doss, Mohan: Comments on NCRP SC 1-25 Draft Commentary, 16 Oct. 2017.
2. Scott, Bobby R.: A critique of recent epidemiologic studies of cancer mortality among nuclear workers. Dose-Response April-June 2018 pp 1-9.
3. Calabrese, Edward J.: From Muller to mechanism: How LNT became the default model for risk assessment. Environmental Pollution 241(2018) pp 289-302.
4. Ducoff, Howard S.: Radiation hormesis: Incredible or inevitable? Korean J Biol Sci 6 (2002) pp 187-193.
5. Tanooka, Hiroshi: Meta-analysis of non-tumour doses for radiation-induced cancer on the basis of dose-rate. Int J Radiat Biol 87(7)(2011) pp 645-652.
6. The linear no-threshold myth and its corollary, ALARA. Invited lecture delivered 1/20/18 at the Conjoint Meeting of the Los Angeles Radiological Society and the Western Regional Society of Nuclear Medicine and Medical Imaging, Pasadena, CA.

Comments by Mohan Doss on NCRP SC 1-25 DRAFT COMMENTARY

Comments to NCRP by: Mohan Doss, Ph.D., MCCPM, Medical Physicist, Associate Professor, Diagnostic Imaging, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111-2497. Phone: 215 214-1707, E-mail: mohan.doss@fccc.edu ; Website: https://www.foxchase.org/mohan-doss

Disclaimer: The comments below are my personal and professional opinion and do not necessarily represent the views of my employer.

– Mohan Doss

Preamble to the comments:

It is common practice to use the linear no-threshold model to extrapolate radiation cancer risks from high doses to low doses. This is based on the assumption that even a single cell transformed into a cancer cell can cause cancer, based on the somatic mutation model of cancer. Whereas a transformed cancer cell is necessary to cause cancer, it is not sufficient, since the immune system would eliminate any cancer cells (that are formed) or keep them under control (Teng et al., 2008), resulting in covert cancers, which almost everyone has (Greaves, 2014). How important is the immune system in preventing cancers? The importance of the immune system in preventing cancers becomes obvious if we examine what happens to cancer rates when the immune system is suppressed, e.g. in organ transplant patients. For ages older than 60, cancer mortality risk increases by a factor of ~2 in organ transplant patients in whom the immune system is suppressed, and for patients under 19 years, cancer mortality risk increases by a factor of ~80 (Acuna et al., 2016). This huge increase in cancers when the immune system is suppressed cannot be explained by the somatic mutation model of cancer, and so the model cannot be considered to be valid. Since the LNT model is justified only based on the somatic mutation model of cancer, the LNT model cannot be considered to be valid either.

How does low-dose radiation affect DNA damage and immune response? Low-dose radiation does cause some DNA damage. However, this would also result in boosting bodily defenses such as antioxidants and DNA repair enzymes (Feinendegen et al., 2013), and with the boosted defenses, there would be less endogenous DNA damage in the subsequent period, with the ultimate result that there would be less DNA damage following low-dose radiation exposures. This has been observed in studies of fruit flies (Koana and Tsujimura, 2010) and in mice (Osipov et al., 2013). The DNA damage due to low-dose radiation also results in up-regulating RAE1 and other ligands of the NKG2D receptor which activates natural killer cells (Gasser and Raulet, 2006). Natural killer cells play an important role in eliminating cancer cells. Many other aspects of the immune system are also activated by low-dose radiation, as explained in the publication (Farooque et al., 2011). With the boosted immune system, we would expect reduced cancers, and this has indeed been observed following accidental or incidental exposure to low-dose radiation in several cohorts (Kostyuchenko and Krestinina, 1994, Berrington et al., 2001, Sponsler and Cameron, 2005, Hwang et al., 2006), as described in (Doss, 2016). Repeated low-dose irradiation of the whole-body or half-body has resulted in improved survival of non-Hodgkin's lymphoma patients undergoing radiation therapy to the tumor, again demonstrating the cancer eliminating effect of low-dose radiation (Sakamoto, 2004). The elimination of the cancers occurred not only in the irradiated parts of the body but also outside the field of radiation in patients given half-body irradiation (Pollycove, 2007). Thus, this elimination of cancer cells due to low-dose radiation appears to be a systemic effect. By

ignoring such publications, international advisory bodies such as NCRP have consistently supported the LNT model. As seen in the comments below, none of the publications that have been cited to support the LNT model in the NCRP SC 1-25 DRAFT COMMENTARY provide evidence for the LNT model.

Comments on specific lines of the NCRP SC 1-25 DRAFT COMMENTARY:

Page 10, Line 254 states: the level of risk from low-LET types of radiation at low doses and low dose rates remains uncertain because of the intrinsic uncertainties in results from the epidemiologic and radiobiological studies of low doses of radiation

This statement (that the level of risk from low dose radiation is uncertain due to intrinsic uncertainties in epidemiological studies) is valid only if the radiation risk increased according to the LNT model in the epidemiological studies. Several epidemiological studies involving total average dose of <100 mSv have shown significant reduction of cancers, e.g. the following three studies:

1. Taiwan apartment residents, Hwang, et al., http://www.ncbi.nlm.nih.gov/pubmed/17178625
2. Radiation workers in Nuclear Shipyard Worker Study, Sponsler and Cameron, http://www.inderscience.com/info/inarticle.php?artid=7915
3. British radiologists who entered service during the period 1955 to 1979. Berrington et al, http://www.ncbi.nlm.nih.gov/pubmed/11459730

Such publications are routinely ignored by NCRP and other advisory bodies, enabling them to make the claim that the level of risk from low doses of radiation is uncertain. These data completely contradict the LNT model and there is not much uncertainty in these results.

Page 10, Line 259-261: For over 40 y the linear nonthreshold (LNT) dose-response model has been commonly utilized for low-LET radiation when developing practical and prudent guidance on ways to protect workers and the public from the potential for harmful effects from radiation while balancing the beneficial, justified, and optimized uses of radiation in our society.

Prudent guidance?? LNT model has led to fear of the smallest amount of radiation and has led to death to over a thousand people in Fukushima because of the evacuations and prolongation of the evacuation. Thus, there is nothing prudent about the guidance given to the governments and the public based on the LNT model.

Page 11, Lines 293-297: resulting in a statistically significant dose response for all incident solid cancer over the dose range 0 to 100 mGy (Grant et al., 2017). Formal dose threshold analyses for both solid cancer incidence and mortality are compatible with no dose threshold, and a pure quadratic model provided a significantly poorer fit than a linear dose-response model (Grant et al., 2017; Ozasa et al., 2012).

Cancer incidence data are not as reliable as cancer mortality data for determining the harm from radiation because of the significant presence of overdiagnosis of cancers that do not develop into metastatic disease and cause illness and deaths (Welch and Black, 2010). Ozasa et al.'s cancer mortality data show a significant curvature in the dose-response for cancer mortality for the dose region of 0 to 2 Gy that is not explicable using the LNT model. Including the data at higher doses does make this curvature insignificant, and so Ozasa et al. have claimed that the overall data are consistent with the LNT

model. However, the inconsistency of the LNT model with the data for the 0-2 Gy range remains. This is due to the significant reduction of cancers observed in the 0.3 to 0.7 Gy range. How can one explain the significant reduction of cancers when the dose increases from ~0.15 Gy to ~0.5 Gy using the LNT model? One cannot, and therefore these results should lead to the rejection of the LNT model, considering the importance of the LSS data. On the other hand, these data are consistent with radiation hormesis (Doss, 2012, Doss, 2013, Sasaki et al., 2014).

Page 12, Lines 319-321, INWORKS found an association between the cumulative external photon dose to the red bone marrow (RBM) and mortality from leukemia [excluding chronic lymphocytic leukemia (CLL) excess relative risk (ERR) Gy–1 of 3.0, 90 % confidence interval (CI) of 1.2 to 5.2].

Please note that there was a negative association between radiation dose and chronic lymphocytic leukaemia mortality rate whereas for other leukemia types there was a positive association. This type of variation in dose–response between leukaemia types—that low-dose radiation risks for specific subsets of leukaemias increase while decreasing for others— is to be expected because of statistical fluctuations, and the increased risk for one or more subsets might meet the statistical criterion for significance, especially when the lower 90% CI is used. Referring to such subset data to imply increase in leukaemias due to low-dose radiation (as was claimed by the INWORKS publication (Leuraud et al., 2015)) is misleading. If the entire leukemia mortality rate is utilized, including for CLL, there would be no significantly increased ERR, even with the 90% CI.

The assumption by the INWORKS study that the occupational radiation dose of radiation workers is the total radiation dose of the workers would be valid for earlier worker cohorts when medical radiation doses were low and occupational doses were high. However, the assumption would not be valid for later years when the medical doses are high and occupational doses are very low. Thus, the dose-response calculated by INWORKS study is not valid and the study's conclusions are questionable. Finally, their claim that they have presented strong evidence for low-dose radiation leukemia risk when they have used 90% CIs is without any merit.

Page 14, Lines 396-398: A recent pooled analysis of external thyroid irradiation in childhood and subsequent thyroid cancer in nine studies showed a significant dose response from 0 to 100 mGy and no evidence of nonlinearity (Lubin et al., 2017).

This publication discusses thyroid cancer incidence. It is well known that thyroid cancer incidence is subject to overdiagnosis and is dependent on screening as well as the use of diagnostic imaging, since incidental observation of thyroid nodules during imaging can trigger additional tests and result in diagnosis of thyroid cancer. Large increases in thyroid cancer diagnosis have not resulted in reducing thyroid cancer mortality in the USA (Welch and Black, 2010) and in South Korea (Ahn et al., 2014), indicating the detected thyroid cancers are not clinically relevant. Therefore, the conclusion of this publication may not be relevant for public health. They should have studied thyroid cancer mortality rather than incidence, for keeping their study relevant to public health.

Page 20, Lines 549-552 states, quoting NCRP Report from 1993 "based on the hypothesis that genetic effects and some cancers may result from damage to a single cell, the Council assumes that, for radiation-protection purposes, the risk of stochastic effects is proportional to dose without threshold, throughout the range of dose and dose rates of importance in routine radiation protection."

This concept, that cancers may result from damage to a single cell, is not consistent with evidence. In fact, almost everyone has covert cancers(Greaves, 2014) (i.e. cancer cells or pre-cancerous cells) in their bodies but everyone is not diagnosed with cancer. Please see the Preamble on Page 1 for more discussion of the invalidity of this concept.

Page 16: Table 1.1

Comments on individual entries in the table

The following studies were rated as providing strong support for the LNT model

Life Span Study (LSS), Japan atomic bomb (Grant et al., 2017)

Cancer incidence data are not as reliable as cancer mortality data for determining the harm from radiation because of the significant presence of overdiagnosis of cancers that do not develop into metastatic disease and cause illness and deaths. Ozasa et al.'s cancer mortality data (Ozasa et al., 2012) show a significant curvature in the dose-response for cancer mortality for the dose region of 0 to 2 Gy that is not explicable using the LNT model. Including data at higher doses does make this curvature insignificant, and so Ozasa et al. have claimed that the overall data are consistent with the LNT model. However, the inconsistency with the LNT model for the 0-2 Gy range data remains. This is due to the significant reduction of cancers observed in the 0.3 to 0.7 Gy range. How can one explain the significant reduction of cancers when the dose increases from ~0.15 Gy to ~0.5 Gy using the LNT model? One cannot, and therefore these results should lead to the rejection of the LNT model, considering the importance of the LSS data.

INWORKS (U.K., U.S., French combined cohorts) (Richardson et al., 2015)

The publication by (Richardson et al., 2015) has attempted to answer the question: "Is protracted exposure to low doses of ionising radiation associated with an increased risk of solid cancer?" by studying the relationship between occupational radiation doses and solid cancers in workers who were employed in nuclear industry during the period 1944-2004 in France, UK, and USA. If occupational radiation doses were the predominant radiation doses of the workers, and other radiation doses were relatively unchanged during the period of the study, their use of occupational radiation dose as a surrogate for total radiation dose in the analysis would be justified. Let us examine if this is indeed true.

As indicated in the article by Thierry-Chef et al., (Thierry-Chef et al., 2015) during the early years of the employment (1950s to 1970s), the annual occupational doses of this cohort were relatively high whereas in later years they were very low, and the mean occupational radiation dose of the cohort was reported to be ~21 mSv by (Richardson et al., 2015). The medical radiation dose the workers would have received, on the other hand, had an opposite time trend, because of the much higher use of diagnostic imaging during the later period compared to the earlier period of the study, assuming the workers had similar rates of diagnostic imaging as the general population. For example, the per capita annual medical radiation dose in the USA was approximately 0.25 mSv in the 1960s (an estimate), 0.5 mSv in early 1980s (NCRP, 2009), and 3 mSv in 2006 (NCRP, 2009). For the 12 year median employment period of the workers, the medical radiation doses would be ~3 mSv in the early years and ~21 mSv in the later years (using the average of data for the early 1980s and 2006). Not accounting for this large change in the medical radiation dose during the period of the study in comparison to the average occupational dose of 21 mSv is a major flaw in the design of the study, rendering the calculated dose-response relationships not trustworthy. Hence, this study does not provide any useful information on the association between prolonged radiation exposure and solid cancers, contrary to the study's claim.

In addition, the use of 90% CIs renders the conclusion of this study weak. In fact, only one of the data points in their graph (Figure 4.2 of the NRCP Draft) would show increased cancer risk if 95% CIs were used.

Tuberculosis fluoroscopic examinations and breast cancer (Little and Boice, 2003)

The underlying data (Boice et al., 1991) has very course dose-binning, with the lowest bin having doses from 0-99 cGy, and so includes low-dose radiation as well as high-dose radiation. Such coarse binning can mask the presence of curvature in the dose response. E.g., the data of Miller et al. (Miller et al., 1989) for the Canadian fluoroscopy study, with finer binning, shows a hormetic reduction of breast cancer mortality in the low-dose range (Pollycove, 1998) whereas the follow-up study of the same cohort by Howe, et al. (Howe and McLaughlin, 1996), with course binning, does not show the hormetic reduction.

Childhood atomic-bomb exposure (Preston et al., 2008)

The data shown in Table 4 of the publication indicates there was no significantly increased risk of cancer for the lowest dose category (0.005 to 0.2 Sv) for childhood exposures.

Childhood thyroid cancer studies (Lubin et al., 2017)

This publication discusses thyroid cancer incidence. It is well known that thyroid cancer incidence is subject to overdiagnosis and is dependent on screening as well as the use of diagnostic imaging, since incidental observation of thyroid nodules during imaging can trigger additional tests and result in diagnosis of thyroid cancer. Large increases in thyroid cancer diagnosis have not resulted in reducing thyroid cancer mortality in the USA (Welch and Black, 2010) and in South Korea (Ahn et al., 2014), indicating the detected thyroid cancers are not clinically relevant. Therefore, the conclusion of this publication may not be relevant for public health. They should have studied thyroid cancer mortality rather than incidence, for keeping their study relevant to public health.

The following studies were rated as providing moderate support for the LNT model

Mayak nuclear facility (Sokolnikov et al., 2015)

Low dose data do not show increased cancer risk. ERR consistent with no increased risk.

Techa River, nearby residents Davis et al., 2015)

Low dose data do not show increased cancer risk. ERR consistent with no increased risk.

Chernobyl fallout, Ukraine and Belarus thyroid cancer (Brenner et al., 2011)

This study measures thyroid cancer incidence, which is not indicative of thyroid cancer, due to the large potential for overdiagnosis. Increased screening for thyroid cancer and increased detection of thyroid cancer have not led to decrease in thyroid cancer mortality (Ahn et al., 2014), confirming the vast overdiagnosis in thyroid cancers. Also, examining only thyroid cancers following radiation exposures, and ignoring the (possibly hormetic) effect on other cancers, is not reasonable since it presents a misleading picture on the overall carcinogenic effect of the radiation exposure. Studies that have examined mortality from both thyroid and other cancers e.g. (Franklyn et al., 1999) have reported significant reduction of mortality from other cancers (e.g. lung cancer) and overall cancers even with increased mortality from thyroid cancers.

Breast cancer studies, after childhood exposure (Eidemüller et al., 2015)

These studies, of skin hemangioma patients treated with radiation, involved high-doses of radiation to parts of breast. Whereas the average dose to the breast may be low, because of the large mass of the

breast, some parts of the breast would be exposed to very high levels of radiation. Such high doses can indeed be carcinogenic and cancers observed in such studies cannot be ascribed to low-dose radiation exposures.

In utero atomic-bomb exposure (Preston et al., 2008)

The data shown in Table 4 of the publication indicates there was no significantly increased risk of cancer for the lowest dose category (0.005 to 0.2 Sv) in utero exposures. A review of a large number of studies, including the above article (Brent, 2013) has indicated that no definitive conclusion can be drawn regarding the carcinogenic effect of in-utero exposures.

In utero exposures, medical (Wakeford, 2008)

The data on postnatal diagnostic medical exposures and childhood leukemia risk are inconclusive, as discussed in this publication.

Canadian worker study (Zablotska et al., 2013b)

This study no longer shows significantly increased cancer risk in the radiation workers following the exclusion of the faulty Canadian data.

The following studies were rated as providing weak to moderate support for the LNT model

Japanese worker study (Akiba and Mizuno, 2012)

This study does not show significantly increased cancer risk in the radiation workers.

Chernobyl cleanup workers, Russia (Kashcheev et al., 2015)

Standardized mortality ratio for all cancers is 0.95 (0.92-0.99 95% CI) (Figure 5 of the publication) indicating reduction of cancers in this cohort following low-dose radiation exposures.

U.S. radiologic technologists (Liu et al., 2014; Preston et al., 2016)

Overall cancer mortality rate for the radiologic technologists was significantly lower, with SMR of 0.82 (0.80, 0.84 95% CI) (see Table A2 in Supplementary materials). This significant result is not even mentioned in the abstract, while mentioning increase of some cancers, presenting a misleading picture of the health effects of low-dose radiation.

Mound facility (Boice et al., 2014)

Overall cancer mortality rate was significantly lower in the radiation workers with SMR of 0.86 (0.79–0.93 95% CI)

Rocketdyne facility (Boice et al., 2011)

Overall cancer mortality rate was significantly lower in the radiation workers, and relative risk for all cancer mortality did not show a significant increase.

Medical x-ray workers, China (Sun et al., 2016)

Data below 0.15 Gy are consistent with no increase in cancer risk (Figure 2 of the publication). Shape of dose-response cannot be determined reliably from these data due to the large error bars.

Background radiation levels and childhood leukemia (Kendall et al., 2013)

ERR for Leukemia was barely significant. Important confounding factors such as breastfeeding and daycare attendance were not considered, and such factors can make the results insignificant. Need better data to make any reliable conclusion.

Taiwan radiocontaminated buildings, residents (Hwang et al., 2008)

This article is an update to the study of the residents of the Co-60 contaminated buildings in Taiwan that was reported in 2006 (Hwang et al., 2006). Hwang at al used Cox proportional hazard models to determine the hazard ratios for cancer incidence in the irradiated residents, and claimed that cancer risks were statistically significant for leukaemia excluding chronic lymphocytic leukaemia. They also

claimed that radiation exposure was associated with a marginally significant increased risk of breast cancer. On the other hand, in the 2006 report, which compared the cancer rates of the irradiated population with the cancer rates of an equivalent control population, 95 cancer cases were observed up to the end of 2002 in contrast to 114.9 expected (Hwang et al., 2006), resulting in standardized incidence ratio (SIR) for all cancers of 0.83 (95% CI: 0.66-0.99), indicating a significant reduction of all cancers following low-dose irradiation. Let us now examine whether SIR in the 2008 updated data shows a significant reduction of all cancers.

The Hwang 2008 publication reported that 117 cancer cases were observed in the cohort up to the end of 2005. To calculate the SIR, we need to know the expected number of cancer cases for the same period. In the 2006 report, Hwang et al reported that the expected number of all cancers was 114.9, and the average age of the irradiated cohort was 33.3 at the end of 2002 (The average age of the population was 17.1 at the time of irradiation and the cohort was followed up for an average of 16.2 years) (Hwang et al., 2006). Hence, for the Hwang 2008 publication, the average age at the end of the study period (end of 2005) would be 36.3. The cancer incidence rates for the ages of 33.3 and 36.3, obtained by interpolation of the average of male and female rates from Taiwan Cancer Registry (TCR, 2008), are 86.3 and 117.7 respectively, indicating there would be an increase in cancer incidence between these two ages by a factor of ~1.37. Therefore, considering the 114.9 expected cases to the end of 2002 (Hwang et al., 2006), the expected cancer cases up to the end of 2005 would be 157, resulting in SIR of 117/157 = 0.75 (95% CI: 0.61-0.88). Thus, the reduction of cancer rate in the irradiated cohort is significant in the Hwang 2008 data also. The NCRP Draft report has failed to discuss this significant reduction of overall cancers in this irradiated cohort.

Note: A similar analysis of the updated data recently published (Hsieh et al., 2017) on this cohort shows that SIR for that study would be 0.84 (95% CI: 0.74-0.95), again indicating reduction of all cancers in the irradiated cohort.

Pediatric CT examinations (Pearce et al., 2012)

These data do not provide any valid evidence for increased cancer risk following pediatric CT examinations because of the potential for reverse causation. Data are not consistent with A-bomb survivor data (Boice, 2013, Boice, 2015).

Childhood leukemia studies (Wakeford and Little, 2003)

A review of a large number of studies (Brent, 2013), that includes the above article, has indicated that no definitive conclusion can be drawn regarding the carcinogenic effect of in-utero exposures.

In utero exposures, Mayak and Techa (Akleyev et al., 2016)

No significantly increased risk was observed for cancers in the irradiated cohort.

The following studies were rated as providing no support or inconclusive support for the LNT model

Hanford 131I fallout study (Davis et al., 2004)

No increased risk of thyroid cancer observed in children exposed to radioactive iodine.

Kerala, India, high natural background radiation area (Nair et al., 2009)

No significantly increased risk was observed for cancers.

Yangjiang, China, high natural background radiation area (Tao et al., 2012)

No significantly increased risk was observed for cancers.

U.S. atomic veterans (Beck et al., 2017)

Only dosimetry mentioned. No cancer risks reported.
Fallout studies (aggregate of eight studies) (Lyon et al., 2006)
No significantly increased risk of thyroid cancers for doses below 410 mGy. Thyroid cancer cases are highly subject to overdiagnosis.

As seen in the comments above, none of the studies listed in Table 1.1 of the NCRP Draft have demonstrated increased cancer risk from low-dose radiation.

The NCRP Draft Report has failed to consider several studies that have shown significant reduction of cancers following low radiation exposures. Some of them are listed below:

1. Residents of Co-60 contaminated buildings in Taiwan, (Hwang et al., 2006) http://www.ncbi.nlm.nih.gov/pubmed/17178625. As discussed on Page 6 of these comments, the 2008 (Hwang et al., 2008) and 2017 (Hsieh et al., 2017) updates of the reports on these cohorts continue to show the hormetic effect of overall reduction in cancers, though it is not discussed in the publications.
2. Radiation workers in Nuclear Shipyard Worker Study, (Sponsler and Cameron, 2005) http://www.inderscience.com/info/inarticle.php?artid=7915
3. British radiologists who entered service during the period 1955 to 1979. (Berrington et al., 2001) http://www.ncbi.nlm.nih.gov/pubmed/11459730
4. Residents of evacuated villages near Mayak Nuclear Weapons facility (Kostyuchenko and Krestinina, 1994) http://www.ncbi.nlm.nih.gov/pubmed/8178130
5. Repeated low-dose irradiation of the whole body or half body for non Hodgkin's lymphoma patients undergoing radiation therapy resulted in improving survival of the patients (Sakamoto, 2004) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2657505/

Epilogue

As seen above, none of the evidence quoted by NCRP committee in support of the LNT model, including the ones claimed to be strong evidence for the LNT model, shows increase of cancers following low-dose radiation exposure. Also, the NCRP committee has failed to even acknowledge the evidence that supports radiation hormesis. In fact, many of the publications quoted by NCRP show reduction of overall cancers in the population groups exposed to low levels of radiation.

The analysis presented above, of the (Hwang, 2008) publication on Page 6, shows that hormetic effects of overall reduction in cancers can be masked by the standard practice of calculating hazard ratios using a linear no-threshold model.

Whereas cancer risk does increase approximately linearly with radiation dose at high doses, extrapolating such linear dependence to low doses, without even a single valid evidence for increased cancer risk at low doses, cannot be justified.

It is unfortunate that advisory bodies including NCRP have failed to recognize the above analyses in the interpretation of published data and have recommended the use of the LNT model. It is also unfortunate that they have ignored and dismissed evidence supporting radiation hormesis and have failed to discuss

and refute publications that have shown the evidence for radiation hormesis when attempting to justify the LNT model.

There have been indeed many major adverse consequences due to the unjustified support of the LNT model by advisory bodies such as NCRP. The claim that there is no threshold dose for increased cancer risk, due to the adoption of the LNT model, has sowed the fear of even the smallest amount of radiation among the public and professionals. This has led to panic evacuations in Fukushima and Chernobyl following nuclear reactor accidents resulting in over 1000 deaths. Such evacuations also destroyed the local economies and livelihoods of hundreds of thousands of people, for no benefit of reduced cancers.

The fear of low-dose radiation is also a major obstacle in conducting clinical trials of low-dose radiation exposures for cancer treatment and prevention, even though there is plenty of evidence supporting the use of low-dose radiation for cancer prevention and treatment.

Please take into consideration the above comments and withdraw your support for the LNT model, to begin a new era in the use of low levels of radiation for improved health. Thanks.

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Commentary

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A Critique of Recent Epidemiologic Studies of Cancer Mortality Among Nuclear Workers

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Abstract

Current justification by linear no-threshold (LNT) cancer risk model advocates for its use in low-dose radiation risk assessment is now mainly based on results from flawed and unreliable epidemiologic studies that manufacture small risk increases (ie, phantom risks). Four such studies of nuclear workers, essentially carried out by the same group of epidemiologists, are critiqued in this article. Three of the studies that forcibly applied the LNT model (inappropriate null hypothesis) to cancer mortality data and implicated increased mortality risk from any radiation exposure, no matter how small the dose, are demonstrated to manufacture risk increases for doses up to 100 mSv (or 100 mGy). In a study where risk reduction (hormetic effect/adaptive response) was implicated for nuclear workers, it was assumed by the researchers to relate to a "strong healthy worker effect" with no consideration of the possibility that low radiation doses may help prevent cancer mortality (which is consistent with findings from basic radiobiological research). It was found with basic research that while large radiation doses suppress our multiple natural defenses (barriers) against cancer, these barriers are enhanced by low radiation doses, thereby decreasing cancer risk, essentially rendering the LNT model to be inconsistent with the data.

Keywords

cancer, dose response, hormesis, LNT, radiation, risk assessment

Introduction

Epidemiologic studies (eg, case–control and cohort) of cancer or cancer mortality risk, if any, associated with low radiation doses (<100 mSv) are seriously flawed and in many cases unlikely to distinguish between alternative risk models (eg, threshold, hormetic, linear no-threshold [LNT], etc) when key sources of uncertainty are addressed and only low-dose data are used.[1] Data manipulations (adjustments) and descriptive (empirical) multivariate models used hide nonlinearity in the dose–response relationships and can create phantom risk (ie, manufactured risk) that increases at low doses.[1] Uncertainty about confounder influences is usually neglected,[2] and no consideration is usually given to biological mechanisms of cancer induction and mechanisms of cancer prevention via the body's powerful natural defenses (barriers) that can be enhanced by low-dose radiation.[1]

The following (A-G) are approaches used in epidemiologic studies that can distort the shape of the dose–response relationship for radiation-induced cancer and can create phantom (manufactured) risk increases at low radiation doses:

A. *Ignoring missing dose*: In some instances, important dose contributions cannot be accounted for, so the contributions are missing from the reported doses, thereby blaming any claimed harm on smaller doses than were actually incurred.
B. *Dose lagging*: An adjustment is used where a part of the radiation dose (a large amount in some cases[3-5]) is simply thrown away, which allows blaming harm (cancer) on a smaller radiation dose irrespective of the cause of the harm. Dose lagging supposedly corrects for dose wasting, irrespective of whether radiation

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exposure is responsible for the observed cancer. However, the thrown-away dose may have contributed to reducing the cancer latent period for those who develop cancer. For those who do not develop cancer, the thrown-away dose may have stimulated the body's natural defenses and if so may have led to preventing the cancer that would otherwise have occurred for other reasons (eg, environmental, dietary, etc). No dose is wasted in either case.

C. *Forced application of the LNT model*: In many studies, the LNT model is applied, irrespective of the data considered. This effectively makes LNT outcome the null hypothesis. This misleading null hypothesis, which along with other procedures employed (eg, intercept locking, negative slope constraint[3-5] but not positive slope constraint) can lead to phantom (ie, imaginary) risks for low doses. Such phantom risks would be far less likely under the more appropriate null hypothesis of no radiation effect when the data analysis is restricted to low doses and addresses variability with repeated measurements (replications).

D. *Intercept locking of the LNT line*: When LNT outcome is the implied null hypothesis, usually the intercept (at assigned dose 0; for controls or baseline consideration) is locked (ie, not treated as a free parameter), so that the intercept location does not reflect the variability in the dose–response data near the origin. Only one free parameter (LNT line slope, not the intercept) related to radiation exposure is used. The intercept locking procedure is mainly used with relative risk (RR) or excess RR (ERR) characterization (or similar measures) as a function of radiation dose or lagged dose.

E. *Averaging over a wide dose interval*: For a radiation dose group considered, doses differ for each individual so that the average dose for the group is used, with no consideration of the dose distribution for the group. Often the doses within a dose group span a wide range. The within-dose-group averaging makes it more difficult to detect a nonlinear dose–response relationship. Such nonlinearity has been revealed when individual-specific rather than group-averaged dose has been used.[6] Modern computational methods allow for individual-specific doses to be used.[6]

F. *Ignoring key uncertainties*: Uncertainty about key covariates (eg, measurement-error related) is often not addressed in epidemiologic studies. Radiation dose errors (random and systematic) are often not addressed and can be quite important for the low-dose region.

G. *Disregarding of biological mechanisms*: The LNT model is not supported by currently known biological mechanisms of cancer development and cancer prevention. Thus, its use requires ignoring the indicated currently known, biological mechanisms both for cancer occurrence and prevention, as is done in many epidemiologic studies.

The hallmarks of cancer (development) include the following[7]: (1) genome instability and mutations, (2) resisting cell death, (3) deregulating cellular energetics, (4) sustaining proliferative signaling, (5) evading growth suppressors, (6) avoiding immune destruction, (7) enabling replicative immortality, (8) tumor-promoting inflammation, (9) activating invasion and metastasis, and (10) inducing angiogenesis. That such complex processes can be jointly caused by a single radiation ionization event (a single radiation hit can cause cancer) is highly implausible. Further, there is a hierarchy of natural defenses[8-11] that are differentially stimulated by low radiation doses that must be overcome for cancer to occur, which are the bases for the hallmarks of cancer suppression.[12]

The hallmarks of cancer suppression include the following: (1) epigenetically regulated DNA damage repair and antioxidant production, (2) p53-independent selective apoptosis (ie, selective removal) of aberrant cells including neoplastically transformed cells, (3) reducing cancer promoting inflammation, and (4) anticancer immunity.[12]

Epidemiologic studies (eg, cohort, case–control) are seriously limited as far as informing about low-dose-radiation-related cancer risks, if any. The limitations in part relate to unaddressed sampling variability,[1] confounding (known and unknown), collinearity of potential covariates, and other issues.[2]

The problem of unaddressed sampling variability (for the baseline cancer risk estimate), although quite important, has been largely ignored for low-dose radiation carcinogenic effects studies.[1] Sampling variation means the changes in results over replication, if replications were to be carried out. However, replications are generally not carried out in epidemiologic studies since it is impractical to do so. Indeed, a claimed increased (or decreased) risk after a low radiation dose may instead relate to variability in the estimated cancer risk (baseline risk estimate) in the absence of a radiation influence or to an invalid extrapolation from high to low doses, yielding hypothetical results.

A cohort study (but not a case–control study) provides an estimate of the population-level baseline cancer risk (BR), and the estimate is used as a reference point for evaluating radiation effects (eg, increased cancer risk). An epidemiologic–study–related estimate of the population-level BR has been called the derived BR (DBR). An epidemiologic–study–related estimation of the population-level cancer RR has been called the derived RR (DRR). Similarly, the estimated ERR has been called the derived ERR (DERR). The definitions of DBR, DRR, and DERR were recently introduced to facilitate addressing variability in outcomes of epidemiologic studies under circumstances where replicate results would be available.[1]

Case–control studies provide estimates of the population-level odds ratio (OR) for cancer. An epidemiologic–study–related estimation of the population-level cancer OR has been called the derived OR (DOR).[1] The DOR for cancer (or cancer mortality) is used by some researchers as an estimate of the DRR. However, the DOR always overestimates the DRR, and

the overestimation increases as both the DOR and the DBR increase.[13]

Case–control studies cannot produce a DBR (for cancer incidence or mortality) and are particularly prone to serious selection bias for a given control group. In fact, selecting controls to adequately match for lifelong exposure to carcinogens (a likely major influence on the DBR) and for unknown confounders (eg, carcinogenic bacteria[14]) is essentially impractical, as such information is not known for controls or cases. In fact, a DRR considered greater than 1 for low radiation doses (which may be reported for case–control studies) may be a phantom increase.[1]

Often, a misleading null hypothesis is used in epidemiologic studies of cancer or cancer mortality RR (or relative mortality rate [RMR] or standardized mortality rate [SMR]): An assumed LNT function of radiation dose is used as the null hypothesis, which is a departure from the type of null hypothesis used in toxicological research using animals (eg, null hypothesis of no radiation effect). With the LNT as the null hypothesis approach, high-dose data are usually included which essentially guarantees a positive slope to the fitted LNT line with a locked intercept (ie, intercept is not a free parameter). Using the indicated null hypothesis along with LNT-line-intercept locking, and including high-dose data, makes it more likely than not that study findings will be insufficient to reject the null hypothesis. In turn, this allows for misleadingly stating that study findings were consistent with the LNT model, so that it is justifiable to use the model-related findings to implicate harm (hypothetical cancers) from very small radiation doses such as are associated with elevated natural background radiation and medical imaging (eg, computed tomography). In addition to using a misleading null hypothesis (LNT model with locked intercept), some investigators also impose a constraint on negative slopes derived in data fitting but not on positive slopes, thereby favoring risk increases over risk decreases. This was done in 3 cancer mortality–related examples (epidemiologic studies) discussed in this article for irradiated humans, which claim evidence for increase cancer risk at low doses.

The DBR for a given type of cancer (or cancer mortality) evaluated in a radiation effects study is influenced by environmental, dietary, and other carcinogens exposures during life and the variable responses to carcinogenic stresses (eg, different genetic susceptibilities, different adaptive responses [adaptive protection]) of the different individuals used in the study. The adaptive protection relates to molecular-, cellular-, tissue-, and organ-level natural defenses against the indicated carcinogenic stresses.[1,10,15-18]

To prevent harm from mild carcinogenic stresses, cells and tissue in the body mount complex responses that are regulated by changes in adaptive-response-gene expression. The gene expression level can differ by more than a factor of 10 for different individuals.[19,20] Interindividual variability is also associated with the hallmarks of cancer suppression. Thus, much greater than 10-fold variation between individuals in their overall responses to low-level stress (eg, low-dose radiation) is highly plausible. Such large variability likely impacts variability in the DBR from replicate epidemiologic studies, where they carried out. Thus, it is important to address variability in the baseline cancer risk estimates in epidemiologic studies of cancer or cancer mortality DRR and related concepts. Not doing so favors obtaining the wrong results for a population of interest, especially for low radiation doses. For example, if the minimum and maximum value for the DBR for a given type of cancer (or cancer mortality) varies by a factor of 2 (ie, 2-fold) over replicate studies directed at a specific population, then a cancer (or cancer mortality) DRR as high as 2 or as low as 0.5 for a study could arise (although with low probability) without any radiation-induced harm or benefit (eg, hormetic effect). Methods described in the next section allow addressing the issue of DBR variation and are applied to show evidence for phantom cancer risk generation in 3 epidemiologic studies and evidence for hormesis/adaptive response in another study of cancer mortality among nuclear workers.

Generating DRR Distributions Under the Null Hypothesis of No Radiation Effect

Using modern computational tools, distributions of the DRR can be generated under the null hypothesis of no radiation effect for an irradiated group. The distribution percentiles obtained (based on sampling from the DBR distribution only) can be used in testing for a plausible increase or decrease in the DRR for a given study. To consider radiation-caused cancer (or cancer mortality) to be plausible for an irradiated group, the DRR obtained in an actual epidemiologic study needs to exceed a criterion value (eg, 95% [percentile] or 97.5% value) based on the distribution of the DRR under the null hypothesis of no radiation effect.

To address the issue of variability in the baseline risk estimate for replicate cohorts of heterogeneous humans with differing life histories, a simulation study was previously conducted[1] where the same uniform distribution for the DBR (for cancer or cancer mortality) was repeatedly sampled (one risk value for controls [baseline] and one paired risk value for the irradiated group per each sampling round) in order to obtain a phantom risk distribution for the DRR under the null hypothesis of no radiation effect. Using the uniform distribution of the DBR is a conservative approach.[1] WinBUGS software[21] was used to generate the phantom risk distribution for DRR.[1]

Percentiles of 2.5% and 97.5% of the phantom DRR distribution were used to evaluate the plausibility of claimed LNT cancer risk increases reported in epidemiologic studies of populations of nuclear workers. Linear no-threshold lines and their 90% or 95% confidence intervals (CIs) reported from the epidemiologic studies were evaluated for their credibility for the low-dose region (doses up to 100 mSv or mGy). Where RMR or SMR was evaluated rather than RR, the same approach was used.

Not considering at least a 2-fold variation (minimum to maximum) in the DBR for a cohort study could lead to accepting a DRR of 1.5 as indicating a 50% increase in cancer risk as

Table 1. Percentiles 2.5% and 97.5% for the Distribution of the Derived Relative Risk (DRR) or Derived Relative Mortality Rate (DRMR) for a Heterogeneous Population of Humans Under the Null Hypothesis of No Radiation Effect When the Derived Baseline Cancer Risk (DBR) or Derived Baseline Cancer Mortality Rate (DBMR) Is Uniformly Distributed (Conservative Assumption) From the Minimum to Maximum Value.

Fold Change From Minimum to Maximum Value of DBR or DBMR	2.5% (Percentile) Value for DRR or DRMR Distribution[a]	97.5% (Percentile) Value for DRR or DRMR Distribution[a]
1.25	0.842	1.19
1.5	0.732	1.37
1.75	0.650	1.54
2	0.588	1.71
2.5	0.497	2.02
3	0.433	2.31

[a]Results for the percentile values are based on Monte Carlo evaluations with WinBUGS software[21] using 10 000 iterations per fold-change category as reported elsewhere.[1] Each iteration represented a study replicate.

a result of low-dose radiation exposure, when there may be no credible evidence for such an increase.[1] Thus, evaluations carried out in this article were based on a 2-fold variation, even though a higher variation could easily be justified.

For case–control studies for which the DOR is used without adjustment as an estimate of RR, the DRR obtained may be overestimated by as much as a factor or 2.[13] This relates to fundamental differences between population OR and population RR. When logistic regression is used in a cohort study (and presumably also for a case–control study), an additional bias (for DRR overestimation) as large as a factor of 2 may occur.[22] Thus, claims of elevated cancer or cancer mortality risk based on logistic regression–related, case–control studies with DOR <3 may be registering phantom-elevated risk.[1]

Results previously[1] obtained using WinBUGS[21] software for the 2.5% (percentile) and 97.5% (percentile) values for the phantom DRR distribution are presented in Table 1 for a 1.25-, 1.5-, 1.75-, 2-, 2.5-, and 3-fold variation in the DBR. Ten thousand iterations were used for each fold-change category. Each iteration simulated the outcome of a study replicate under the null hypothesis of no radiation effect. Table 1 can be used to assess the plausibility of a risk increase or decrease (hormetic effect/adaptive response) after low radiation doses.

In using Table 1, it is important to consider that DBR and similar concepts are not based on the total population (eg, total population of the United States) but rather a relatively small group (eg, nuclear workers in the United States) as used in cohort studies. Thus, larger variability in DBR (which is based on a relatively small group) is more likely than for the total population as reflected by annual changes. The variability reflected in Table 1 is based on a very conservative approach (assumed uniform distribution). Other distributions could also be considered, but this is beyond the scope of this publication.

Results of Recent Epidemiologic Studies of Nuclear Workers and Why They Are Unreliable

Evidence of Manufactured (Phantom) Risks From a 2007 Cancer Mortality Study

A 15-country collaborative cohort study was conducted by researchers[3] to supposedly provide direct estimates of cancer risk following protracted low doses of ionizing radiation. Their analyses were based on 407 391 nuclear industry workers monitored individually for external radiation exposure and 5.2 million person-years of follow-up. What the researchers referred to as ERR is here referred to as DERR (which varies over replicate studies should they be carried out). The researchers reported that a significant association was seen between radiation dose and increased cancer mortality (DERR/lagged- Sievert (Sv): 0.97, 90% CI: 0.28-1.77; 5233 deaths) for all cancer deaths. Lagged radiation dose in Sv (10 years of dose thrown away) was used by the researchers. Poisson regression was employed along with the default LNT model (misleading and inappropriate null hypothesis) to look for associations between lagged radiation dose and cancer mortality. The intercept for the LNT line was locked at DERR = 0, and a constraint was placed on the value of a negative slope (could not be more negative than −1/maximum dose), but no constraint was imposed on positive slope values (another misleading LNT-model-linked procedure used in epidemiologic studies). The study was indicated to be the largest analytical epidemiologic study of the effects of low-dose protracted exposures to ionizing radiation at the time it was conducted and implicated increase cancer risk from radiation doses <100 mSv.

Throwing away radiation dose is common for the indicated group as well as for some others. Throwing away dose artificially inflates the DERR per unit dose. Taking at face value, the DERR per unit dose of 0.97/lagged-Sv and related 90% CI yields corresponding values of 0.00097/lagged-mSv (90% CI: 0.00028/lagged-mSv to 0.00177/lagged-mSv). For a dose of 100 mSv, the calculated upper 90% CI value on the DRR would be 1.177 which according to Table 1 (for a reference 2-fold variation in the DBR for mortality and uniform distribution) is nowhere close to being a plausible increase as the value is well within the phantom risk increase region. The upper risk estimate needs to be larger than the percentile 97.5% value of 1.71 to be considered as a plausible increase. The corresponding percentile 95% value (not shown in the table) for phantom risk increases is 1.60 which is clearly larger than 1.177. There is no evidence for harm from radiation doses up to 100 mSv (low-dose region).

Evidence of Manufactured (Phantom) Risks From a 2015 Cancer Mortality Study

Epidemiologists[5] carried out another cohort study related to nuclear workers to evaluate associations between protracted low-dose radiation exposures and cancer mortality (excluding

leukemia mortality). Excess relative mortality rate (ERMR) was evaluated and here is referred to as derived ERMR (DERMR) to be consistent with other terminology used related to subsets of a total population of interest in that variability in study outcome would be expected with replication. The DERMR per Gy (ie, LNT line slope) for mortality from cancer (excluding leukemia) is the focus in their paper which inappropriately used LNT as the null hypothesis. Both LNT-line-intercept locking and constraints on negative (but not positive) slopes were used. Follow-up encompassed 8.2 million person years. Of 66 632 known deaths by the end of follow-up, 17 957 were due to solid cancers. The reported DERMR per Gray of lagged radiation dose for cancer mortality was 0.48/lagged-Gy (90% CI: 0.20/lagged-Gy to 0.79/lagged-Gy; 10 years of dose accumulation was thrown away). With 10 years of radiation dose being thrown away (ie, lagged), monitored radiation-exposed persons working for 10 years or less were apparently assigned no radiation dose. In addition, the cumulative doses from natural background radiation sources and from diagnostic imaging during medical examinations were excluded. Importantly, the zero-dose group does not actually represent no radiation exposure since natural background radiation and medical exposure were not accounted for and assigning a dose of 0 impacts the slope of the LNT line.[23]

Taking the above-derived risk coefficients of the researchers[5] at face value gives 0.00048/lagged-mGy (90% CI: 0.0002/lagged-mGy to 0.00079/lagged-mGy) for the DERMR per lagged-mGy. For a dose of 100 mGy, the calculated upper 90% CI value on the derived relative mortality rate (DRMR) would be 1.079, which, according to Table 1 and for a reference[1] 2-fold variation in the DBR for mortality and uniform distribution, is also nowhere close to being a plausible increase as the value is well within the phantom risk increase region (upper risk value needs to exceed the percentile 97.5% value of 1.71). The corresponding percentile 95% value is 1.60 (not shown in the table). There is no evidence for harm from radiation doses up to 100 mGy (low-dose region).

Evidence of Manufactured (Phantom) Risks From a 2015 Leukemia Mortality Study

Epidemiologists[4] conducted a cohort study which quantified possible associations between protracted low-dose radiation exposures and leukemia mortality among radiation-monitored (for external radiation) adult nuclear workers employed in France, the United Kingdom, and the United States. A cohort of 308 297 radiation-monitored workers employed for at least 1 year by the nuclear industry was used. The cohort comprised 8.22 million-person-years of follow-up with a focus on deaths from leukemia, lymphoma, and multiple myeloma. Some workers may have had internal contamination by various radionuclides (isotopes of uranium, plutonium, etc), but doses from such exposures could not be evaluated and therefore are not accounted for in the assigned radiation doses.

Regression based on an assumed Poisson distribution of outcomes was used, along with the default LNT model (an inappropriate null hypothesis as previously indicated) to investigate possible associations between assigned red bone marrow absorbed radiation dose (estimates) and leukemia mortality. The DERR was evaluated with stratification by country, calendar period, sex, and age. The researchers reported DERR per unit lagged dose for leukemia mortality, excluding chronic lymphocytic leukemia. The reported value for the DERR was 2.96/lagged-Gy (90% CI: 1.17/lagged-Gy to 5.21/lagged-Gy), with 2 years of dose accumulation thrown away. This corresponds to 0.00296/lagged-mGy (90% CI: 0.0017/lagged-mGy to 0.00521/lagged-mGy). For a dose of 100 mGy, the calculated upper 90% CI value on the DRR would be 1.521 which also according to Table 1 (for a reference[1] 2-fold variation in the DBR and uniform distribution) is an implausible increase as the value is within the phantom risk increase region (upper risk value needs to exceed percentile 97.5% value of 1.71 to be considered plausible). The corresponding percentile 95% value is 1.60 (not shown in the table) for phantom risk which is also greater than the upper risk estimate of 1.521. There is no evidence for harm from radiation doses up to 100 mGy (low-dose region).

Evidence for Possible Hormetic Effects in a 2017 Cancer Mortality Study

Another epidemiologic study focused on a cohort of French nuclear workers that were badge-monitored for external radiation exposure.[24] Annual exposure to external ionizing radiation (mainly γ rays) expressed in Sv was assessed for each worker and expressed as personal penetrating photon dose equivalents in soft tissue at a depth of 10 mm (Hp(10)). Some workers were exposed to neutrons and some may have had internal contamination from radionuclides (isotopes of plutonium, uranium, and others), but radiation doses were not known so were not included in their dose estimates. The average cumulative photon dose equivalent (Hp(10)) for exposed workers was 25.7 mSv.

The mortality of 59 004 nuclear workers was followed-up between 1968 and 2004, with the average follow-up being 25 years. At the end of the follow-up, workers average age was 56 years and 6310 workers had died. Using national mortality rates as a reference, SMR was calculated. The SMRs were stratified by calendar period in 7 categories (1968/1973/1978/1983/1988/1993/1998+), sex, and attained age in 5-year intervals (<20/25/30/.../75/80/85+). Byar approximation was used to estimate 95% CI for the SMRs.

Use of this cohort allowed for comparing the mortality of irradiated nuclear workers to that of the French general population. The focus was on cancer and circulatory disease mortality. Interestingly, the derived SMRs (DSMRs) were less than 1 (suggestive of hormetic effect/adaptive response) for death from all causes, death from solid cancers, death from tumors of the lymphatic and hematopoietic tissue, death from circulatory diseases, and death from digestive diseases as shown in Table 2. For these causes of death, the DSMR ranged from 0.37 (digestive diseases) to 0.81 (tumors of the lymphatic and

Table 2. Mortality in a French Nuclear Worker Cohort Compared to That of the French Population, 1968 to 2004 Based on 2017 Publication.[24]

Cause of Death	Observed Deaths	Derived Standardized Mortality Ratios (DSMR)	95% Confidence Interval (CI)
All causes	6310	0.60	0.59-0.62
Solid cancers	2356	0.68	0.65-0.71
Tumors of lymphatic and hematopoietic tissue	196	0.81	0.70-0.94
Circulatory diseases	1483	0.62	0.59-0.65
Respiratory diseases	200	0.41	0.36-0.47
Digestive diseases	270	0.37	0.32-0.41

hematopoietic tissue) with the upper 95% CI value ranging from 0.41 (digestive diseases) to 0.94 (tumors of the lymphatic and hematopoietic tissue) and the lower 95% CI value ranging from 0.32 (digestive diseases) to 0.7 (tumors of the lymphatic and hematopoietic tissue).

The DRMR results in Table 1 can be used to assess the importance of these findings for DSMR because they also apply to DSMR under the null hypothesis of no radiation effect. Results for mortality from respiratory diseases and from digestive diseases are clearly consistent with the possibility that the nuclear workers radiation exposures may have helped to protect them (hormetic effect/adaptive response) from the indicated diseases. As demonstrated for residential radon exposure, chronic low-level irradiation can reduce the occurrence of lung cancer mortality.[6,25] However, the researchers did not consider the possibility the results in Table 2 may be due to hormesis/radiation adaptive response. Rather they claimed the results to demonstrate strong healthy worker effects.

Because of the results presented in Table 2, it makes no sense to forcibly apply the LNT model to such data. Even so, the researcher applied the LNT model anyway and in most cases LNT line slopes were not significantly positive, as should be expected.

Implications of Findings Presented

The indicated findings reported in this article point to the unreliability of epidemiologic studies, such as carried out by a highly influential group,[3-5,24] so far as informing about cancer risks, if any, associated with low radiation doses. Even so, some group members[5] misleadingly concluded regarding one of their studies that "The study provides a direct estimate of the association between protracted low-dose exposure to ionizing radiation and solid cancer mortality." Equally of concern, the World Health Organization issued a press release[26] related to the indicated study that states "This study strengthens the evidence of a causal relationship between solid cancers and exposure to low doses of ionizing radiation." This is quite unfortunate, given the serious flaws in many epidemiologic studies and the unreliability of the research findings as also pointed out elsewhere.[1,23]

In trying to implicate a causal relationship between cancer mortality and occupational exposure to low doses and dose rates of ionizing radiation, the indicated group of epidemiologists[3-5,24] not only ignored major sources of radiation exposure (medical and natural background radiation exposure, neutrons, and internal α and other forms of radiation) but also failed to recognize that cumulative occupational radiation dose over years for nuclear workers is correlated with cumulative exposure to many other carcinogens (dietary, airborne, carcinogenic bacteria, etc) by a given age. Thus, there is no way to convincingly prove a causal relationship between cancer mortality and cumulative occupational radiation exposure to low doses (eg, <100 mGy or 100 mSv) delivered at low rates.

Because usage of the LNT model for low-dose radiation risk assessment for cancer induction (or cancer mortality) is now mainly justified based on epidemiologic studies, it is important to be aware of the following, which can strongly bias study findings:

A. Radiation dose uncertainties should be well characterized. However, this is most often not the case including studies of A-bomb survivors where radiation doses from black rain–related radioactive fallout[27] have been disregarded and may represent a large part of the total dose for some individuals.
B. Epidemiologists (but not toxicologists) in many cases throw away a large part of the radiation dose (ie, they use lagged dose) when evaluating radiation risks. There is no validity to arbitrarily throwing away radiation dose, since for a given cancer victim, the cancer may not be related to radiation exposure. Even for instances where radiation is responsible for the cancer as may occur after a high dose, the thrown-away dose may have reduced the latent period and thus was not wasted. Also, for those not developing cancer, the dose that is thrown away may have helped to prevent (ie, via enhancing the body's multiple natural cancer barriers[11,12]) cancer induction by other carcinogens, in which case would not be wasted but rather beneficial. Indeed, natural cancer barriers are enhanced by low but not high radiation doses.[12]

Researchers[2] previously assessed limitations of epidemiologic studies so far as demonstrating causality for cancer. They discussed challenges related to addressing the following: (1) selecting the appropriate cancer risk model, (2) errored covariate (confounders) assignments (eg, wrong or missing covariates), (3) accounting for different genetic backgrounds, (4) variable coding and multiple selection, (5) measurement errors for independent variables, (6) diagnostic suspicion and recall biases, and (7) classification errors. A main finding of their

work was that statistical modeling alone may be unreliable for establishing causal links. This is indeed the case for the low-dose and dose-rate results[3-5,24] reported by epidemiologists for nuclear workers.

A misleading procedure often used by LNT advocates is to use the LNT model (related to radiation dose) as the null hypothesis. As might be expected given the indicated complexities of epidemiologic data analyses, LNT as the null hypothesis is unlikely to be rejected in cases where high-dose data are included and the intercept is locked rather than being a free parameter.[1] This was the case for a number of studies,[3-5,24,28-30] some of which received wide news media and other coverage related to claiming harm (cancer) from low radiation doses and dose rates, with supporting statements by the World Health Organization[26] for one such study.

Importantly, it appears that methods used in epidemiologic studies have not been rigorously tested for reliability and accuracy so far as generating reliable radiation dose–response relationships. Now there is a way to unmask any serious flaws (should they exist) in the epidemiologic study methods for studies of low-dose radiation carcinogenic effects as discussed below.

Modern computational methods (random-variable-based) allow for generating simulated epidemiologic data sets using stochastic-multivariate models that allow for covariate errors (eg, radiation dose error, smoking history error, dietary carcinogen intake error, etc) and for stochastic cancer (or cancer death) occurrence or for loss to a competing risk. Different data sets for use in epidemiologic studies generated by modelers using a set of plausible hidden, stochastic, multivariate models (known only to those who generate the data) could be provided to different epidemiologists who would then use their preferred data analysis methods (for covariates such as radiation dose, age at exposure, gender, smoking history, alcohol consumption, etc) and models to analyze the data set (or sets) they were provided.

The indicated approach would allow for assessing the reliability of the epidemiologic methods employed in cohort, case–control, and other studies of populations exposed to low radiation doses and dose rates in addition to other risk factors. For example, if the hidden model for the population RR for cancer of a specific type was of the radiation-dose-threshold or hormetic or other nonlinear type and the epidemiologic study using the simulated data (for a cohort rather than the total population, with some high-dose data included) and preferred data analysis methods concluded that the DRR (or corresponding derived absolute risk or DERR) as a function of radiation dose was consistent with the LNT model, then this would reveal the study methods used as being unreliable.

Rigorously revealing serious flaws in the epidemiologic study methods, should this occur, may promote interest in making improvements in the methods. Without such improvements, then it would be in the best interest of the world community to rely less on findings from epidemiologic studies of health effects of low radiation doses and dose rates. An international effort (with stochastic modelers, epidemiologists, and other specialists as needed) could be mounted to address the study methodology reliability issue and could perhaps be sponsored by organizations such as the Department of Energy, the Environmental Protection Agency, the Nuclear Regulatory Commission, and the National Institutes of Health.

A major finding of this research and supported by research findings elsewhere[6,23,25,31-35] is that cancer risk estimates derived for low radiation doses with forced use of the LNT model in epidemiologic studies should be seriously questioned. In addition, they appear to be phantom risks. Further, such risk projections are radiation phobic and the phobia has been proven to cost thousands of lives related to the Chernobyl (abortions) and Fukushima (overly stressed fragile elderly evacuees) nuclear accidents.[1] The scientific, medical, and regulatory communities need to be made aware of LNT misuse (eg, used as null hypothesis and employed with locked intercept and constraining negative but not positive slopes and including high-dose data to force a positive slope) by LNT advocates among the epidemiological community, the serious harm LNT has caused and is likely to cause in the future if the misuse problem is not addressed.

Alternative approaches for conducting epidemiologic studies not requiring forcibly applying the LNT or any other model to cancer data are now recognized and should be considered.[6,25,35]

Findings reported in this commentary related to large variation in the baseline risk estimate (ie, DBR) are based on the conservative assumption of a uniform distribution (from minimum to maximum) by as much as a factor or 2 or more. The assumed large variation is supported by combined DRR data from multiple epidemiologic studies (ecological and case–control) of lung cancer morbidity related to residential radon exposure that were analyzed by Dobrzyński et al[36] in their recent publication. The reported large variation in DRR (more than a factor of 3) at low annual equivalent doses (<10 mSv) can be explained on the basis of large variation in the baseline risk estimate since there was no correlation between lung cancer morbidity DRR and annual equivalent dose to the lung.

Conclusions

Seriously flawed epidemiologic studies of cancer or cancer mortality risk, if any, associated with low radiation doses and dose rates are the main bases for the current use of the radiation phobia–promoting, biological mechanisms–devoid, LNT model. The promoted fear of even small, harmless radiation doses has led to thousands of lives being lost related to the Chernobyl and Fukushima nuclear power plant accidents and to many avoidances of potentially lifesaving diagnostic imaging with low radiation doses. Basic radiobiological research has revealed that low doses of radiation enhance our body's natural cancer barriers, while high doses reduced the barriers, rendering the LNT model inconsistent with the data. Risk of cancer from low radiation doses should not be based on epidemiologic studies that forcibly apply the LNT model as the default model (null hypothesis) and use data analysis

procedures that greatly favor an LNT outcome, irrespective of the cancer data, as was done in studies critiqued in this article.

Authors' Note

The views and conclusions contained herein are those of the author and should not be interpreted as necessarily representing policies or endorsement of his affiliated institution.

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From Muller to mechanism: How LNT became the default model for cancer risk assessment☆

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ABSTRACT

This paper summarizes the historical and scientific foundations of the Linear No-Threshold (LNT) cancer risk assessment model. The story of cancer risk assessment is an extraordinary one as it was based on an initial incorrect gene mutation interpretation of Muller, the application of this incorrect assumption in the derivation of the LNT single-hit model, and a series of actions by leading radiation geneticists during the 1946–1956 period, including a National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel (Anonymous, 1956), to sustain the LNT belief via a series of deliberate obfuscations, deceptions and misrepresentations that provided the basis of modern cancer risk assessment policy and practices. The reaffirming of the LNT model by a subsequent and highly influential NAS Biological Effects of Ionizing Radiation (BEIR) I Committee (NAS/NRC, 1972) using mouse data has now been found to be inappropriate based on the discovery of a significant documented error in the historical control group that led to incorrect estimations of risk in the low dose zone. Correction of this error by the original scientists and the application of the adjusted/corrected data back to the BEIR I (NAS/NRC, 1972) report indicates that the data would have supported a threshold rather than the LNT model. Thus, cancer risk assessment has a poorly appreciated, complex and seriously flawed history that has undermined policies and practices of regulatory agencies in the U.S. and worldwide to the present time.

1. Introduction

While a role of the environment in affecting the occurrence of cancer has long been known (e.g., the occurrence of testicular cancer in chimney sweeps) (Pott, 1775), transitioning this recognition of concern into an experimental science proved to be difficult as seen in the series of failures to induce skin cancer in animal models during the early years of the 20th century. Finally, after many failed attempts, in 1918 Japanese researchers made the experimental breakthrough by the repeated administration of coal tars to the ears of rabbits to produce papillomas and carcinomas (Yamagiwa and Ichikawa, 1918). This seminal finding paved the way for experimental research to assess possible environmental causes of cancer.

In a similar manner, researchers early in the 20th century began to explore whether it was possible to induce mutations in plants and animals (Campos, 2015). While it took nearly three decades, Muller (1927a) reported that X-rays induced gene mutations in fruit flies, narrowly beating three independent teams of botanists who likewise reported inducing transgenerational phenotypic changes with X-rays/radium.[1] Muller's findings, like that of the Japanese cancer researchers, quickly transformed the field. For his discovery, Muller received the Nobel Prize in 1946. The current paper clarifies the historical foundations of the LNT single-hit dose-response model, its unique dependence upon the gene mutation interpretation of Muller in 1927, and how this interpretation became accepted by the scientific community and regulatory agencies. Most importantly, it will be shown that: (1) Muller's claim that the X-ray-induced transgenerational phenotypic changes were due to gene mutations was an interpretation lacking convincing evidence; (2) the induced transgenerational phenotypic changes

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[1] In January 1927, in the *Proceedings of the National Academy of Sciences* (Communicated January 14, 1927), Gager and Blakeslee (1927) were the first to report cases of gene mutations. Thus, Muller's July 1927 publication was the second to report the gene mutation phenomenon. Muller gained acclaim because he produced many mutations quickly. However, Gager and Blakeslee repeatedly reminded the field of their primacy. In his effort to secure scientific honors, Muller (1927a, 1928a) failed to cite the earlier work of Gager and Blakeslee (1927).

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were due to chromosomal deletions and aberrations, not Muller's proposed gene "point mutations"; (3) these developments undermine the historical and scientific foundations of the LNT single-hit model since it was built upon Muller's gene mutation interpretation (see Calabrese, 2017a for a significantly expanded analysis of this issue); (4) Muller and other leading U.S. radiation geneticists would collude in a series of articles to promote acceptance of the LNT, making deliberate deceptions and misrepresentations of the scientific record; (5) the deceptive practices would infiltrate and culminate in the actions of the U.S. NAS BEAR I Genetics Panel that recommended adoption of the LNT model by regulatory and public health agencies in 1956 (Anonymous, 1956) (See Calabrese, 2015a, b, c); (6) the mouse data used to provide the experimental basis for the subsequent reaffirmation of the LNT for cancer risk assessment was similarly problematic, that is, the BEIR I NAS/NRC (1972) Committee used a flawed historical control group that significantly overestimated risk in the low dose zone, yielding a linear dose response (see Calabrese 2017b, c); (7) use of a corrected historical control value yields a threshold rather than the linear dose response and; (8) this new assessment indicates that the LNT has been flawed from the start, yet national and international regulations have continued to be based upon it (Calabrese, 2015a, 2017d).

2. Muller and mutation

Hermann J. Muller, a radiation geneticist at the University of Texas/Austin, truly burst upon the national and international scene following his presentation at the 5th International Genetics Congress in Berlin during September 1927. His highly anticipated presentation convincingly demonstrated to an eager and massive grouping of geneticists from around the world that X-rays could induce transgenerational phenotypic changes in *Drosophila* perhaps providing a mechanism for evolution. Muller claimed that these changes were the result of induced gene mutation, tiny genomic changes, with Muller coining the term "point mutation". Muller not only claimed to be the first to ever artificially induce gene mutation, he produced copious numbers of them. Muller's presentation drew especially great anticipation since his article in the journal *Science*, published about three months earlier, only discussed some of the new findings, inexplicably failing to show any data. Thus, Muller, with a flair for the dramatic, disproved the doubters and set himself on a path that 19 years later would result in another trip to Europe, Stockholm, to receive the Nobel Prize in Biology and Medicine.

Muller's stunning results soon inspired: (1) numerous laboratories to redirect their research to the assessment of ionizing radiation induced mutations (Campos, 2015); (2) the creation of the Genetics Society of America (GSA) (1931) a few years later, bringing zoologists and botanists who were researching genetics under one integrated professional society; (3) the concept of a Proportionality Rule that describes the linear dose response for the ionizing radiation induced mutation response (Muller, 1930a); (4) the interdisciplinary collaboration of leading physicists and radiation geneticists to create the first mechanism-based cancer risk assessment model (LNT single-hit model) using target theory (Timofeeff-Ressovsky et al., 1935) and (5) the discovery of chemically induced mutations by Charlotte Auerbach in the 1940s (Auerbach and Robson, 1946). The reach of Muller was long and influential, inspiring the focus of Carson (1962) in her seminal book *Silent Spring*, that is normally given credit for starting the environmental revolution of the late 1960s and 1970s and continuing to the present. Muller wrote a powerfully supportive review of *Silent Spring* in the New York Herald Tribune published on the Sunday prior to the book's publication four days later (Muller, 1962). Thus, the X-ray induced "gene" mutation findings of Muller and his leadership over the next 40 years would profoundly affect the environmental movement and the fields of genetic toxicology, cancer risk assessment and numerous medical, radiation and public health practices.

There is therefore little question that Muller had a major influence on the scientific community and the general public, originating from the belief that he had actually demonstrated that X-rays produce gene mutations in the fruit fly. While the above summary highlights some of the societal impact of Muller, there are important parallel concerns with Muller's scientific legacy. In brief, Muller (1927a) made the critical assumption that the numerous X-ray induced transgenerational/heritable phenotypic changes that he reported were the result of induced gene mutations. Muller knew that transgenerational/heritable phenotypic changes via X-ray-induced chromosomal aberrations was not a significant finding (Muller, 1928b). This had been reported previously and would not affect an understanding of basic biological themes such as evolution and its potential mechanism. This was why Muller (1927a) entitled his groundbreaking July 22, 1927 article in *Science* "The Artificial Transmutation of the Gene".

3. Point mutations vs gene deletions

Within three months of his presenting these findings at the Genetics Congress[2] in Berlin (September, 1927) (Muller, 1928a), Muller (1927b) would publically express concerns that some might think that all he had done was to shoot large holes (i.e., deletions) throughout the genome with the high doses of X-rays used, noting that such concerns/questions were initiated by his longtime friend, close colleague, collaborator and confidante, Edgar Altenburg, a professor of genetics at Rice University. Within this anticipatory defensive context, at the December 1927 AAAS meeting at Nashville, Tennessee and in an April 1928 presentation to the U.S. National Academy of Sciences (NAS) Muller (1928b) tried to discount the possibility that his reported transgenerational phenotypic changes were due principally to heritable chromosome changes, suggesting as proof observations of reverse mutations (e.g., X-ray-induced reversible changes in eye color – red to white). Patterson and Muller (1930) would subsequently publish a massive 82-page paper supporting his argument. This was proof enough for Muller that X-rays induced small mutations in genes rather than vast and large deletions as suggested by Altenburg. Muller used apparent reverse mutation findings to preempt potential challenges to his gene mutation interpretation. Muller argued further that the assumed point mutations closely mimicked the type of gene mutation changes underlying the mechanism of evolution as might be seen with spontaneous gene mutations, spending much of the next

[2] The proceedings of this Congress contains Muller's paper, which included the data used for the basis of the Nobel Prize in 1946. The Congress proceedings paper of Muller had substantial limitations, being somewhat sloppily written, having three experiments, each with important weaknesses. It also lacked a methods section and provided no references, including no acknowledgement of the report by Gager and Blakeslee (1927) that preceded his *Science* paper (Muller 1927a) for the reporting of ionizing radiation induced gene mutation by six months. The general substandard quality of the manuscript made me wonder whether the Nobel Prize paper of Muller from the Congress proceedings had ever been peer-reviewed. A July 8, 1946 letter from Muller to Altenburg (Muller 1946a) revealed that the manuscript that he read at the Congress was exactly the same as published in the subsequent proceedings. Thus, it is virtually certain that the Nobel Prize research of Muller was not peer-reviewed (Calabrese, 2018). However, Muller had been acculturated into the need for and process of peer-review by Thomas Hunt Morgan, his Ph.D. advisor at Columbia University. Morgan helped to create the *Journal of Experimental Zoology* in 1903, which had a modern peer-review process from the start. In fact, Muller would publish several articles in this journal by 1920 (Harrison, 1945). Thus, Muller was part of a culture of peer-review as a necessity and expectation. Yet, he avoided it for the seminal findings for which he would be honored with the Nobel Prize.

Table 1
Stadler's challenge to Muller. quotes from Stadler (1932, 1954).

Stadler (1932). **Proc 6th Intern Cong Genet 1:274–294**
"To state that an induced variation is a gene mutation is not to explain it but merely to label it."
Page 274-275
"We do not demonstrate that a chemical change has occurred; we simply infer, since no mechanical explanation can be found, that the variation must be due to this invisible mechanism."
Page 275
"We may define mutation as a transmissible change in the gene. But we identify mutation by experimental tests, and these tests are not such as to establish conclusively, in specific instances, that a change within the gene has occurred."
Page 275
"In effect, any Mendelizing variation which cannot be shown to be due to a change involving more than one gene is a mutation."
Page 275
"... the occurrence of reversion is not proof that the original mutation could not have been due even to a deficiency."
Page 292
Stadler (1954). **Science 120(3125):811–819**
"But there was no test to identify mutations due to a change within the gene; it was simply inferred that the mutants that could not be identified as the result of specific mechanical causes were, in fact, due to gene mutation in the ideal sense (11)."
Page 813

40 years in this quest for a mechanism for evolution.

While these findings would temporarily satisfy the questioning and doubtful Altenburg and others, supporting the X-ray-induced point mutation interpretation, this concern would not go away but actually grew principally due to the persistent questioning and new research insights of the plant radiation geneticist Stadler (1932, 1954), Muller's most staunch, yet objective, respected, competitor and critic (Calabrese, 2017e).

4. Stadler challenges gene mutation interpretation

4.1. Cytogenetic advances

At the time of his groundbreaking mutation publication, Muller's (1927a) research suffered from an acknowledged limited cytogenetic evaluative capacity which prevented fine structure chromosome resolution ("... Drosophila cytology is elusive in its finer details" – page 721, Muller, 1928b), and thereby a reduced capacity to detect chromosomal deletions. Markedly improved chromosome cytogenetic resolution capacity was developed by the Cornell plant cytogeneticist, Barbara McClintock, in the prophase stage of meiosis with maize (McClintock, 1929). Two years later she would apply this novel technique to Stadler's X-ray treated corn in the summer of 1931. It revealed that what was once believed to be X-ray induced "gene" mutagens were sizeable chromosomal deletions. While these findings would force Stadler to re-evaluate and challenge his previously published X-ray induced "gene" mutational findings in barley (Stadler, 1928), they would make him raise the question of whether Muller's gene mutation interpretation with fruit flies was also incorrect. While Stadler would cautiously share his new doubts with the research community in several 1931 publications (Stadler, 1931a,b) and in private correspondence with leaders in plant genetics research like Karl Sax (Stadler, 1931c), Stadler (1932) would finally challenge the Muller gene mutation interpretation in a very public manner during his Plenary Address at the Sixth International Genetics Congress at Cornell University in the presence of Muller (Table 1).

From this opening round of public debate, Muller and Stadler would challenge each other over whether Muller had induced true gene mutations in his highly publicized high dose X-ray experiments. This research-generated debate would continue until the death of Stadler in 1954 (Stadler, 1954), involving numerous radiation geneticists trying to resolve this fundamental question (Calabrese, 2017a ; Lefevre, 1950; Voss and Falk, 1973). Copies of Stadler's research grants and interim reports to the U.S. NRC that describe his progressive series of multi-year research plans, research methods and experimental developments reveal a focused, high quality and productive research activity with numerous publications that challenged Muller's gene mutation interpretation (State Historical Society of Missouri, Stadler Papers). An extensive review of Muller's gene mutation hypothesis along with supportive and non-supportive literature findings is provided in the dissertation of Lefevre (1949), Stadler's Ph.D. student. In this instance Stadler would show his flair for excitement and self-confidence by directing his student (with the assistance of *Drosophila* specialists and with some formal assistance of Muller) to challenge Muller's gene mutation interpretation with Muller's own biological model. In this extensive study, Lefevre (1949, 1950) found no support for Muller's gene mutation interpretation based on reverse mutations.

To the outside viewer it suggested two outstanding scientists locked in a scientific dispute, with Muller compelled to protect his reputation, future, and legacy. These longstanding competitive research activities of Stadler and Muller were much like a high-level chess match in which all moves (e.g., research publications, professional society presentations) contributed important information. By the late 1930s and/or early 1940s Stadler and others had methodically shown that Muller lacked the needed proof for his gene mutation assertions (Calabrese 2017a). The subsequent development of improved cytogenetic staining for *Drosophila* chromosomes by Painter (1934) would reveal that the use of the very high X-ray doses and dose rates similar to Muller's key findings, like that of Stadler's research with barley and corn, produced copious chromosome aberrations including a high proportion of deletions, along with few, if any, possible gene (i.e., "point") mutations.

Muller's use of the reverse mutation concept was also found unconvincing as multiple papers showed several mechanisms (e.g., position effect) by which reverse transgenerational phenotypic traits could occur without any change in the gene[3] (Bedford and Dewey, 2002; Lefevre, 1950). Thus, every move that Muller made was seemingly countered by the research of Stadler or spin-off ideas his research had inspired. Furthermore, Stadler's and related publications would yield insights that were incrementally more definite, insightful and over time, more convincing than Muller's, much like forcing Muller into a corner.

[3] See the discussion from Lefevre (1949) dissertation for a detailed assessment of reverse mutation and position effect as related to Muller's gene mutation interpretation.

4.2. McClintock's new X-Ray induced mutation mechanisms

Complementing the Stadler gene mutation criticism were new mechanistic findings of Barbara McClintock's study with her breakfusion-bridge-cycle model of X-ray induced genetic damage (Comfort, 1997, 2001) which then led to strikingly new and transformative transposable element induced mutational insights. Her novel mutable gene concept was particularly attractive to Muller's University of Indiana Colleague and future Nobel Laureate Salvadore Luria (McClintock, 1948; Muller, 1948) as well as Muller's closest colleague and friend, Edgar Altenburg. In the case of Altenburg, he would devote much effort to understand the scientific foundations of McClintock's findings and its role in spontaneous and exogenously induced mutations. The McClintock discovery had very broad biological and biomedical implications. However, it would also take Altenburg back to his 1927 suggestion that Muller had been blasting large holes in *Drosophila* chromosomes by high dose X-ray treatments. Extensive and detailed correspondence between Altenburg and McClintock in the early 1950s reveal the significance that Altenburg placed on her findings and how it stripped much significance from Muller's gene mutation model.

Altenburg would repeatedly encourage Muller to study and assimilate the findings of McClintock (Altenburg, 1952a,b,c, 1953a). Altenburg would provide Muller with a 25-page manuscript on McClintock's transpositional element concept and its relationship to X-ray-induced mutations (Altenburg, 1953a,b). However, Muller (1953) claimed he was too busy to read the manuscript while also being dismissive, claiming that no one could understand the "jumping gene" (i.e., transposable element) concept (Altenburg, 1953a; Muller, 1953), a common technique to distract attention from a perceived competitor while protecting one's legacy. However, Muller was not successful in drawing Altenburg back into his sphere of dominance, but rather, Altenburg (1957) would devote an entire chapter to McClintock's mutable gene (transposable element) concept in the second edition of his Genetics textbook. Altenburg, an excellent writer, made the challenging writings of McClintock readily understandable for geneticists and interested biologists. In this chapter, he claimed that a substantial proportion of high dose X-ray-induced mutations are due to chromosome deletions/rearrangements rather than Muller's "point mutations" and that such genetic damage was likely mediated by transposable elements (Table 2). The profound intellectual transformation of Altenburg to the McClintock model was a significant sign that the era of Muller was waning. During this same period Russell et al. (1958) would publish his highly influential dose rate challenge to Muller. With multiple scientific challenges facing him, Muller would transform his laboratory into one that would try to extend the findings of Russell into *Drosophila* rather than exploring the dramatic and more complex new ideas of McClintock. Within a month of the Russell et al. (1958) publication Muller was exploring dose rate. In the six years of redirected and intense research on this topic Muller's laboratory was plagued with a series of apparent false starts and a generally ambivalent finish. Thus, the final years of Muller's laboratory productivity were weak, perhaps a function of aging and health deterioration (Calabrese, 2017b).

Of further importance, as suggested above, was the discovery by McClintock (1950, 1951, 1953) that transposable chromosomal elements affected the occurrence of both spontaneous and exogenously induced mutations, including mutations induced by ionizing radiation and chemical mutagens such as mustard gas as used by Auerbach with *Drosophila*. Subsequent findings indicate that the early X-ray-induced transgenerational phenotypic findings of Muller (1927a) and Timofeeff-Ressovsky et al. (1935) were likely the result of X-ray activation of McClintock's transposition element process which induced massive chromosomal damage, such as small to massive deletions and other types of chromosomal aberrations (Ratner et al., 2001). These collective developments served to strongly reinforce the fundamental criticisms by Stadler of Muller's gene mutation interpretation, while supporting the McClintock transpositional element mediated mutation model.

5. LNT single-hit model, dose rate and the Manhattan Project

While Muller was in serious dispute with Stadler throughout the 1930s for his gene mutation interpretation, there was nonetheless a worldwide mesmerizing euphoria of Muller's mutation discovery (see Campos, 2015), one element of which resulted in a unique interdisciplinary collaboration between leading physicists and radiation geneticists as led by Delbruck and Timofeeff-Ressovsky, respectively. From the mid-1930s their research provided the LNT model with a hypothetical mechanistic basis via the use of target theory (Timofeeff-Ressovsky et al., 1935). This concept was then transformed into a biostatistical model (i.e., LNT Single-Hit model) which revealed that the shape of the dose response in the low dose zone was largely a function of the assumed number of target hits required to produce a gene mutation (Zimmer, 1941). The fewer the hits needed to produce gene mutations the closer the linear dose response for gene mutation was approached.

Since his X-ray induced gene mutation interpretation had experienced serious scientific challenges and setbacks through the 1930s, Muller needed another approach to redirect the mutation debate to restore support for his gene mutation interpretation and low dose linearity model and their integrative linkage. Muller's idea was an intriguing one that served, at least in part, both purposes, with a new application of a "dose x time = constant" experiment as seen in the Bunsen-Roscoe Law or with Haber's Law. Over the decade of the 1930s using his Proportionality Rule Muller had asserted that X-ray induced mutation damage was progressively cumulative and could not be repaired. As a result of these characteristics the damage should be predicted by the total dose, not by dose rate. If the total dose hypothesis were true, then the dose response for mutation should be linear at low dose, all the way down to a single ionization. Muller would test this idea in a

Table 2
Quote from Altenburg E. (1957). Genetics. Holt, Rhinehart and Winston, New York, NY.

Are all mutations due to chromosomal rearrangements?

... The possibility, therefore, arises that mutations might often be due to invisibly small deletions, rather than to an actual change in a gene–a change that we refer to as a "point" mutation. We cannot be sure, for example, that the yellow body-color mutant in Drosophila has a "yellow" gene in place of a "gray" (the normal allele of yellow). For all we know, the body color of the mutant might be yellow because the normal allele has been deleted. In fact, yellow mutants of independent origin differ somewhat in the intensity of their yellow pigmentation and, in the case of certain "extreme" yellow, it is very likely that the mutation is due to a very small deletion. In general, there is no way of telling from the outward appearance of a mutant what sort of genetic change caused the mutation. Inversions and duplications are also known to have mutant effects–inversion because of a "position" effect, and duplications either for the same reason or because of the genic unbalance they cause.

Now deletions, inversions, and duplications are all the results of chromosome breakage and rearrangement. Therefore, in the present state of our knowledge, all mutations might conceivable be due to such rearrangement and not to any actual alteration in the gene itself."

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dissertation by Ray-Chaudhuri at the University of Edinburgh using X-rays and mature spermatozoa of *Drosophila.* The findings of this dissertation matched up very well with Muller's predictions supporting the total dose/LNT hypothesis. These results provided support at a critical stage to Muller's gene mutation theory. In fact, during Muller's (1946b) Nobel Prize lecture, he cited the research of Ray-Chaudhuri (1939, 1944).

The problem with this newly adopted dose-rate vs total dose strategy to defend the gene mutation interpretation was that the study of Ray-Chaudhuri had a series of important design and execution limitations, requiring corrections, improvements and replication (Calabrese, 2011, 2017a). In fact, there were so many limitations (e.g., limited sample size, quality control issues, changing animal models during the experiment, lacked documentation of essential methods, major statistical errors, failure to collect critical information), it suggested that the normally critical Muller might have lowered his academic standards in order to provide support to his sagging gene mutation interpretation.

The Ray-Chaudhuri dissertation in some ways served as a pilot study for the far more substantial efforts lead by Curt Stern, University of Rochester, during the Manhattan Project starting in 1943. Stern would initially direct an acute study by Warren Spencer, a highly regarded *Drosophila* specialist who was on leave from his faculty position at the College of Wooster (Ohio, USA). While the Spencer part of the study went as planned, a significant problem for Muller, a paid consultant on this project, occurred when the data from the low dose chronic genetic toxicity study, led by Ernst Caspari, revealed a significant dose-rate effect and a threshold for mutagenicity, contradicting the Ray-Chaudhuri (1939, 1944) conclusions. These findings by themselves had the potential to land a severe blow to the LNT single-hit theory. These findings were just preceded by 15 years of research lead by Stadler that successfully weakened the plausibility of Muller's gene mutation interpretation and now along with new mechanistic insights of McClintock on X-ray-induced mutations. This situation became sufficiently threatening to the policy goals of key leaders of the radiation genetics community such as Muller and Stern who strongly advocated the adoption of the LNT single-hit model. What happened next to the field of radiation genetics could not have been predicted.

The above set of events, which collectively placed the LNT single-hit model at risk, set the stage for what is referred to as "LNTgate" (Calabrese, 2015c, 2016, 2017d), a series of obfuscations, deceptions, and misrepresentations of the scientific record all designed to ensure that the LNT single-hit theory would replace the threshold model for cancer risk assessment. This sequence of events has been reported in detail over the past seven years via a series of progressively informed historical discoveries (Calabrese 2011, 2013, 2015a,b,d, 2016, 2017b,c,e).

The LNTgate actions were mediated via the leadership of Curt Stern and Hermann J. Muller during the second half of 1946, continuing for more than a decade. These efforts lead to the actions of the NAS BEAR I Genetics Panel to sustain and integrate these successful manipulations into the scientific record and government regulatory policies. These ideologically directed activities would be guided by the academic "offspring" of Muller and Stern, such as Jim Crow, Bentley Glass, and other esteemed leaders of the radiation genetics community. The process became fully successful when the next generation uncritically accepted as scientific fact, the mistakes, deceptions, and misrepresentations handed down by the icons of the field. This is, in fact, the domain where key features of the fields of regulatory policy and cancer risk assessment are today.

6. Saving the hit model

The LNTgate process had an unexpected spontaneous origin. It began when Ernst Caspari informed Stern, his supervisor, that his dose-rate findings contradicted those of Ray-Chaudhuri (total dose). As noted above, the observation of a threshold response for mutation was not only not expected but, as it turned out, actually "not permitted", resulting in Stern refusing to accept the Caspari findings (Calabrese, 2011). Giving the appearance of objectivity, Stern blamed Caspari's threshold "discovery" on the use of a faulty control group that he insisted was aberrantly high. Stern did not provide any evidence to support this critical judgment. However, Stern was aware of earlier publications with control group responses for this model that supported the Caspari interpretation based on prior correspondence (Stern, 1938), but he either forgot this or refused to share it. Regardless, the Caspari year-long study had reached an impasse with the Stern judgement, a major crisis.

Showing some degree of independence, Caspari would not accept Stern's judgement that his control group displayed aberrantly high values. He dove into the literature and found a series of papers, which explicitly addressed the control group question, with all supporting his position (Calabrese, 2011). When Caspari assembled these findings, Stern withdrew the control group criticism. During this period, Caspari informed M. Demerec, head of the Genetics Department for the Carnegie Institute, of his mutation threshold dose-response findings and the problems it was creating. This prompted the influential Demerec to write Caspari asking "what can be done to save the hit model" (Caspari, 1947). This statement seemed to express what Stern and Caspari might well have been thinking. With the control group issue no longer a viable means to discredit the Caspari findings, the "save the hit model" strategy of Stern became publishing the manuscript, but framing the discussion to prevent the data from being accepted/used, while still showing competence of the research team, thereby securing the LNT/Ray-Chaudhuri framework. This seemed like the best possible outcome for Stern and Caspari.

The strategy adopted was to assert that the Caspari data could not be accepted or used until it could be determined why he obtained a threshold in the chronic study, while Warren Spencer obtained an apparent linear dose response a year earlier in an acute study with the same fruit fly model while working under Stern. This created a false standard, as the two studies had more than 25 methodological differences; there would be no possible practical means to determine why the studies differed (Calabrese, 2011). The only way that this highly nuanced perspective (i.e., the recommendation not to use the Caspari findings until it resolved the differences with the Spencer study) could have been published was if Stern was the journal (i.e., *Genetics*) editor and there was no peer-review, and this was most likely just what happened (Calabrese, 2011)! In fact, even though Stern proposed this unrealistic situation, no one, of course, ever explicitly accepted this challenge over the next 70 years, including himself, Caspari or Muller. It was a tactical move in the broader strategy to "save the hit model". So Caspari and Stern prepared this manuscript with this obfuscation and sent it to Muller for review on November 6, 1946 with Muller answering on November 12, 1946 (Calabrese, 2011). Muller indicated that he was upset that Caspari found a threshold since this could be a serious problem for LNT acceptance and Stern needed to replicate the study (not to explain why the Caspari study differed from the Spencer study as emphasized in the discussion as this was impossible to do). Thus, Muller was fully informed that the strongest study (i.e., chronic exposure to ionizing radiation) to date (i.e., Caspari experiment) showed a threshold for mutation one month prior to the Nobel Prize lecture of December 12, 1946 (Muller, 1946b). The linearity supporting acute exposure experiment of Spencer had a series of methodological limitations (e.g. inadequate temperature control, inexplicably combining different dose-rate groups with the same total dose, inadequate X-ray machine

calibration) that affected the reliability of the low dose study results (Calabrese, 2011). Yet Stern, Muller and others never identified such limitations, even in Muller's detailed review of this research (Muller, 1946c). These criticisms of the Spencer study (Spencer and Stern, 1948), were first reported more than six decades later (Calabrese, 2011).

In his crucial moment of making scientific history, Muller (1946d) deceived the world with his statement that there is no possibility for a threshold response ("no escape from the conclusion that there is no threshold") to ionizing radiation induced mutation and that risks needed to be assessed via the LNT single-hit model (Nobel Prize lecture, Dec 12, Muller, 1946b). Muller made this statement having seen the Caspari study and not offering any technical or other criticism (Muller, 1946e). Thus, a type of collusion began to take shape between Stern, Caspari, and Muller to do as Demerec urged. In a follow up letter to Stern (Muller, 1947) Muller supported publishing of the Caspari paper since there were enough caveats (i.e., obfuscations) and restrictions to make the paper non-threatening to the LNT acceptance.

In 1949 Stern manipulated or colluded with the leadership of *Science* to ensure LNT would be strongly promoted (Uphoff and Stern, 1949). This was similar to how Muller (1927a) was treated two decades earlier showing no data on his Nobel Prize experiments nor seven years later (1956) in the journal's dealings with the fraudulent NAS BEAR I Genetics Panel publication (Anonymous, 1956). Here is how it happened. While the Stern research team hoped that the follow-up replication studies would put an end to the Caspari study-created crisis, it simply created a new one. The first replication experiment (i.e., led by a new master's student Delta Uphoff) was unacceptable to Stern, this time because the control group was aberrantly low. The control group's values were so outside the norm that Stern had to check with Muller who strongly affirmed (in writing) that the Caspari control group values were appropriate while rejecting Uphoff's (see Calabrese, 2015a,b for the letter correspondence documentation). The troubled Stern would go so far as to blame her for having been biased [i.e., "may reflect a personal bias of the experimenter" (Uphoff and Stern, 1947)], with this leading to the low control group values (Calabrese, 2015b). This phrase was stated in the Discussion of the manuscript that was sent to the Atomic Energy Commission (AEC) (and which was immediately classified). This amazing statement should have raised a plethora of questions by the scientific community for Stern and Uphoff but it was hidden from view. For example, how did the alleged bias start? How long did it continue? How might it have affected other experiments, other team members and others, the data analysis and manuscript write up? A follow-up experiment by Uphoff also suffered the same fate with an aberrant control group value. This situation was turning into a professional disaster. So the question was not just what could be done to save the hit model but also the reputations of Stern, Caspari, and Uphoff and other members of the Manhattan Project at the University of Rochester. Stern would again show his creativity (or deviousness). Since essentially no one had read the classified material discounting the results and blaming Uphoff and her alleged biases leading to the uninterpretable findings, Stern used his contacts with the journal *Science* to publish a one page technical note of the experiments of Spencer, Caspari, and Uphoff. In this limited technical note, Stern showed no transparency, neglecting to inform the reader that he had found the low control studies of Uphoff unacceptable less than a year before and now he concluded these findings were fully acceptable. No criticisms of the Spencer study were mentioned despite its obvious significant limitations (Calabrese, 2011). Stern also reintroduced criticism of the Caspari study without evidence. In this mini-meta analysis, Stern restored the LNT model, literally "saving the hit model". In the final paragraph, Uphoff and Stern (1949) promised the *Science* readers to provide a comprehensive paper with methods, materials, missing data and other relevant information. Yet, they never did.

Muller and Stern actually promoted the discredited findings of Uphoff while marginalizing the Caspari paper. More specifically, at the time Stern asked Muller to help resolve the Caspari-Uphoff control group issue, Muller had been studying spontaneous mutations in the fruit fly in his ongoing disputes with Stadler concerning whether he induced gene mutation (Calabrese, 2017a). Thus, Muller was sitting on a treasure trove of control group spontaneous mutation data. As noted earlier, in multiple letters to Stern, Muller unequivocally sided with the Caspari findings while rejecting those of Uphoff (Calabrese, 2015a, b). With this as prologue we now fast forward a few years and find Muller (1950, 1954a) rejecting the Caspari study based on this control group being abnormally high, contradicting the literature, his own data/publications and his multiple letters to Stern, while never providing proof for his statements. The evidence reveals Muller dishonestly strove to discredit the Caspari study, and preserve LNT, while protecting himself from being accused of lying during his Nobel Prize Lecture. The 1950 paper of Muller was just preceded and perhaps inspired by an article by MIT's Robley P. Evans in *Science* (Evans, 1949) criticizing the LNT model, using the threshold findings of Caspari (Caspari and Stern, 1948). After Muller read the Evans article, he wrote to Stern criticizing the paper of Evans, blaming the criticism of LNT on the findings of Caspari (Muller, 1949). Muller urged Stern to contact Evans and discredit the Caspari work. No evidence has yet been found that Stern communicated with Evans on this matter.[4] However, shortly after that letter exchange with Stern, Muller published his false criticisms of Caspari's control group. Furthermore, on August 10, 1949 Altenburg (1949) wrote Muller about the Caspari threshold findings, acknowledged the reliability of the findings yet in search of a mechanistic explanation. Apparently, Muller had thought that Stern and his efforts had fully neutralized the threshold findings of Caspari, but this was not apparently the case.

7. LNT and the NAS BEAR Genetics panel

The next stage of the LNT story would take place with the NAS BEAR I Genetics Panel which first convened in early November, 1955 at Princeton University. As Muller had learned from many earlier frustrations, success within Advisory Committees is highly dependent upon who is selected. In the case of the BEAR I Genetics Panel, the answer was clear from the start, as the Panelist Tracy M. Sonneborn, a Muller colleague at the University of Indiana, read their radiation geneticist mantra into the recorded proceedings with no debate or dispute. All firmly believed that mutational damage was cumulative and irreversible with the dose response being linear down to a single ionization. Multiple notable radiation geneticists at that time were not advocates of the Muller perspective but they were either directed to other NAS BEAR I panels such as was the case of Ralph Singleton (agriculture panel) or not selected as was the case of McClintock. In retrospect, the deck was stacked along with an administrative leadership that would keep the panel focused on the big picture goals of the Rockefeller Foundation (RF) that both funded and directed the Panel while in

[4] The papers of Evans have been preserved at MIT. However, they have yet to be organized for scholarly use and it is unknown when they will be available. Of interest would be whether Stern ever sent Evans the letter Muller suggested. A check of the Stern files at APS revealed no record of a letter of Stern to Evans.

the administrative structure of the NAS.[5]

Despite the endorsement of the LNT single-hit model by leading research geneticists and physicists it was widely recognized that the fundamental data to support the LNT single-hit model was inappropriate. The model was dependent on point mutations, not large deletions, gene rearrangements, and other gross aberrations. In his final and masterful paper, published posthumously in *Science*, Stadler (1954) would illustrate how Muller's mutational data could not provide a credible biological basis for the LNT single-hit model. Despite the prominence of the journal *Science*, the stature of Stadler and the timeliness of the article, this criticism of the LNT single-hit model was never discussed by the NAS BEAR I Genetics Panel. In fact, not once in the transcribed pages of the Panel meetings were Stadler or McClintock's research on gene mutation ever mentioned.

At the second meeting of the Panel (in Chicago), Warren Weaver, Chair of the Genetics Panel and Director of Research for RF, tried to entice members of the Panel with RF funding if the Panel Report would support RF initiatives (e.g., LNT). Weaver indicated he would "try to get a very substantial amount of free support for genetics if at the end of this thing we have a case for it. I am not talking about a few thousand dollars, gentlemen, I am talking about a substantial amount of flexible and free support to geneticists" (Anonymous, 1956 - BEAR I Genetics Panel Transcript, February 5, 1956, page 35).[6] Weaver would further state that "There may be some very practical results — and here is the dangerous remark — don't misunderstand me, we are all just conspirators here together". The Weaver remarks obviously link the Panel deliverables to RF funding for geneticists, including those sitting in the room. Further discussions of the Panel during the February 5/6, 1956 meeting would reveal that to be successful in the eyes of Weaver, the Panel would need to present strong agreement/consensus for the estimation of genetic risks to the U.S. population assuming a linear dose response. However, an unanticipated problem came about 4–5 weeks later (March 1956) when the Panel members displayed multiple profound disagreements: they argued about whether it was possible to even estimate population risks, how to derive the estimations, how any derived estimates of damage related to true (real) risks, and what the risks actually were. With this confusion, the highly divergent results of the independent risk estimates that were carried out over 10 generations were seen as an unusable scientific "mess", such that Panel member, Jim Crow, would claim that no one would believe the policy recommendations of the Panelists since they could not agree amongst themselves. In a March 29, 1956 Letter to Warren Weaver, Crow (1956) stated that:

> "The limits presented on our estimates of genetic damage are so wide that the readers will, I believe, not have any confidence in them at all."

Lacking authority to do so, Crow, who was to organize the technical reports for Panel discussion, decided to arbitrarily drop the three lowest estimates of risk; by so doing he markedly reduced the variation, giving the false impression of more expert Panelist agreement than was the case. Even after dropping the three, there remained considerable uncertainty, being still too large to show to the scientific community and general public. One might have thought that the Panelists whose estimates were dropped would have strongly fought to have them retained. There is some evidence of significant disputes between Demerec and Muller on this matter based on a letter from Muller to Beadle in August 1956 (Muller, 1956) indicating that Muller did not want to be part of writing a scientific justification for their LNT recommendation. He indicated that he was already too frustrated with his debates with Demerec over the value of *Drosophila* versus bacteria in their risk estimations and did not want to air the so-called dirty laundry in public. He had thought that they had agreed to disagree. However, the available record does not reflect the details of this matter, as it likely occurred in the March 1956 meeting once Crow received the detailed write-ups for which there was no meeting transcript. Muller also noted his unresolved debates with the human geneticists of the Panel further confirming his unwillingness to seek a consensus report justifying their scientific recommendations. This lack of blatant open dispute/rebellion suggests that the group consensus was to present a united front that Weaver had earlier pointed out was necessary, perhaps using this funding carrot to achieve agreement. However, panelist James Neel, who refused to provide an estimate, strongly disputed the legitimacy of the proposed genetic damage estimation activity (Neel 1956 a, b). He argued that any consensus agreement was an illusion based on a self-fulfilling decision to reduce variability by forcing the use of similar models with similar process assumptions. Even with Crow stacking the deck, the risk estimates were still too variable, leading Weaver and Crow to encourage/coerce the Panel not to show their range of estimates to the outside world since it would destroy their credibility. The Panel would keep it private. There was no "minority" report nor leaking to the media. The "control" of the group was evident as those such as Demerec and Neel would not publically challenge the group view despite fundamental differences.

8. The NAS BEAR I Committee Genetics panel *science* publication story

The BEAR I Genetics Panel published a major article in *Science* (Anonymous, 1956) on their findings and recommendations. This paper had three significant misrepresentations of the Panel's research record. The first involved the Panel stating that the 12 geneticists of the Panel were invited to provide estimates of genetic risks for the entire U.S. population exposed to a certain dose of ionizing radiation, but only six accepted the challenge and provided the write up. Yet, nine of the 12 actually did, with Crow dropping three estimates as noted earlier.[7] In fact, I had obtained the nine detailed assessments. Second, the *Science* paper indicated that the minimum and maximum estimates of genetic damage range was ±10 or 100 fold. However, the actual average minimum-maximum damage range was about 750 fold. Third, the Genetics Panel *Science* paper neglected to report that three Panelists refused to participate, principally because they believed that such estimates could not be reliably done.

A written record exists that documents that the NAS BEAR I Committee Genetics Panel voted not to share their data with the scientific community and others (Calabrese, 2015a). After the Panel's publication in *Science* it was specifically challenged by

[5] Dr. Detlev Bronk was President of the Rockefeller Institute for Medical Research (later named Rockefeller University) and President of the National Academy of Sciences (NAS) during this time, confusing the roles of the Rockefeller Foundation and the NAS in this BEAR I Genetics Panel process.

[6] The concept of self-interest science (i.e., exaggerating fears of radiation to enhance research funding) of some members of the BEAR I Genetics Panel was documented via uncovered correspondence (Calabrese, 2014).

[7] It is interesting to note that the three estimates that Crow dropped (i.e., Demerec, Wright, and Kauffmann) were the areas with which Muller (1956) acknowledged serious issues in his letter to Beadle. Since Muller and Crow had a very close professional and personal relationship, it is tempting to speculate that Muller may have influenced Crow to drop the three estimates. This perspective is attractive since it is doubtful that Crow, one of the youngest members of the Panel, would have acted so precipitously without significant senior backup support. This would have been especially the case if he were doing Muller's bidding. Further documentation will be need to evaluate this hypothesis.

several leading U.S. academic researchers to share the scientific basis for the report and again the Panel formally voted not to do this as well (Calabrese, 2015a). Of significance is that the Panel had never even written such a scientific basis for their LNT recommendation. This should be seen as failed leadership by the NAS President Detlev Bronk and Chairman Weaver, a sign of scientific arrogance, or a type of defense posture. The Panel vote during August, 1956 not to provide a scientific basis for this major recommendation to adopt the LNT single-hit model for risk assessment was then passed on to NAS president Bronk, who accepted their decision. The NAS administration was therefore fully complicit in this process (Calabrese, 2015a).

The NAS BEAR I Committee Genetics Panel therefore falsified the research record, creating a significant cover up. Providing a detailed write up of their process would have revealed the deliberate misrepresentations of the research record. It would also have revealed a highly embarrassing fundamental lack of competence by such prestigious leading geneticists who simply could not properly address this risk estimation problem, as highlighted by Crow's amateurish and incorrect response (Calabrese, 2015a, b). It would also have taken considerable effort to complete such a report, something that should have been done during the activity of the Panel.

The goal of the NAS BEAR I Genetics Panel was to recommend adoption of the LNT in the U.S. and worldwide. Within about two years the LNT recommendation was adopted by national and international advisory committees, eventually becoming worldwide policy for cancer risk assessment. Thus, the most significant policy recommendation for cancer risk assessment lacked a written scientific basis. Most striking is that the Panel, including Muller, and the president of the NAS made this decision. It is ironic that the U.S. National Committee for Radiation Protection and Management (NCRPM) adopted LNT for cancer risk assessment in December 1958, based on the documentation-lacking NAS BEAR I Genetics Panel report days prior to the publication of Russell et al. (1958) demonstrating the existence of dose rate for ionizing radiation in the mouse model. Apparently, the status of the Genetics Panel and the NAS was so high that no documentation was needed for governments worldwide to adopt their transformative recommendations. As recently noted by Calabrese (2017a), seven of the members of the highly prestigious NAS BEAR I Committee Genetics Panel had no research experience with the effects of ionizing radiation on mutations. In fact, Crow, who had never published on the topic, made the decision on which estimates to retain. It is also ironic that Demerec and Neel, who were amongst the most appropriately experienced, did not contribute to the radiation risk estimates. Thus, the vision that the country was being guided by the most prestigious and experienced grouping of geneticists on the matter of radiation induced genetic damage was yet another myth to enhance acceptance of the LNT.

9. LNT, William Russell and the dose rate challenge

Within 2.5 years of the June, 1956 NAS BEAR I Genetics Panel *Science* publication, another *Science* publication would challenge one of the basic tenets of the BEAR I, Genetics Panel's recommendations. The paper was by William L. Russell of the Oakridge National Laboratory, also a member of the NAS BEAR I Genetics Panel. During June and July of 1958 Russell's group (Calabrese, 2017a, b) made a major discovery, that dose-rate, not total dose, was the key predictor of ionizing radiation induced mutation for mouse spermatogonia and oocytes. The Oak Ridge group kept this breakthrough discovery quiet, not presenting the findings at the International Genetics Congress in Burlington, VT in the middle of August. Russell did share the findings with a New York Times reporter during the Conference who wrote an article (Schmeck, 1958). The breakthrough paper was published on December 19, 1958 and with it was a timed release front page story by a Pulitzer Prize journalist (i.e., Nate Finney) for the Buffalo Evening News who specialized in atomic energy (note that the NY Times was then on strike) (Finney, 1958; Russell et al., 1958).

The Russell research revealed that damage from ionizing radiation was not cumulative, but reversible and had the potential to yield a threshold, suggesting the existence of DNA repair, a possibility that Altenburg shared with Muller soon after publication of the paper (Altenburg, 1958). In effect, Russell had discredited the mantra of the radiation geneticist community, creating a major problem. His strategy would be to promote the acceptance of his research while, at the same time, creating an impression of adhering to the radiation geneticist mantra. Russell did not want to be ostracized and marginalized from his field by his ideological radiation geneticist peers. Russell had seen the dominating and uncompromising personality of Muller in action many times while a member of the Genetics Panel (Crow, 1995) and with James Neel, whose paper Muller tried to prevent from being presented at an international genetics conference during the summer of 1956. In fact, Russell's supervisor, Alexander Hollaender, negotiated a follow up "reconciliation" meeting between Neel and Muller (January 1957) at Oakridge, essentially in the presence of Russell (Neel, 1956a, b; Neel, 1957a, b; Novitski, 1956) (Table 3). Thus, Russell knew only too well how hostile Muller could get if one deviated from the radiation genetics ideology. Russell would walk this dose-response tight rope until after the death of Muller in April 1967, after which Russell would unleash a profound set of criticisms of the radiation genetics mantra and the LNT concept (Russell, 1969, 1973).

Despite these findings, their massive expansion by Russell and their powerful challenge to the LNT single-hit recommendation of BEAR I, it would take some 14 years before a new powerful NAS Committee, now called the BEIR I Committee with the Genetics Subcommittee being chaired by Muller's protégé Jim Crow to reconsider the LNT recommendations of BEAR I. During this process the BEIR I Genetics Subcommittee re-examined the BEAR I report and made two clear initial determinations (Calabrese 2017a,b). The first was that the risk assessment recommendation of BEAR I (Anonymous, 1956) needed to be based on a mammalian model rather than on a fruit fly. The second factor was their acknowledgement that the BEAR I Genetics Panel (Anonymous, 1956) made a mistake in denying dose-rate. The recognition that dose-rate rather than the total dose best predicted mutation damage, meant that the radiation geneticist belief of cumulative and irreversible damage with each dose would be replaced. This finding also meant that linearity may be at risk of being replaced by the threshold dose response, reversing the 1956 position of the BEAR I Genetics Panel. However, despite these new challenges to the LNT model, the Genetics Subcommittee still had a strong disciple of Muller in charge with Crow[8] and would find some rationale to keep the linear dose response model as the default if possible.

Even though the findings of Russell revealed a true threshold for oocytes, the same could not be said for spermatogonia, where the dose-rate related damage, which was mediated by DNA repair, was only able to reduce total mutations induced acutely by 70% and not the 100% needed to achieve a threshold (Figure 1). The BEIR I Genetics Subcommittee therefore concluded that even though it was now known that an ionizing radiation threshold existed for mouse

[8] Toward the end of his career, Crow would acknowledge that Muller and he were amongst the strongest advocates of LNT and that they were too extreme in their views and actions (Crow, 1995).

Table 3
Quote from Neel (1959) letter to Beadle, September 14, 1959.

"There is no mind in science today for whose brilliance I have greater respect than that of Dr. Muller. In the first upsurge of concern concerning the effects of the increasing exposure of the human species to the radiation which followed World War II, it was Muller who had thought most about the problem, and Muller whose point of view dominated the picture. When Jack Schull and I pulled together our monograph on the findings in Japan, we felt obligated to try to fit these findings into the context of present knowledge. The outgrowth of that attempt, our Chapter 15, was a number of questions concerning Muller's argument. We couldn't prove that he was wrong, but we didn't feel he could prove that he was right. In other words, we felt that there were a number of unvalidated assumptions behind a good many of his points. One aspect of this evaluation of ours was a little critique of the significance of mutation rate studies. This critique I delivered at the WHO Study Group on the Effect of Radiation on Human Heredity which met in Denmark in the summer of 1956. I regarded it as part of the normal scientific interchange, but Dr. Muller apparently regarded it as an attack upon his life's work. There developed a rather strained relationship which persists until the present day, I am afraid, and keeps coming back to me in small ways which I consider beneath the dignity of a great man. Be that as it may, Alex Hollander was Chairman of that meeting in Denmark. Muller apparently insisted to Hollander that my statements were unacceptable and should be modified, to the point where Hollander arranged a meeting between Muller and myself at Oak Ridge, in an effort to reconcile the differences of opinion. At this point a number of the British participants in the WHO Study Group got wind of what was afoot, through no efforts of my own, and got their own backs up. It so happened that they agreed with my point of view and in effect transmitted the message that if any pressure were brought upon me, they would withdraw their own papers."

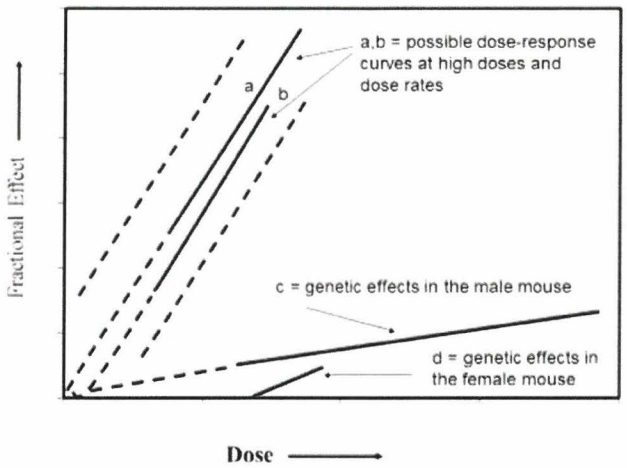

Figure 1. BEIR dose rate graph 1972. Hypothetical dose-response curves for leukemia and genetic effects (Source: NAS/NRC 1972 – page 98). Solid line = observed. Dashed extension of solid lines = unobserved. Line "a" and "b"; possible dose-response curves at high doses and dose rates. Parallel dashed lines = rough limits of error for lines a and b. Lines c and d represent genetic damage in the male and female mice, respectively.

oocytes, the LNT would be based on responses of the mouse spermatogonia. While this logic was convincing to the Genetics Subcommittee one would have to wonder why this didn't require further evaluation. Could there be an evolutionary explanation for why oocytes might show a threshold while spermatogonia didn't? Do oocytes have a more efficient DNA repair system than spermatogonia? Are responses of reproductive cells directly applicable to somatic cells?

These above noted questions were not explored or debated by the BEIR I Genetics Subcommitee. The point here is that the Genetics Subcommittee failed to broadly consider the question and were directed by the Crow leadership to obtain the desired outcome. Thus, Crow and his Genetics Subcommittee retained the LNT based on the non-threshold mutation data of the mouse spermatogonia. These views were accepted by a non-inquisitive U.S. EPA in 1975 and reaffirmed in 1977 all with reference back to the Russell research (Calabrese, 2017c).

The findings of Russell were critical for modelling cancer risk assessment for ionizing radiation based on the Atomic Bomb Survivor data for cancer outcomes. However, these epidemiological findings have limited detectability at low doses (Taubes, 1995), and findings need to be extrapolated toward background exposure. In this key low dose extrapolation process the assumption of linearity was made by the BEIR I Genetics Subcommittee (NAS/NRC, 1972) with the findings of Russell serving as the biological dose-response "homing" device for the LNT model. In the late 1970s the U.S. EPA directly extended this linearity model based on ionizing radiation to chemical carcinogens (Albert et al., 1977). The EPA linear cancer risk assessment policy would be challenged in 2017 when Calabrese (2017b,c) reported that the Russell historical control had been found in error (Selby 1998a, b), and had been corrected for a massive error in 1996 by the Russells (Russell and Russell, 1996). Calabrese showed that if the corrected historical data had been used by the BEIR I (NAS/NRC, 1972) Genetics Subcommittee the male mouse would have shown a threshold while the female would show an hormetic response. These findings indicate that the basis for the LNT assumption was incorrectly formulated and that the adoption of LNT for risk assessment was incorrect.

10. Discussion

The present paper reveals that Muller did not discover what he claimed, that is, the "artificial transmutation of the gene" and this finding challenges the validity and application of the LNT single-hit model for cancer risk assessment (Calabrese, 2017a; Crow and Abrahamson, 1997). Muller was also incorrect on the issue of dose-rate (Russell et al., 1958) which had a significant impact on acceptance and promotion of the LNT single-hit theory (Calabrese, 2017b,c). Although complex, Muller's career was fundamentally centered on his quest to be the first to produce gene mutations, and then to defend this interpretation the rest of his life, against the findings of Stadler (1931a, b, 1932, 1954) and others and then over the remaining six years of his research career (1959–1964) on the issue of dose-rate (Calabrese, 2017a, b), while trying to avoid the alternative gene mutation model of McClintock (1950, 1951, 1953) and its advocacy by Altenburg (1957).

Current scientific understandings, therefore, reveal that Muller could not sustain the conclusion that his high dose X-ray induced artificial transmutations of the gene were "real" gene mutations. The strong preponderance of evidence in the 1930s suggested chromosome level heritable genetic changes based on advances in cytogenetic staining, findings that have been confirmed with nucleotide sequencing technologies (Calabrese, 2017a). Since Muller was incorrect with his gene mutation interpretations the LNT single-hit theory of Timofeeff-Ressovsky et al. (1935) lacked a scientific relationship with the data that was used as its foundation (as pointed out by Stadler, 1954). Despite being wrong on the fundamental biological issues, the Muller-led faction of the radiation genetics community was successful in achieving the adoption of LNT worldwide. This was largely due to its highly organized radiation geneticist network focus, profound exaggeration of risks, and collusions with the Rockefeller Foundation and the U.S. NAS (Calabrese, 2013, 2015a,b,d), and their massive LNT-promotion campaign immediately following BEAR I which affected

government, the scientific community, the media and the general public.

Since the deceptions (e.g., BEAR I) and significant errors (e.g., BEIR I) can be traced back to major scientific historical figures, Nobel Prize winners (i.e. Hermann Muller, George Beadle and Max Delbruck), prestigious U.S. NAS Committees (i.e. BEAR I and BEIR I) and at least one past NAS president (i.e. Detlev Bronk) (Calabrese, 2015a, b), it is important that the ideological history of cancer risk assessment in the U.S. be documented and become a part of the scientific and regulatory agency historical record to help ensure that vital public health policies and practices do not continue to be the offspring of a scientifically incorrect and dishonest past.

This historical assessment reveals a complicated dynamic amongst researchers, their colleagues, and rivals, all within a framework of politics, policies, social philosophies and personalities. Hermann Muller led the field, starting with redefining the concept of mutation and finding improved ways to assess it. Muller worked on these matters within a framework of wanting to be first, gaining recognition and its benefits and pushing this to extremes. One example of this obsession is seen when Muller claimed credit for an important discovery (i.e., first reported in *Drosophila* in which both genetic and cytological evidence of translocation were combined) that Curt Stern had made (Muller, 1929a, b; Muller and Painter, 1929; Stern 1926, Stern, 1929a, b). This resulted in getting the normally reserved Stern to confront Muller via correspondence. Muller was forced to publically apologize and correct the matter. However, symptomatic of this behavior and in this same general period, Muller would apparently manipulate an editor at *Science* to publish his discussion on X-ray induced mutation without providing any data, simply doing so as a means to ensure that he would be first - a tactic that was enormously rewarded.

Much of what Muller did over the next four decades was to preserve and defend the legacy of his breakthrough gene mutational findings/interpretation and the formulation of the Proportionality Rule (the LNT concept). In so doing, Muller would become the intellectual leader of the radiation genetics community, helping to ensure its importance and create new professional and funding opportunities. The principal challenge for Muller was the thoughtful reflections of Stadler and his capacity to create and test key hypotheses, the data from which would challenge Muller's interpretation of his "groundbreaking" findings. Stadler, who was unrelenting, objective and insightful, seemed to follow in the footsteps of Muller's Ph.D. advisor T.H. Morgan. These researchers, according to Muller (1946f), "abhorred what they termed "speculation", that they even distrusted the validity of the most essential lines of reasoning." Stadler and Morgan were leaders in that wave of skepticism whose participants "doubted the doubt 'til they doubted it out." (Muller, 1946f). In the end, Muller's interpretations were revealed via such follow up experimentation to be incorrect, that is, the very high doses he used produced heritable chromosomal, not gene, phenotype changes. More than 50 years later, with advances in nucleotide assessment methods, it would be shown that ionizing radiation could produce some gene mutations but at far lower doses (Asakawa et al., 2013; Colussi et al., 1998; Colussi and Lohman, 1997; De Serres, 1991; De Serres et al., 1967; Fossett et al., 1994; Furuno-Fukushi et al., 2003; Liu et al., 2003; Mognato et al., 2001; Nakamura et al., 2005; Nelson et al., 1994, 1995; Nohmi et al., 1999; Okudaira et al., 2010; Park et al., 1995; Russell and Hunsicker, 2012; Schwartz et al., 2000; Sudprasert et al., 2006; Thacker, 1986, 1992; Thacker et al., 1990; Toyokuni et al., 2009; Webber and De Serres, 1965; Yamada et al., 1996).

Muller loyalists, such as Charlotte Auerbach (1976) and others, would strain the limits of credibility by arguing that Muller was proven to be correct. These examples of revisionist history were based on an incorrect interpretation of his findings. Muller would excite the world with the claim he produced 40 gene mutations one weekend afternoon, more than the entire field had produced in a decade (Carlson, 1981). Yet, we now know that he was not producing gene mutations. In fact, Auerbach (1978) would eventually support Stadler noting that "Stadler tested many X-ray mutations of a particular gene in maize and found that all of them were deficiencies. Not long ago this conclusion was confirmed by experiments on a different gene in maze. Muller's evidence, gained from work with *Drosophila*, was less direct ..." (Auerbach, 1978). While Auerbach (1978) gave the proverbial nod to Stadler's perspective, this was done even more emphatically by two very close colleagues and friends of Muller. Crow and Abrahamson (1997) acknowledged that Stadler's deletion interpretations had been convincingly supported with modern analytical methods and that Muller was simply too stubborn, holding on too long to a discredited position. However, old deeply held and self-serving beliefs such as Muller's original error of interpretation, would mesmerize the scientific community making it impossible to change, as it became an accepted myth leading to the creation of the LNT single-hit model for cancer risk assessment, affecting vast changes in public health risk assessment policies and risk communication strategies, while being susceptible to political and ideological manipulation.

The Muller story reveals a conflicted character, the discoverer of an apparent major breakthrough, something that he greatly desired. At the same time, Muller was tortured with the possibility that he was wrong, spoke too soon, that his mutations were really only holes that the X-rays had poked in the chromosomes. He knew only too well that if his mutations were really only poked holes there really wasn't much new or great with his "breakthrough" discovery. Thus, we have a life that sought to "hold on", while trying to prove that he actually had produced "real" mutations.

Eventually the scientific story of Muller's chromosomal rather than gene mutations would progressively emerge, even if it would take up to five decades after he received his Nobel Prize. The influence of Muller continues to be dominantly reflected in current regulatory policy, which was based on poorly formulated science, in need of corrective transformation by major agencies, such as the U.S. EPA, which however have been unable or unwilling to do.

The story of Muller's discovery of gene mutation also speaks to the broader issue of science being self-correcting. Due to the courage and focus of Stadler, Muller's interpretations were challenged and tested in the laboratory. This inspired others, including perhaps a desperate Muller, to seek the truth.[9] These challenges would be tested in the domains of cytogenetics, position effects, transpositional elements, reverse mutations, and eventually with the use of the Southern Blot, PCR and other DNA technologies. We now know that Stadler was correct when he said that it was critical for the scientific community not to confuse the observation of transgenerational phenotypic changes at high doses with its unknown mechanism(s). In the end, Muller was trying in 1927 to discover the mechanism of evolution, and he "knew" that it must be gene mutation. However, he convinced the world (at least for a while), and maybe himself, that he had done so with his high dose *Drosophila* experimentation. However, the scientific community can thank Stadler and his collaborator McClintock for creating the necessary doubt that would eventually lead to science displaying a self-correction for Muller's claim. An important follow up question is whether regulatory agency "science", like that of experimental science, can be self-correcting. Now many years after Muller's

[9] In private letters with Altenburg (Altenburg, 1953c; Muller, 1953; 1954b,c), Muller would acknowledge problems with his reverse mutation explanation, the significant role of position effect and the influence of the mutable genes of McClintock.

incorrect interpretations were revealed, society still lives with a risk assessment model based on a mistaken set of Muller's interpretations. In 1995 Crow would reflect upon the impact of his generation of radiation geneticists in estimating ionizing radiation induced risks. With his then 20-20 hindsight Crow stated that Muller's leadership and action "oversold the dangers, and should accept some blame for what now seems, to me at least, to be an irrational emphasis by the general public and some regulatory agencies on low-level radiation …. ."

In the aftermath of the BEIR I (1972) recommendation and the adoption of the LNT perspective for regulatory agency policy and practice came a spate of biostatistical models offering estimates of cancer risk in the low dose zone following the linearized perspective. The broad range of linearized models were highly speculative attempts to estimate risks at very low doses often using some feature of enhanced biological plausibility, such as the number of theoretical stages in cancer development, the role of interindividual variation, the incorporation of carcinogen bioactivation and DNA repair and other approaches (Cornfield, 1977; Crump et al., 1976; Hoel et al., 1975; Krewski and Brown, 1980; Rai and Van Ryzin, 1981). This type of modeling started, for the most part, in 1961, with the Mantel and Bryan paper, based on the carcinogen contamination Cranberry scare during the Kennedy-Nixon election of 1960 followed by a hiatus until the mid-1970s after the creation of EPA and OSHA when legislative and regulatory activities intensified. These models were constrained by linear assumptions as provided by the BEAR I Genetics Panel, the BEIR I Committee and the official adoption of LNT from BEIR I in 1975 by EPA [see recommendation to support the LNT single-hit model by a subcommittee of the U.S. Department of Health & Welfare (Hoel et al., 1975)]. In between these two NAS committees there were many advisory groups of a national and international nature that followed BEAR I (Calabrese, 2013, 2015a). The linear assumption of these models in the mid-1970s and later were based on the predecessor NAS committees, with BEIR I having the latest and most direct impact since it was based on mice rather than fruit fly model of BEAR I. Given the above historical reconstruction, the risk assessment modeling activities would have been considerably different had EPA determined that the default should be a threshold or hormetic model. The rapid dominance of linear cancer risk assessment modeling in the late 1970s would not have occurred without the recommendations of the two NAS committees. These modeling activities were derived from biostatisticians who tried to derive more biologically motivated linearized models, not being aware of the plotting, scheming, deceptions, misrepresentations and mistakes of the two NAS committees. In the end, the real leaders were Muller, his radiation geneticist followers and their institutional partners. The subsequent linearized modeling was simply the following of the linearity script as written by the NAS BEAR I Genetics Panel.

These convergent entities reached a type of critical mass during the NAS BEAR I Committee Genetics Panel, facilitating no less than a scientific, social, psychological and politically-based risk assessment revolution within the U.S. and essentially all other countries adopting the LNT model for cancer risk assessment.

11. Conclusions

1. Muller incorrectly assumed he induced gene mutations in 1927 when he demonstrated that X-rays induced transgenerational phenotypic changes in *Drosophila* (Calabrese, 2017a).
2. The Muller findings had a major impact on the scientific community. His non-peer-reviewed data (Calabrese, 2018) and incorrect interpretations were widely accepted (Campos, 2015).
3. This incorrect gene mutation mechanistic interpretation lead to the development of the "Proportionality Rule" for dose response in 1930 by Muller and the LNT single-hit dose response model in 1935 by Timofeeff-Ressovsky et al. (Calabrese, 2017a).
4. Muller's gene mutation interpretations were strongly challenged in the genetics community, especially by Lewis J. Stadler and Barbara McClintock, who showed that Muller's gene mutation interpretation lacked scientific proof and could be explained by other mechanisms (Calabrese, 2017a).
5. Limited research directed by Muller supported a conclusion that X-ray induced mutations were best explained by total dose, not dose rate and the genetic damage was cumulative, irreversible and the dose response was linear (Ray-Chaudhuri, 1939,1944)
6. Muller's total dose findings were strongly challenged in Manhattan Project research with far stronger studies (Calabrese, 2011a). These findings were improperly marginalized by leaders of the U.S. radiation genetics communities including Stern and Muller who misrepresented the data via deceptions, false statements and obfuscations (Calabrese, 2011a, 2015b, 2016).
7. The inappropriate awarding of the Nobel Prize in 1946 to Muller for producing "gene" mutations gave an enormous credibility to the LNT risk assessment model, facilitating its acceptance within the scientific, medical, regulatory and political communities. It is likely that the award had long lasting societal impact that facilitated worldwide acceptance of LNT.
8. It was incorrectly assumed by the scientific/regulatory communities and prestigious advisory groups (e.g. U.S. NAS BEAR I Committee, Genetics Panel) (Anonymous, 1956) in the late 1950s that the responses of mature spermatozoa to ionizing radiation induced "gene" mutation which were linear at high doses and independent of dose rate and such doses could be generalized to all cell types, doses and dose rates (Calabrese, 2015b, 2016).
9. These assumptions were incorrect because it was later (i.e. early 1960s) determined that mature spermatozoa lacked DNA repair, thereby preventing its capacity to repair radiation and chemically induced mutation as could occur in somatic cells (Calabrese, 2017b, c).
10. The NAS BEAR I Genetics Panel deliberately misrepresented their own research findings and hid their contradictory findings to promote the acceptance of the LNT model for regulatory agency risk assessment (Calabrese, 2015b, 2016).
11. William L. Russell at the Oak Ridge National Laboratory starting in late 1958 demonstrated that ionizing radiation induced mutations in mouse spermatogonia and oocytes were dependent upon dose-rate, not total dose as had been assumed, due to their capacity to repair DNA damage (Calabrese, 2017b, c).
12. The BEIR I (NAS NRC, 1972) Genetics subcommittee acknowledged the "mistake" of the NAS BEAR I Genetics Panel on dose-rate but still retained the LNT recommendation because the significant reduction in mutation rate in the spermatogonia as shown by Russell et al. had not regressed to control values as in oocytes. Nonetheless, the BEIR I Genetics Subcommittee suggested that findings from spermatogonia had greater capacity for generalization to somatic cells, due to repair capacities, as compared to mature spermatozoa. Russell referred to failed DNA repair capacity as an "odd phenomenon, restricted to spermatozoa and

occasioned by the peculiar nature of the specialized spermatozoan cell." (Calabrese, 2017b,c)

13. Selby (1998a,b) in 1995 detected a significant error in the Russell mouse specific locus test historical control group. This error was subsequently acknowledged and corrected by Russell and Russell (1996) along with Selby (1998a,b). If this error had not been made or had been corrected prior to the creation of BEIR I the mouse spermatogonia data that was used to support continuance of the LNT model would have supported a threshold or hormetic model based on the Russell and Selby corrections, respectively (Calabrese 2017b,c).
14. Summary: The LNT for cancer risk assessment originated due to (1) a critical mistake by Muller that he had discovered X-ray induced "gene" mutation, (2) the adoption of the LNT single-hit model was based on this assumption, (3) a mistake in generalizing the use of the DNA-repair deficient mature spermatozoa for somatic cells by BEAR I (4) deceptions and misrepresentations of the scientific record by leaders of the radiation genetics community, including the NAS BEAR I Genetics Panel and (5) failure to detect the error in the Russell Mouse Specific Locus Test control group, which would have precluded support for LNT. EPA then extended the error by adopting LNT for cancer risk assessment, stating in 1975 and 1977 that it was based on the now recognized erroneous dose rate findings of Russell as cited in BEIR I (1972).
15. It is ironic that the misrepresentation of the scientific record by this NAS BEAR I Genetics Panel to promote their ideological agenda stands in sharp contrast to the memorialized quote on the Einstein statute on the very grounds of the U.S. NAS in Washington, DC. It states: "The right to search for truth implies also a duty; one must not conceal any part of what one has recognized to be true." As the historical record shows the NAS BEAR I Genetics Panel did not follow the guidance of Einstein.

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Conflict of interest

The authors declares no conflict of interest.

Declaration of interest

None.

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Radiation Hormesis: Incredible or Inevitable?

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It has long been recognized that exposure to low levels of toxic chemicals could have beneficial effects, such as increased resistance to related chemicals or stimulation of growth or development. The notion of radiation hormesis, that exposure to low levels of ionizing radiation could produce beneficial effects, developed seriously in the late 1950's, and was, to most radiation scientists, incredible. This was due in part to the then prevailing ideas of radiobiological mechanisms, in part to the sweeping generalizations made by the leading proponents of the radiation hormesis concept, and in part to the many failures to confirm reports of beneficial effects. More recent understanding of the mechanisms of radiation damage and repair, and discoveries of induction of gene expression by radiation and other genotoxic agents [the adaptive response] make it seem inevitable that *under suitable conditions*, irradiation will produce beneficial effects.

The term hormesis generally implies a beneficial effect of exposure to a toxic agent, but the term has also been described as a stimulatory effect or, in a striving for objectivity, as a response to low levels which could not be predicted from the effects of high levels of such an agent. Most writings in the field do not discuss the obverse situation: toxic effects at high levels of substances hailed as beneficial at lower levels! The notion of chemical hormesis was widely accepted as the Arndt-Schultz Law, but in recent years has come into disuse, if not active rejection, at least in part because of concerns about effects of environmental pollution. The subject of chemical hormesis and its history has been reviewed in masterly fashion (Calabrese and Baldwin, 2000a). The notion of radiation hormesis is much more recent, and the debate over its existence much more acrimonious and therefore, perhaps, more interesting. I shall discuss current notions of radiation hormesis and their development from a historical perspective, partly to account for some of the acrimony, partly to create a model for some types of scientific progress, and partly to permit my airing of some personal prejudices.

Some Pertinent Aspects of the First 55 Years of Radiation Science

The need for quantitative methodology

In 1895, W. Roentgen, Professor of Physics at the University of Wurtzburg, discovered that Crookes tubes, already common tools in physics laboratories, emitted some form of electromagnetic radiation which could affect photographic media. The mechanism for this effect was not clear, and in testing one theory of the photoreaction a French chemist, H. Becquerel, discovered radioactivity. Shortly afterwards, the Curies discovered and isolated radium. These discoveries were exciting to the general populace – and to entrepreneurs – as well as to the world of science, and soon there were advertisements for sale of thorium and other radioactive materials, for treatment of various human ills, including sexual impotence in elderly men! In 1906 two French physicians recognized as radiotherapy specialists enunciated the Law of Bergonie and Tribondeau, that the radiosensitivity of a tissue is proportional to its proliferative activity and inversely proportional to its degree of differentiation. This law guided radiation oncologists for the next 50 years.

Radiotherapy [and radiation research] were hampered by the lack of reliable dosimetry and of a rational dose unit. The unit used in the clinic was the SED, the skin erythema dose, or the minimum exposure to produce reddening of the skin [usually, on the radiologist's arm] within 48 hours. Aside from the poor physics and the variability in radiosensitivity of the skin of different radiologists, by the early 1920's it was apparent that chronic exposure to moderate X-ray doses was causing a high incidence of cancer among the radiologists.

General public interest in radiation science waned, but became highly emotional, particularly in the United States, when the plight of the radium dial painters was publicized. Major manufacturers gave subcontracts to small businesses to prepare radium-painted dials for

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clocks and watches. Most of the employees were women in their 20's or late teens. They used small brushes, moistening them on their lips to have fine points for the free-hand painting. Much of the paint would be absorbed into the women's bodies, with the radium, chemically similar to calcium, winding up in the jaws and other bones. Bone cancer occurred with extremely high incidence! Again, it was clear that prolonged exposure to moderately high radiation doses caused high rates of cancer!

Quantification of dose

In 1926 there were 2 related events: 1) An international commission agreed on an X-ray *exposure* unit, the roentgen, R, defined as the amount of radiation producing 1 electrostatic unit of charge in 0.001293 grams [i.e., 1 cubic centimeter] of dry air. This amounts to absorption of 83 to 97 ergs/gram, depending on whether the absorber is air, water, soft tissue, or bone. [When it was decided, after World War II, to develop a unit of *absorbed* dose, the **rad** was defined as absorption of 100 ergs/gram. More recently the SI system, with the Joule as the basic unit of energy and the kg as basic unit of mass, a new unit of dose, the gray, was defined as absorption of 1 J/kg, which = 100 rad.] 2) An American physicist, John Victoreen, developed a condenser meter to measure the number of ions [and, thence, of roentgens] produced within the known volume of air in the dosimeter.

Development of target theory

With a readily and reliably measurable unit now available, some physicists began to perform radiation experiments on simple biological materials, chiefly enzymes [the only molecules whose activity or "survival" which could be scored at this time] and on bacteria. Radiation-survival curves for these molecules were exponential, like radioactive decay curves, without any threshold or shoulder, suggesting that a single critical event [a "hit"] in the right place [the "target"] was sufficient to inactivate the molecule or bacterium. By assuming, logically, that the "hit" was a cluster of ionizations, and applying Poisson considerations [that is, an average of one hit per target produced e^{-1} or 37% survival] the researcher could estimate the size of the critical target. For a variety of enzymes, the target size calculated was approximately the molecular weight, suggesting that a hit anywhere within the molecule was sufficient to inactivate the entire molecule, a perfectly reasonable concept. Comparable studies and reasoning with bacteria, however, led to target-size estimates much larger than known for any molecule, but much smaller than the cell. Nevertheless, an English biophysicist, Douglas Lea (1947) and a pair of investigators (Timofeeff-Ressovsky and Zimmer) in Germany almost simultaneously published books on Target Theory as applied to cells, the core notion being that *within each cell there is a critical target—a volume or an organelle—within which a single hit is necessary and sufficient to inactivate the entire cell.* Most biologists could not accept that notion, because they could not conceive of any such critical entity within the cell. Note, at that time the critical role of DNA had not yet been recognized, and bacteria were not credited with having nuclear material!

Despite the misgivings of most biologists, Target Theory was a very good theory, in that it accounted for most of the pertinent facts known at the time, and, more importantly, it made predictions which were amenable to experimental test.

These predictions were:

1) Densely ionizing radiation would be less effective, because of energy wasted: far more than one cluster of ionizations would be deposited in the target.
2) External or environmental factors would have little or no influence.
3) There could be no repair of damaged targets.

During the 1950's, each of these predictions was proven incorrect, but many of the concepts of target theory remain useful today.

The legacy of World War II

Target Theory was developed, primarily in Great Britain and in Germany, just prior to World War II. During the war, little radiation science was performed in either of these countries. The United States, however, largely out of fear that Germany was preparing atomic weaponry, mounted a large "Atom Bomb Project" with supporting research on whole animal and genetic responses to acute radiation exposure. After the war there was widespread euphoria, both in the general population and in the scientific community, not only about the political future, but about the benefits which would accrue to mankind from the availability of cheap, safe, and plentiful atomic power. Atomic energy was considered so important by the United States government that the Congress established a "joint committee" [that is, one composed of members of both houses, the Senate and the House of Representatives] on atomic energy. There were some in the general populace who were terrified of any radiation, but they were not taken seriously. There were some in the scientific community, however, who did not argue that radiation was necessarily unsafe but, rather, that we did not have enough information to judge whether or not occupational exposure to fairly low doses posed any hazard. One of the most influential of these was a biophysicist, Egon Lorenz, who had worked at the Manhattan [atomic bomb] Project during the war, and who held appointments in both the National Cancer Institute and the AEC [Atomic Energy Commission] Argonne National Laboratory. Lorenz appeared before the Joint Committee, and convinced them to fund a

[for that time] extremely large research program to follow the entire life spans of mice, rats, and guinea pigs exposed to sublethal doses: 100 or 200 R at one time, or a few R/day, 5 days/week, to mimic possible exposure in the work-place. The preliminary results of the Lorenz project suggested that the rodents exposed to low doses had shorter life expectancies than their controls, but the differences were rarely, if ever, statistically significant. Deaths in a laboratory animal population are distributed over a very long time period, so the standard error of mean survival time is very large. Before he could compile more experimental data or apply more sophisticated statistical procedures, Lorenz himself passed away. This left the AEC in a quandary: Should they search for outstanding personnel to take over and continue this very expensive program, or conclude that there were no important data coming from it and end its support? In short, they needed a thorough and objective analysis of the Lorenz findings. To perform this task, they called upon George Sacher, a mathematically-gifted and erudite young biologist at the Argonne Laboratory. Sacher, too, was frustrated by the lack of statistically significant differences. He either knew, or learned from his extensive reading, about the Gompertz function in human longevity studies. [Benjamin Gompertz was not a biologist, but an insurance actuary]. In 1825 Gompertz had pointed out that the age-specific mortality rate, R, in various human populations increased exponentially as a function of age, beginning about the time of puberty:

$$R = R_p e^{kt}$$

Sacher applied the formula to the Lorenz data, confirming that life tables of laboratory animals also followed Gompertzian kinetics. Actually, Simms (1946), a biochemist at Columbia University's medical school, had "rediscovered" the Gompertz function, showing that it applied to many different specific causes of death in humans; using a few sets of data published by earlier workers, Simms also suggested that it applied to rats and to *Drosophila*! This type of analysis is now a common tool in experimental gerontology. More directly pertinent to the Lorenz project: Gompertz plots for animals irradiated acutely at young ages were shifted up [to the left], as if the radiation had added an increment of age. Some of the groups first irradiated late in life showed small shifts to the right, however; the slopes of the exponential portions were essentially unchanged. The slopes for chronically [5 days/week] exposed animals were increased, as if the aging process was being steadily accelerated. Most of Sacher's work first appeared in Argonne Laboratory reports, not readily available to investigators outside the radiation science community; Sacher, like Lorenz, was particularly interested in the effects in chronically exposed animals, and most of his pertinent publications in the open literature focussed on these. But results similar to Sacher's for singly-exposed animals were found in the large studies of mice exposed in the atom bomb tests (Upton et al., 1960) and in smaller studies with rats (Jones and Kimeldorf, (1964).

Consequences of the Lorenz-Sacher Study

The subdiscipline of experimental gerontology

The demonstration of significant life shortening in the fashion of induced aging was very exciting to radiation biophysicists and other physical scientists, and attracted investigators trained in mathematically rigorous disciplines. Sacher himself became a distinguished gerontologist, serving as president of the American Gerontological Society, and was for many years the North American editor for the journal Experimental Gerontology. Howard Curtis, a biophysicist, stepped down from the directorship of the Biology Division in the AEC's Brookhaven Laboratory to set up a large gerontology research unit there, and later wrote an exceptionally readable textbook of gerontology (Curtis, 1966). Bernard Strehler, a biophysicist previously known for ultra-violet light studies and work on bacteriophage, became a full-time gerontologist and long-time editor-in-chief of the journal Mechanisms of Aging and Development. These developments were initiated by the belief that radiation induced aging, and could be as powerful a tool for gerontology as it was for genetics. Interest in gerontology among biophysicists continued, however, even after it became evident that virtually all of the life-shortening effects of radiation were attributable to early induction of cancer (Walburg, 1975).

Does radiation accelerate aging in Drosophila and other insects?

It was obviously attractive to examine the effect of radiation on longevity of *Drosophila*. There was a potential complication, however. Radiation induces acute lethality in mammals in a matter of weeks, a small fraction of their normal life-span; death is clearly the result of events following killing of the proliferative cells of the intestinal lining (high doses) or of the proliferative hemopoietic cells (moderate doses). In most adult insects, somatic cell proliferative activity is limited to the regenerative nidi of the mesenteron, and there is considerable evidence (Ducoff, 1972) that radiation-induced death of beetles and most other adult insects is the eventual result of cytocidal effects in these cells. But in adult Diptera, including *Drosophila*, there is no somatic cell renewal; these insects appear very radioresistant, and simply die off more rapidly, without a clear period of acute mortality, after high radiation doses. Several investigators, including Sacher (1963) did measure Drosophila longevity after low radiation doses, found that life span increased, and abandoned that approach. One group, however, conducted more detailed studies, and noted that the

increase occurred in the females, but not in the males (Lamb, 1965). The female flies, even when not mated, lay eggs, and it was found that the irradiation inhibited egg-laying; apparently the irradiated female had proteins and/or energy sources which would otherwise have been expended in egg-laying available for her own somatic tissues, and so lived longer! [In a later review, Lamb (1978) cited and discussed other investigators who either supported or argued against this explanation.] Another possible explanation, however, was suggested by the observation (Baxter and Blair, 1969) that young Drosophila exposed to low doses of ionizing radiation became resistant [overrecovery] to later high-dose challenge! Subsequently, Bhatnagar et al. (1965) working with house flies, noted that sexually-segregated males lived longer after irradiation. Both Rockstein's group (Rockstein, 1956) and Sohal's (Ragland and Sohal, 1973; Allen and Sohal, 1982), in a series of papers, correlated wing abrasion and loss with aging in male flies, and noted that wing loss was increased with mating or other physical activity, but was reduced after irradiation. Patterson (1957) had noted that resistance, *usually* by female flies which had mated previously, but *sometimes by males*, to males seeking mating, often led to wing damage or loss. Thus, physical and mating (including homosexual rape) activity were reduced after irradiation, and this probably explained the longevity enhancement!

Radiation hormesis: the concept

We have noted that the Gompertz curve of some of the Lorenz-Sacher groups [mostly those exposed acutely at fairly advanced ages] was shifted to the right, or down; that is, they appeared to have *gained* life expectancy. This phenomenon caught the attention of a biochemist, T. D. Luckey, who had been involved in the early studies indicating that incorporation of antibiotics into the diets of young chicks enhanced their growth and development. So here was another inhibitory agent, ionizing radiation, enhancing viability! Luckey did painstaking searches of the literature, and found many hundreds of published papers in which authors had reported explicitly, or their data seemed to suggest, radiation effects which were beneficial or stimulatory. He published (1980) a large informative volume on *Radiation Hormesis*, as well as many journal articles.

Luckey did not simply describe examples of beneficial effects. He argued that life had evolved in an environment which included radiation, and that radiation was essential to life. He also argued that benefits of irradiation were a law of nature! The idea that cells could benefit from irradiation was not compatible with target theory, and so had important implications for basic radiation science. The idea also had political and economic implications. Development of nuclear power was often opposed as too greatly risking people to radiation exposure or as a threat to the environment; but if low-dose exposure is beneficial.. On the other hand, if cells may benefit from some radiation exposure, radiotherapy protocols would have to be reassessed. And perhaps crops could benefit from irradiation; a Soviet scientist, A. Kuzin, became a leading investigator in this area.

Scientific shortcomings of the hormesis concept

Although there were hundreds of reports of stimulatory or apparently beneficial effects of radiation, many did not include adequate statistical analysis (Miller and Miller, 1987) or could not be repeated by other workers. An early study of stimulatory effects in plants (Skok et al., 1965) dismissed the effect as being too small to matter. About the only "hormetic" phenomenon confirmed in various laboratories and for many species was the radiation-enhanced longevity of adult insects. [Probably the earliest report of such enhanced longevity was that of Davey (1919), using the flour beetle, *Tribolium confusum*. Davey (1917) first studied beetle lethality following higher doses, and, reviewing much of the published work on animals other than man, suggested that radiation might resemble drugs in that low doses could be stimulatory, moderate doses produce a destructive effect after a latent period, and high doses produce instant destruction.] If enhanced longevity was the result of inhibited reproductive activity or behavior, however, it was not biologically beneficial. Among the stimulatory effects cited was increased potassium extrusion; but cells take in K^+ against a concentration gradient, and K^+ extrusion is generally considered an indicator of membrane damage! Classifying radiation as a law of nature made the concept even less acceptable, since its occurrence was rarely verifiable; furthermore, if a phenomenon is a law of nature there is little incentive to seek a mechanism!

A personal perspective

In 1961 I began to use insects, particularly *T. confusum* and *T. castaneum*, as the experimental tools in my radiobiological research. I wanted to use insects because of their previously mentioned lack of dependence on somatic cell proliferation, and chose flour beetles because their nutritional requirements were known and so, like some nematode worms, they could be grown on defined media. I hoped (naively) that I would be able to learn which metabolic pathways were involved in recovery from radiation damage and, possibly, in the aging process. I soon found a paper (Cork, 1957) reporting that irradiating newly emerged adult flour beetles [a physicist, he wrote of *newly-hatched individuals*, but correspondence with one of his associates confirmed that he had meant *newly-eclosed*]. Neither Cork nor Davey separated the sexes. Using *T. castaneum*, I found (Ducoff, 1975) that irra-

diation markedly increased mean life expectancy in sexually-segregated adults of both sexes. There was little or no increase in maximum life span, but great reduction or delay in early mortality. This pattern has been reported, or is seen in published data, for several insect species and by various authors. Being familiar with the publications on *Musca* and on *Drosophila*, I did not regard the effect as necessarily beneficial, and so I avoided (or evaded) the hormesis controversy. This left me free to worry about mechanism!

The usual manifestations cited for chemical hormesis are induction [by low doses of a chemical] of resistance to later challenge by the inducing chemical or by similarly-acting chemicals, or increased rates of growth or development, but not enhanced longevity. Could radiation induce resistance to subsequent irradiation? After Elkind and Sutton (1959) demonstrated that cells could repair damage by ionizing radiation, numerous investigations at the molecular level showed that many radiation-induced DNA lesions are eliminated by excision-repair processes similar to those acting on UV-induced lesions. It was recognized that, at least in bacteria, there was an UV-inducible repair process [SOS-repair] for DNA lesions produced by UV radiation. More pertinently, desmids exposed to low doses of ionizing radiation developed radioresistance (Howard and Cowie, 1976). Would induced radioresistance affect longevity of insects not deliberately irradiated? Hart and Setlow (1974) measured the UDS [unscheduled DNA synthesis, a manifestation of excision repair] by fibroblasts taken from various mammals [from shrews to elephants] and found remarkable correlation between UDS following standard UV exposure and the mean lifespan of the species, but there was no influence by the age of the donor. Furthermore, they pointed out that many endogenously generated chemicals, such as reactive oxygen entities, produce DNA lesions similar to those produced by radiations. Thus, it appeared logical that low dose irradiation might induce greater capability to repair metabolism-caused DNA damage, thereby enhancing longevity. But if so, why do insects benefit consistently, whereas mammals do not?

Noting that Hart and Setlow had found no influence of donor age on UDS activity in fibroblasts, I postulated (Ducoff, 1976) that the [recognized] DNA damages which occurred during replication maintained repair activity at a genetically-determined high level, but that repair capability would decline over time in terminally-differentiated tissues, and accumulated lesions would interfere with gene transcription and, therefore, with adaptation to stresses. Thus, in mammals and other organisms highly dependent on cell proliferation, even low radiation doses would primarily be detrimental, but in organisms like insects, composed primarily of postmitotic cells, radiation-induced increases in repair capability would lead to benefits from retardation of age-related decline in ability to adapt.

The advantage of this concept was that it might be tested experimentally: If we could identify some stressors to which resistance declined with age, radiation exposure of young adults should retard the age-related decline in resistance. We did find that adult flour beetles became steadily more sensitive to hyperbaric oxygen (Lee and Ducoff, 1983) and to heat, and that beetles which had been irradiated were more resistant to these stresses (Lee and Ducoff, 1984; Ducoff and Lee, 1984). The problem was that stress resistance in the irradiated beetles was considerably greater than in the young controls, so the effect was not simply a retardation of aging! The probable explanation was found in two publications from other groups: Krueger and Walker (1984) found that germicidal UV light stimulated *E. coli* to synthesize heat stress proteins, recognized as the basis for heat-induced heat resistance, and Mitchel and Morrison (1984) reported that UV or ionizing radiation induced development of heat resistance in yeast. Suddenly, there appeared to be a possible mechanism not only for radiation enhancement of insect longevity (Ducoff, 1986), but for many types of radiation hormesis.

The Adaptive Response - Is Hormesis Inevitable?

Why apparently beneficial responses now seem inevitable

Studies with yeast led to an estimate (Ruby and Szostic, 1985) that there were some 80 genes inducible by damage to DNA, and by no means were they all known to be involved in DNA repair! Extensive work on mammalian cells (reviewed by Fornace, 1992; Fornace et al., 1992) showed that many damage-induced genes are associated with growth responses, some stimulatory and some negative.

Perhaps the most influential report in this field was an investigation by Sheldon Wolff, a highly regarded cytogeneticist, and his colleagues (Olivieri et al., 1984) who reported that prior treatment with very low doses of tritium led to an adaptive response in human lymphocytes subsequently challenged with X-rays, and Wolff et al. (1988) gave further evidence that low X-ray doses also rendered the cells refractory to X-ray induction of chromosome aberrations. Subsequent work by this group (Youngblom et al., 1989) showed that the effect was inhibited by cycloheximide, indicating that induction of radiation resistance required protein synthesis. There is now widespread agreement that DNA damage, induced by any of a number of agents, can induce expression of numerous genes including not only those for DNA repair but also some genes for resistance to stresses by prevention, such as binding heavy metals, and some of as yet unknown function. For example, UV irradiation induces synthesis of metallothioneins, the -SH proteins known to protect against heavy metal toxicity (Fornace et al., 1988). Not

all damaging agents produce the same array of expressed genes, however. Woloschak and Chang-Liu (1990) have shown that even different forms of ionizing radiation elicit different arrays! These considerations have led to the concept of the *adaptive response*. It is interesting to recall that a brief exposure to high temperature was found (Maynard Smith, 1958) to enhance longevity of *Drosophila*!

Why, then, were hormetic effects so frequently denied?

My answer is at least partially speculative, and Calabrese and Baldwin (2000b) express a very different view. The early advocates rushed into publication on the basis of few experiments and, often, as pointed out by Miller and Miller (1987) with inadequate or no statistical analysis. Also, induction of stress-resistance proteins provides no benefit in short-term experiments, unless the system is subjected to external stresses; skeptical investigators who tested reports of better growth, development, or survival were extremely careful to control external factors such as temperature, pH, solvent purity, etc., so benefits, if any, were minimal. Luckey himself (1980, p. 49) commented *The effect is usually magnified by unfavorable conditions.* I have already noted that in our own work on insect longevity, the irradiation primarily reduced early mortality, making the survivorship curves more rectangular; clearly, our conditions [and those of most laboratory experiments with insects] are far from ideal!

Does radiation hormesis require that risk assessment be greatly altered?

Clearly, we do not have enough knowledge to make quantitative estimates of how much radiation exposure might be beneficial, rather than detrimental. The amount and the profile of gene expression induced varies not only with the type of radiation, but with the stage of the cell cycle exposed. The time interval between exposure and induction is usually a matter of several hours; the duration of the induction is rarely measured but appears to be somewhat longer. Would a low dose have to be repeated regularly for long-term benefit in a long-lived creature like *H. sapiens?*

The qualitative problem is even more disturbing. The breadth of the adaptive response spectrum—that is, the variety of stress genes induced—is matched by the breadth of the spectrum of inducing agents. How does low dose radiation exposure interact with low dose exposure to other environmental inducers? I am not aware of any studies designed to examine such interactions, although many reports indicate that increasing the size of the "low radiation dose" has little or no greater inducing effect. Would there be synergism, additivity, or antagonism if inducing doses of radiation and of heat or heavy metals were administered at the same time?

Conclusion

We have seen that the "modern era" of radiation hormesis study began with Sacher's analysis of the Lorenz rodent data. It is fitting to conclude this review with Sacher's (1963) concluding remarks in his paper reporting increased longevity in irradiated *D. melanogaster*, written long before there was any concept of a molecular basis for the phenomenon. He had noted a reduction in variability of mean after-survival between replicates of the irradiated samples, and he attributed both the reduction of variability and the improved survival to a reduction in the effectiveness of a deleterious environmental variable:

> *It cannot be determined whether this reduced effectiveness results from an inactivation of the environmental factor or from an increase in resistance induced in the flies by the radiation exposure.*

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Meta-analysis of non-tumour doses for radiation-induced cancer on the basis of dose-rate

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Abstract

Purpose: Quantitative analysis of cancer risk of ionising radiation as a function of dose-rate.

Materials and methods: Non-tumour dose, D_{nt}, defined as the highest dose of radiation at which no statistically significant tumour increase was observed above the control level, was analysed as a function of dose-rate of radiation.

Results: An inverse correlation was found between D_{nt} and dose-rate of the radiation. D_{nt} increased 20-fold with decreasing dose-rate from 1–10^{-8} Gy/min for whole body irradiation with low linear energy transfer (LET) radiation. Partial body radiation also showed a dose-rate dependence with a 5- to 10-fold larger D_{nt} as dose rate decreased. The dose-rate effect was also found for high LET radiation but at 10-fold lower D_{nt} levels.

Conclusions: The cancer risk of ionising radiation varies 1000-fold depending on the dose-rate of radiation and exposure conditions. This analysis explains the discrepancy of cancer risk between A-bomb survivors and radium dial painters.

Keywords: *radiation cancer risk, non-tumour dose, dose-rate*

Introduction

The dose-rate of ionising radiation that humans have been exposed to from natural to accidental radiation sources varies over a wide range from 10^{-9} to 10^{7} Gy/min. Radiation dose-rate affects the magnitude of cancer risk even for the same total dose, and in addition changes the shape of the dose-response curve. For assessment of cancer risks of ionising radiation resulting from different exposure conditions, ideally, a set of dose response curves is needed for each dose-rate.

Currently, the estimation of human cancer risk from low doses of radiation is an important problem and data have been extensively reviewed (Committee on the Biological Effects of Ionizing Radiation [BEIR]/National Research Council [NRC], United Nations Scientific Committee on the Effects of Atomic Radiation [UNSCEAR] 1986, 2000, National Council on Radiological Protection and Measurements [NCRP] 1980, BEIR V 1990, BEIR VII 2005, National Radiological Protection Board [NRPB] 1995, Duport 2003). The dose and dose-rate effectiveness factor (DDREF) for cancer risk was determined as 2–10 depending on the target organ (NCRP 1980, International Commission on Radiological Protection [ICRP] 1991, UNSCEAR 1993, NRPB 1995). The application of the linear non-threshold (LNT) model, based on the apparently linear dose-response relation of cancer mortality obtained from extremely high dose-rate cases of A-bomb survivors, was recommended for the estimation of the cancer risk of low dose radiation for protection purposes (NCRP 2001, Brenner et al. 2003, BEIR VII 2005, ICRP 2006); however, the LNT model was questioned for its validity from experimental and epidemiological evidence (Kondo 1993, Académie des Sciences 1997, Tanooka 2001, Tubiana et al. 2006, Feinendegen et al. 2007). The history of the LNT model explains how the idea of a tolerance dose was changed to the linearity concept by incorporating the view of the geneticist (Calabrese 2009). However, a recent review of new biological and epidemiological data still adopted the LNT model (Mullenders et al. 2009). Whatever the model, there exists both linear and threshold type dose-response relations for

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radiation-induced cancers in experimental and epidemiological data. For example, the shape of the dose-response curve for cancer incidence may conform to a linear type for leukemia and solid cancers in A-bomb survivors (Chomentowski et al. 2000), while it is non-linear, or even threshold-like, for bone tumours in radium dial painters (Rowland et al. 1978) and liver tumours in thorotrast-injected patients (Anderson and Storm 1992). This discrepancy remained still to be explained.

In a previous study, non-tumour dose, D_{nt}, was defined as the highest dose at which no statistically significant tumour increase was observed above the control level. It was proposed as a measure of the upper limit of radiation dose for non-detectable cancer and D_{nt} values were surveyed for in the literature. The results showed that D_{nt} depended on exposure conditions, i.e., acute, protracted, and chronic exposures for whole body and partial body radiation for either low linear energy transfer (LET) or high LET radiation, respectively, with an inverse correlation between D_{nt} and dose-rate (Tanooka 2001). The present study aimed to show the dose-rate dependence of D_{nt} more quantitatively as a function of the dose-rate of radiation.

Data base

Dose-response data covering ionising radiation exposures from non-tumour to tumour-inducing doses were surveyed in the literature and are listed in Table I. These include D_{nt} values, and corresponding dose-rates of radiation in mice, rats, dogs, and humans with different tumour types obtained under different exposure conditions. Data in the previous study (Tanooka 2001) and additional data were used for the present quantitative analysis. The data numbers in the previous study were unchanged for the convenience of comparison.

Estimation of dose-rate

The values for the dose-rate were obtained from each published paper. For external radiation, the dose-rate was clearly presented in the literature either for whole body or partial body exposures. However, for internal radiation from radioactive nuclides, the estimation of dose-rate required assumptions and calculations depending on whether internal radioactive nuclides were distributed in the whole body or deposited partially in the target organ. Moreover, the radioactivity decayed with time and the radioactive nuclide was cleared from the body. In the present analysis, an average dose-rate was estimated from the total dose divided by the exposure time or, when a decay curve was available, an average dose-rate over the 70% decay time was taken. This calculation may have resulted in a lower estimate of dose-rate and a higher estimate of D_{nt}, provided that the radiation dose given only in the first half of the exposure time was effective for tumour induction. However, correction for this gave little change in the plot of D_{nt} versus dose-rate on a bi-logarithmic scale.

Results and discussion

Numerical values for D_{nt} and corresponding dose-rates obtained from various tumour systems are listed in Table I. These values were divided into four groups, i.e., whole body irradiation with low LET and high LET radiation and partial body irradiation with low LET and high LET radiation, respectively. Figure 1 shows a plot of D_{nt} against dose-rate on a bi-logarithmic scale and regression lines fitted to the data for dose-rates below 1 Gy/min. A clear dose-rate dependence of D_{nt} is seen for the four exposure patterns.

For whole body irradiation with low LET radiation, D_{nt} increased when lowering the dose-rate below 1 Gy/min and became 20-fold higher at 10^{-8} Gy/min (Figure 1a). Only one point for humans was available for the high dose-rate 10^{7} Gy/min, based on the assumption that the A-bomb radiation was delivered in 1 μsec. It appeared that D_{nt} is constant for dose-rates between 1 and 10^{7} Gy/min, as shown by the horizontal line in Figure 1a. For high LET irradiation of the whole body, there were few data available, but the dose-rate dependence of D_{nt} was seen at a level about 10- to 20-fold lower than for low LET radiation, although high LET radiation has been considered to have no dose-rate effect.

For partial body irradiation, the dose-rate dependence of D_{nt} was again seen for both low LET and high LET radiation (Figure 1b). Dose-response data for dose-rates higher than 10 Gy/min were not available in the literature. The D_{nt} level of partial body radiation was about 5- to 10-fold higher for low LET radiations and 3- to 5-fold higher for high LET radiations than those for whole body radiation.

At an extremely high dose-rate for whole body radiation, A-bomb survivor data (Shimizu et al. 1990) gave a D_{nt} of 0.2 Gy for leukemia mortality; while mouse data from nuclear detonation experiments at similar dose-rates showed a significant increase in pituitary and Harderian gland tumours at the same dose, 0.2 Gy (Furth et al. 1954). Consequently, humans seem to be more tolerant to radiation than mice and the regression lines drawn from animal data may under-estimate D_{nt} for humans. D_{nt} values, for partial body high-LET radiation to radium dial painters (Rowland et al. 1973, 1978) and thorotrast-injected patients (Anderson and Storm 1992), were much larger than those for experimental animals (Figure 1b), again indicating a higher radiation

Table I. Dose-rate of radiation and non-tumour dose, D_{nt}.

Data number	Subject		Radiation[a]	Tumour	Dose-rate, Gy/min	Non-tumour dose D_{nt}, Gy	Reference
I. Acute exposure							
1	Mouse	RFM/Un	WB γ-ray	thymic lymphoma	0.45	0.1	Ullrich et al. (1976)
2	"	"	"	Harderian tumour	0.45	0.1	"
3	"	"	"	uterine tumour	0.45	0.25	"
4	"	"	"	mammary tumour	0.45	0.25	"
5	"	"	"	myeloid luekemia	0.45	0.25	Ullrich & Storer (1979a)
6	"	"	"	reticulum cell sarcoma	0.45	*>3	Ullrich et al. (1976), Ullrich & Storer (1979a)
7	"	"	"	ovarian tumour	0.45	0.1	Ullrich et al. (1976), Ullrich & Storer (1979b)
8	"	"	"	pituitary tumour	0.45	0.25	"
9	"	"	"	lung adenoma	0.45	2	"
10	"	"	"	thymic lymphoma	0.45	0.1	Ullrich & Storer (1979c)
11	"	"	WB γ-ray, protracted	"	5.8×10^{-5}	0.5	"
12	"	"	"	ovarian tumour	5.8×10^{-5}	0.5	"
13	"	"	PB X-ray	lung adenoma	4	2.5	Ullrich et al. (1979)
14	"	"	PB neutron	"	5×10^{-2}	0.1	"
15	"	BALB/c	WB γ-ray	lung adenocarcinoma	0.4	0.1	Ullrich (1983)
16	"	"	"	ovarian tumour	0.4	0.1	"
17	"	"	WB fission neutron	"	5×10^{-2}	0.025	"
18	"	"	WB ^{252}Cf neutron	"	7×10^{-5}	0.05	Ullrich (1984)
19	"	"	WB γ-ray	thymic lymphoma	4	2	Maisin et al. (1983)
20	"	BC3F1	WB X-ray	hepatocellular carcinoma	1.3	0.5	Di Majo et al. (1986)
21	"	"	"	solid tumour, malignant lymphoma	6×10^{-2}	0.64	Covelli et al. (1988)
22	"	"	WB neutron	"	1.7×10^{-5}	0.04	"
23	"	Swiss	PB electron	skin tumour	5.5	0.8	Albert et al. (1972)
24	"	CBA/H	PB β ray fractionated	"	5.5, split	*60	Hulse & Mole (1969)
25	Rat	WAG/Rij	WB γ-ray, fractionated	mammary carcinoma	4×10^{-4}	1	Bartsra et al. (2000)
26	"	Long-Evans	PB X-ray	thyroid adenoma	2.5	1	Lee et al. (1982)
27	"	Sprague-Dawley CD	PB β-ray	skin tumour	5	10	Burns et al. (1975, 1993)
28	"	"	PB electron	"	5, split	*20	Burns et al. (1975)
29	"	"	PB proton	"	1.38	0.75	Burns et al. (1978)
30	Human	A-bomb survivor	WB γ ray, neutron	leukemia	1×10^{8}	*0.2	Shimizu et al. (1990)
II. Chronic exposure							
1) Internal radiation							
31	Mouse	CF1	PB ^{90}Sr β-ray, injected	bone sarcoma	2×10^{-5}	20	Finkel et al. (1959)
32	"	BC3F1	WB ^{3}H β-ray, oral	thymic lymphoma	6.4×10^{-7}	0.71	Yamamoto et al. (1998)
33	Rat	Long-Evans	PB ^{131}I β-ray, injected	thyroid adenoma	1.7×10^{-4}	3.3	Lee et al. (1982)
34	"	Sprague-Dawley	PB ^{237}Np β-ray, inhaled	lung tumour	7×10^{-4}	1	Dudoignon et al. (1999)
35	"	"	PB ^{222}Rn α-ray, inhaled	"	3×10^{-5}	0.19	Morlier et al. (1994)

(*continued*)

Table I. (*Continued*).

Data number	Subject		Radiation[a]	Tumour	Dose-rate, Gy/min	Non-tumour dose D_{nt}, Gy	Reference
36	〃	Wister	PB $^{238}PuO_2$ α-ray, inhaled	〃	2.5×10^{-4}	0.25	Sanders et al. (1977)
37	〃	〃	PB $^{239}PuO_2$ α-ray, inhaled	〃	3.4×10^{-7}	0.05	〃
38	〃	〃	PB $^{244}CmO_2$ α-ray, inhaled	〃	1.9×10^{-5}	0.18	Sanders & Mahaffey (1978)
39	Dog	beagle	PB ^{90}Sr β-ray, injected	bone sarcoma	6×10^{-3}	30	Mays & Finkel (1980)
40	〃	〃	〃	〃	3.2×10^{-3}	6.7	White et al. (1993)
41	〃	〃	PB ^{144}Sr β-ray, inhaled	lung tumour	1.3×10^{-5}	5	Hahn et al. (1999)
42	〃	〃	PB ^{226}Ra α-ray, injected	bone sarcoma	5×10^{-7}	0.9	White et al. (1994)
43	〃	〃	〃	〃	7×10^{-7}	2	Rowland et al. (1973)
44	〃	〃	PB ^{228}Ra β-ray, injected	〃	2.8×10^{-7}	5	〃
45	Human	thorotrast patient	PB $^{232}ThO_2$ α-ray, injected	liver cancer	1.1×10^{-7}	*2	Anderson & Storm (1992)
46	〃	dial painter	PB $^{226}Ra + ^{228}Ra$ α + β, oral	bone sarcoma	4.9×10^{-7}	*10	Rowland et al. (1978)
2) External radiation							
47	Mouse	RFM/Un male	WB γ-ray	myeloid leukemia	3×10^{-5}	1.5	Upton et al. (1970)
48	〃	RFM/Un female	〃	〃	5×10^{-6}	2.5	〃
49	〃	CBA/H	PB ^{204}Tl β-ray, skin	skin tumour	2×10^{-2}	16	Hulse et al. (1983)
50	〃	ICR	PB $^{90}Sr-^{90}Y$ β-ray, skin	〃	1.5 Gy/week, 6 months	*40	Ootsuyama & Tanooka (1991, 1993)
51	Dog	beagle	WB γ-ray, continuous	myeloproliferative disease	2×10^{-6}	8.6	Thompson (1989)
52	Human	high radiation background area in India	〃		1.3×10^{-8}	*no cancer increase	Nair et al. (1999)
53	〃	high radiation background area in China	〃		5.7×10^{-9}	*no cancer increase	Chen & Wei (1990)
Data added							
54	Dog	beagle	PB ^{226}Ra α-ray	bone sarcoma	7×10^{-7}	0.44	Raabe (1984)
55	Mouse	C.B-17	WB γ-ray	thymic lymphoma	5×10^{-1}	1	Ishii-Ohba et al. (2007)
56	〃	C57BL/6j	〃	〃	2×10^{-5}	*>7	Ina et al. (2005)
Natural background radiation level					1.8×10^{-9}		

[a]WB: Whole body radiation. PB: Partial body radiation.
*Not included in calculation for the regression line.

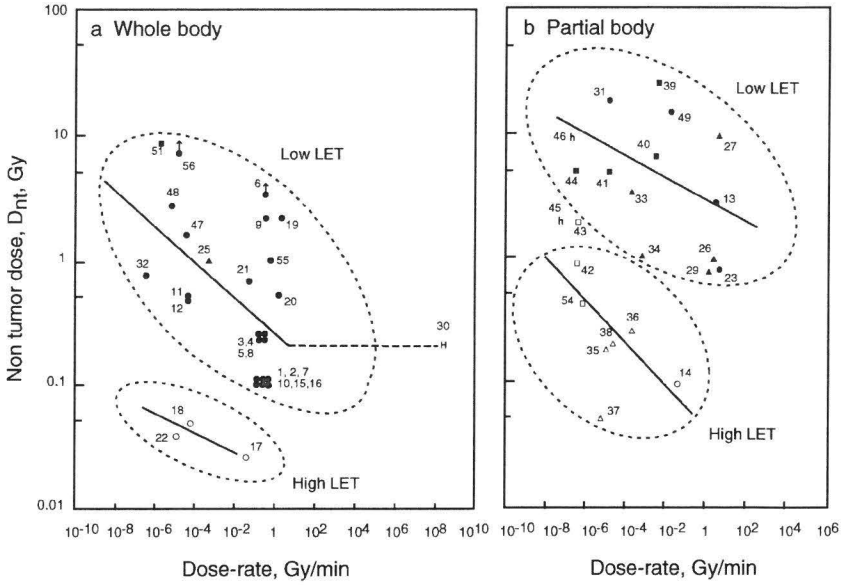

Figure 1. Non-tumour dose, D_{nt}, plotted as a function of the dose-rate of radiation. (a) Whole body radiation. (b) Partial body radiation. Block symbols, low LET; open symbols, high LET. Mouse (●, ○); rat (▲, △); dog (■, □); human, whole-body low LET (**H**); and human, partial body high LET (**h**). Arrows indicate D_{nt} higher. Numbers affixed to each point are data numbers (see Table I).

tolerance of humans. The other extreme case is the absence of thymic lymphoma induction in mice irradiated at 2×10^{-5} mGy/min with a total whole body dose of 7.2 Gy; whereas, acute radiation given in four fractions with the same total dose yielded a 90% tumour incidence (Ina et al. 2005), as was originally found in the early experiments of Kaplan and Brown (1952).

Fractionation of radiation dose at a fixed dose-rate within a defined time interval lowers cancer incidence, as shown in the induction of skin tumours by local irradiation in rats (Burns et al. 1973, 1975, 1993). However, fractionation necessarily involves repetitive irradiations, which results in a tumour-enhancing effect as seen for mouse thymic lymphoma induction (Kaplan and Brown 1952) and also in mouse skin tumour induction (Ootsuyama and Tanooka 1991). It should be noted that the repetitive treatment is efficient for chemical induction of tumours. This contradictory effect should be considered in analysing the dose-rate effect.

Figure 2 summarises the regression lines for the four exposure patterns. These four lines are thought to cover all possible radiation exposure cases and hopefully to serve as a measure of cancer risk for any exposure situation in the human environment. Total whole body radiation doses received over 70 years from the natural environment high background radiation areas in Kerala, India (Nair et al. 1999) and Yanjiang, China (Chen and Wei 1991) are much smaller than D_{nt} for the respective dose-rates in each district (Figure 2). The radiation dose to astronauts in space (Horneck et al. 2003) is also shown in Figure 2, indicating a value close to D_{nt} even with a radiation shield. The cancer risk of medical examination with computer tomography (CT) has been analysed on the basis of whole-body data of A-bomb survivors (Berrington de Gonzalez and Darby 2004); however, this risk should have been analysed on the basis of partial body data. The highest possible dose for CT was still far lower than the corresponding D_{nt}. Recently, Tubiana et al. (in press) reported the dose response of second cancer incidence after radiation therapy with a D_{nt} of about 1 Gy based on a large number of patients. This study provides important data on human exposure to partial body low LET radiation.

There are differences in the radiation sensitivity of tumour induction, depending on the type of tumour and host sensitivity. D_{nt} is much smaller in repair-deficient mice compared to wild-type mice (Ishii-Ohba et al. 2007), indicating that the regression lines represent the wild-type character of the hosts. Currently, a large scale life-time exposure of mice to external γ rays with graded dose-rates from 1–800 mGy per 22 h a day (dose-rate: 7.5×10^{-6} – 6×10^{-3} Gy/min, total dose for 3 years: 1.1 – 876 Gy) together with control mice is being conducted and chromosome aberration data have been reported (Tanaka et al. 2009). Such experiments will give more accurate data for the effect of dose-rate on tumour induction. Further data will be needed to cover the whole dose-rate range for tumour induction.

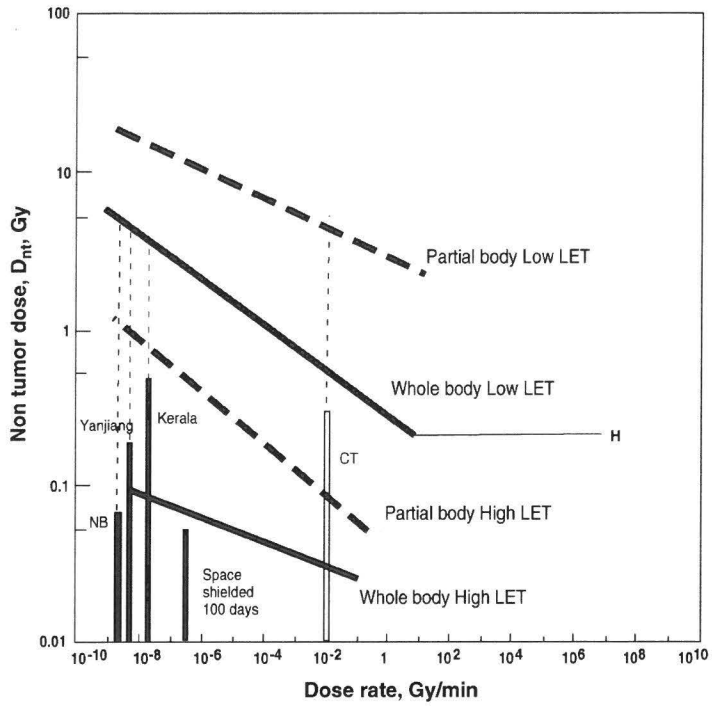

Figure 2. Summary of regression lines for non-tumour dose, D_{nt}, versus dose-rate of radiation. Regression lines for dose-rate range from 10^{-8} to 1 Gy/min: whole body low LET, $Y = 0.258\ X^{-0.141}$, $R^2 = 0.320$; whole body high LET, $Y = 0.0207\ X^{-0.0733}$, $R^2 = 0.781$; partial body low LET, $Y = 2.69\ X^{-0.0857}$, $R^2 = 0.147$; partial body high LET; $Y = 0.0439\ X^{-0.167}$, $R^2 = 0.303$. Bars: radiation doses received by residents in natural (NB) and high background areas in Kerala, India, and Yanjiang, China, over 70 years. CT: possible highest dose to patients under CT examination. Space: possible highest dose in space using a 10 g/cm^2 shield for six months. Dotted vertical lines indicate the difference between exposure dose and corresponding D_{nt} value.

Summary

Meta-analysis of the non-tumour dose, D_{nt}, of ionising radiation showed a clear dependence on dose-rate over a wide range for four exposure conditions, i.e., whole body irradiation with low LET or high LET radiation and partial body irradiation with low LET or high LET radiation. From the regression lines for the relation between dose-rate and D_{nt}, a cancer risk or tolerance level of radiation could be estimated for a variety of exposure conditions. An apparent discrepancy in radiation-induced tumour data could be explained in terms of dose-rate.

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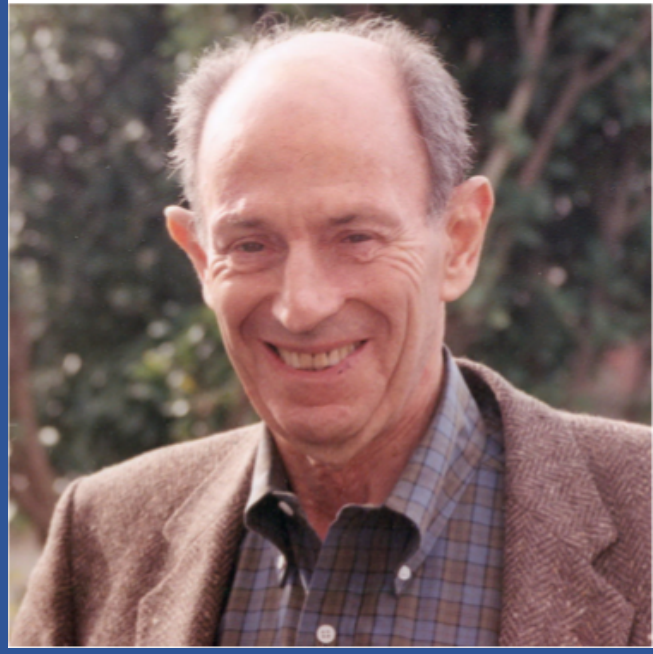
THE LINEAR NO-THRESHOLD (LNT) MYTH AND ITS COROLLARY, ALARA

Carol S. Marcus, Ph.D., M.D.
David Geffen School of Medicine at UCLA

THIS PRESENTATION IS DEDICATED TO THE MEMORY OF MYRON POLLYCOVE, M.D., A CALIFORNIA NUCLEAR MEDICINE PHYSICIAN WHO WORKED FOR TWENTY YEARS TO DESTROY THE LNT AS A BASIS FOR RADIATION REGULATION.



I WISH TO DEEPLY THANK THE PEOPLE WHO HAVE HELPED ME WITH SLIDES AND MATERIAL FOR THIS PRESENTATION. IN ALPHABETICAL ORDER:

WADE ALLISON, JERRY CUTLER, MOHAN DOSS, LUDWIG FEINENDEGEN, ALAN FELLMAN, ROBERT HARGRAVES, T.D. LUCKEY, MARK MILLER, DOUG OSBORNE, MYRON POLLYCOVE, JEFF SIEGEL, MICHAEL STABIN, REBECCA TERRELL, AND BRANDT ULSH.

THE CONCEPT OF LNT APPEARS TO BE VERY CONTENTIOUS THESE DAYS, BUT IT ISN'T REALLY CONTENTIOUS. IT'S JUST WRONG.

Let's start by looking at its definition.

THE LNT STATES THAT:

ONE RADIATION HIT CAN CAUSE A DNA MUTATION THAT CAN CAUSE A CANCER THAT CAN CAUSE DEATH.

ALL RADIATION DOSES ARE ADDITIVE AND THE DOSE RATE DOES NOT MATTER, SO A DOSE RECEIVED INSTANTANEOUSLY CAUSES THE SAME DAMAGE AS THE SAME DOSE RECEIVED VERY SLOWLY OVER A LONG PERIOD OF TIME.

NO PROCESSES EXIST AT LOW DOSE THAT DO NOT EXIST AT HIGH DOSE. THEREFORE, THERE IS NO SUCH THING AS RADIATION REPAIR.

LET'S LOOK CRITICALLY AT THESE ASSUMPTIONS:

"ONE RADIATION HIT CAN CAUSE A DNA MUTATION THAT

CAN CAUSE A CANCER THAT CAN CAUSE DEATH."

STEM CELLS THAT GIVE RISE TO CANCER CONTAIN THOUSANDS OF MUTATIONS INCLUDING NUMEROUS ESSENTIAL DRIVER MUTATIONS. ACCORDING TO MICHAEL BISHOP, NOBEL LAUREATE DISCOVERER OF THE ONCOGENE, "A SINGLE MUTATION IS NOT ENOUGH TO CAUSE CANCER. IN A LIFETIME, EVERY SINGLE GENE IS LIKELY TO HAVE UNDERGONE MUTATION ON ABOUT 10^{10} SEPARATE OCCASIONS IN ANY INDIVIDUAL HUMAN BEING. THE PROBLEM OF CANCER SEEMS TO BE NOT WHY IT OCCURS, BUT WHY IT OCCURS SO INFREQUENTLY."

LET’S LOOK AT WHAT CAUSES THESE MUTATIONS.

THE GREATEST POISON IS……..

OXYGEN!!

10^{6} DNA MUTATIONS/CELL/DAY ARE PRODUCED BY ABOUT 10^{9} FREE RADICALS/CELL/DAY DERIVED FROM THE METABOLISM OF OXYGEN.

10^{-7} MUTATIONS/CELL/DAY ARE PRODUCED BY LOW LINEAR ENERGY TRANSFER (LET) BACKGROUND RADIATION (X AND GAMMA RAYS, BETA PARTICLES) AMOUNTING TO 0.1 CGY (RAD) PER YEAR. THESE MUTATIONS ARE ALSO CAUSED BY FREE RADICALS.

LET'S LOOK CRITICALLY AT THE NEXT ASSUMPTION:

ALL RADIATION DOSES ARE ADDITIVE AND THE DOSE RATE DOES NOT MATTER, SO A DOSE RECEIVED INSTANTANEOUSLY CAUSES THE SAME DAMAGE AS THE SAME DOSE RECEIVED VERY SLOWLY OVER A LONG PERIOD OF TIME.

INCONTROVERTIBLE RESEARCH HAS SHOWN THAT DOSES RECEIVED GRADUALLY ARE FAR LESS HAZARDOUS AND CARCINOGENIC THAN THE SAME RADIATION DOSE RECEIVED INSTANTANEOUSLY.

THE INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION (ICRP), AN ABSOLUTELY COMMITTED LNT ADVOCATE ORGANIZATION, HAS CAVED AND INTRODUCED A "DOSE AND DOSE RATE EFFECTIVENESS FACTOR" OF 2 TO RECOGNIZE THE DECREASED EFFECT OF LOW DOSE RATE. WHILE THIS FACTOR ISN'T *NEARLY* ENOUGH, THE ADMISSION OF DECREASED LOW DOSE RATE EFFECT BASICALLY IS AN ADMISSION THAT LNT IS NOT TRUE.

ONE OF THE MOST OBVIOUS EXAMPLES IS THE WHOLE PRACTICE OF RADIATION ONCOLOGY, OVER A CENTURY OLD. IF A DOSE OF 60 GY (6000 RADS) IS TO BE DELIVERED, WE DON'T GIVE IT ALL AT ONCE. WE'D BURN A HOLE IN THE PATIENT. WE GIVE IT GRADUALLY, FIVE DAYS A WEEK OVER ABOUT SIX WEEKS. WHY? BECAUSE NORMAL TISSUE REPAIRS ITSELF MUCH MORE EFFICIENTLY THAN DOES CANCER TISSUE, SO LONG AS THE REPAIR MECHANISMS ARE STIMULATED BY A DOSE THAT ISN'T TOO LARGE.

LET'S LOOK CRITICALLY AT THE LAST ASSUMPTION:

NO PROCESSES EXIST AT LOW DOSE THAT DO NOT EXIST AT HIGH DOSE.

THEREFORE, THERE IS NO SUCH THING AS RADIATION REPAIR.

THIS IS THE CRUX OF THE PROBLEM WITH LNT. AFTER LOW DOSE AND DOSE RATE RADIATION, NUMEROUS TYPES OF REPAIR MECHANISMS ARE SEEN THAT ARE INHIBITED AFTER HIGH DOSE RATE RADIATION.

OVER 3000 PAPERS HAVE SHOWN REPAIR MECHANISMS FOR DNA.

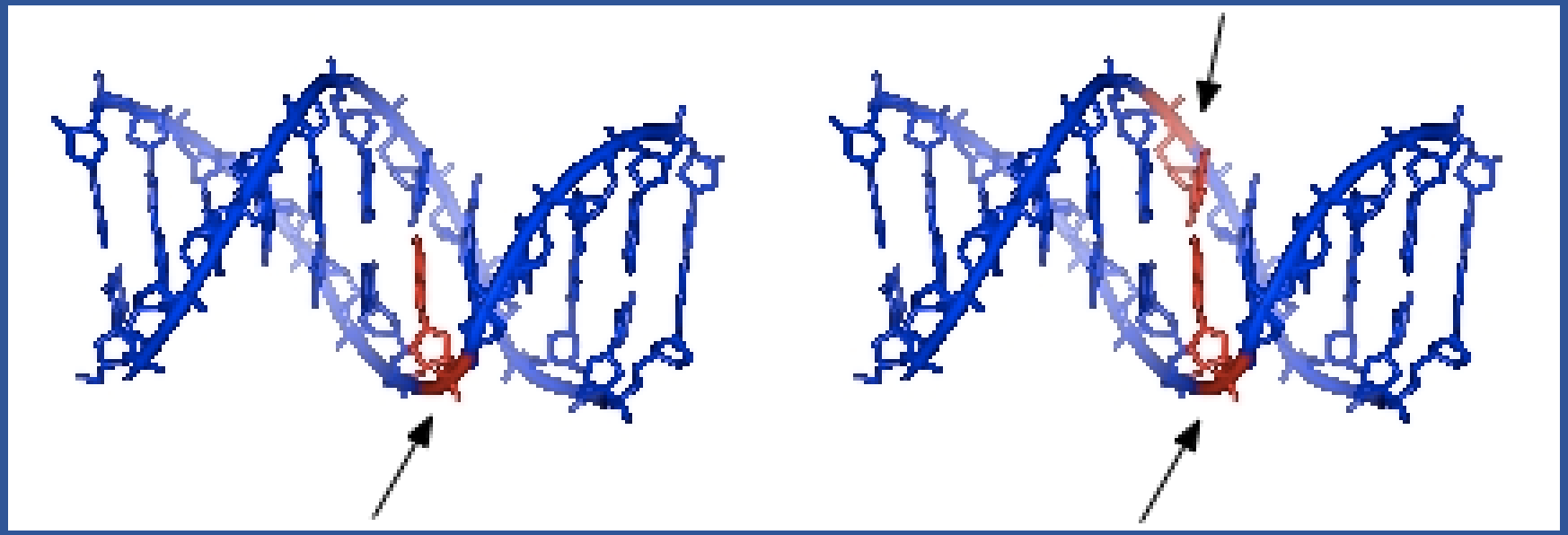
OVER 150 GENES HAVE BEEN IDENTIFIED THAT MAKE COMPOUNDS INVOLVED IN DNA REPAIR.

THE 2015 NOBEL PRIZE IN CHEMISTRY WENT TO TOMAS LINDAHL, PAUL MODRICH, AND ARIZ SANCAR FOR “MECHANISTIC STUDIES OF DNA REPAIR”.

IT IS COMPLETELY IRRATIONAL TO ARGUE THAT DNA REPAIR MECHANISMS DO NOT EXIST. THE EXISTENCE OF REPAIR MECHANISMS AT LOW DOSE AND DOSE RATE DISPROVES THE LNT.

DNA STRAND BREAKS OCCUR FREQUENTLY

Ionized oxygen molecules from metabolism are the principal causes.

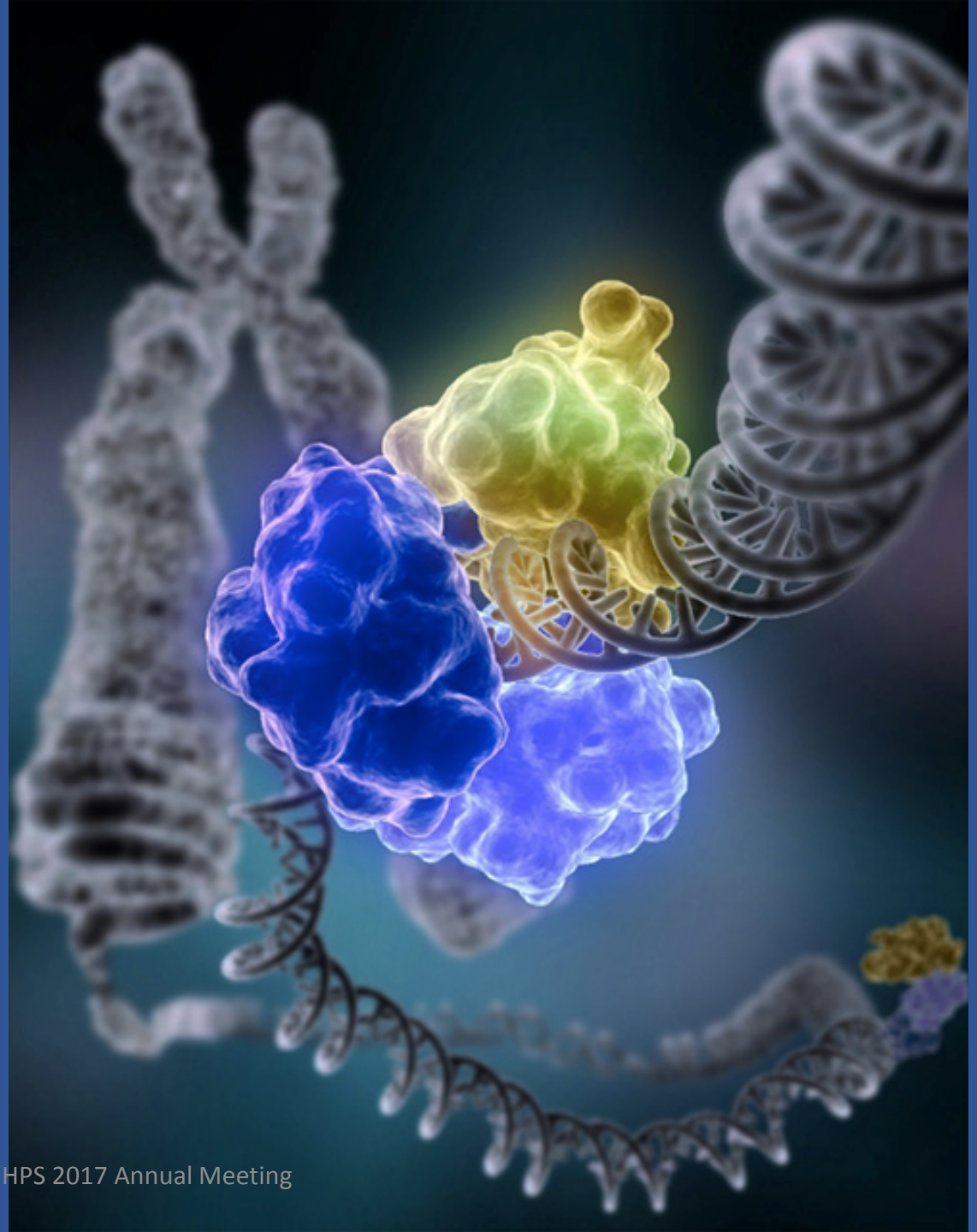


Single strand breaks occur 10,000 times per day per cell. 100 mSv/y radiation adds 12 per day per cell. So EPA's 12 mrem causes an increase to 10,000.01 per day per cell

Double strand breaks occur 10 times per day – 1 per week per cell.
100 mSv/y radiation adds 1 per year.

DNA IS REPAIRED

Special enzyme DNA ligase encircles the double helix to repair a broken strand of DNA.



WHERE DID THE LNT IDEA COME FROM, ANYWAY?

IN 1946 HERMANN J. MULLER WON THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE SHOWING THAT MODERATE TO LARGE DOSES OF RADIATION CAUSED GENETIC MUTATIONS IN FRUIT FLIES. *HOWEVER, HE CLAIMED THAT RADIATION CAUSED MUTATIONS ALL THE WAY DOWN TO ZERO DOSE (LNT).*

HERMANN MULLER'S 1946 NOBEL PRIZE FOR HIS 1926 DISCOVERY OF X-RAY MUTATION OF FRUIT FLIES

…these principles have been extended to total doses as low as 400 r, and rates as low as 0.01 r per minute, with gamma rays. They leave, we believe, no escape from the conclusion that there is no threshold dose, and that the individual mutations result from individual "hits", producing genetic effects …" Muller's *low* doses were really *high.*

THIS CLAIM WAS NOT CHALLENGED AT THE TIME. IT APPEARS TO HAVE BEEN A PLOY TO OBTAIN EXTRA GRANT MONEY FOR GENETICS RESEARCH.

IN 1956 THE NATIONAL ACADEMY OF SCIENCES (NAS) RECOMMENDED THE LNT AS THE BASIS OF RADIATION SAFETY REGULATIONS. MULLER WROTE THE NAS REPORT.

THE ICRP ACCEPTED LNT AS A WORKING MODEL, BUT LATER ACTUALLY BEGAN TO BELIEVE IN IT WITH RELIGIOUS FERVOR.

Binomial statistics applied to fruit fly mutation data measured by Ogura et al. 2009

Dose Gy	Number Lethals y	Chromo somes n	Mutat'n Freq. p = y/n	q = 1–p	Var σ^2 n•p•q	Std. dev. σ	2σ/n %	p + 2σ/n %	p – 2σ/n %
0.005	9	10,500	0.0009	0.9991	9.441	3.07	0.06	0.15	0.03
0.1	2	1507	0.0013	0.9987	1.957	1.399	0.186	0.32	-0.06
1	6	2662	0.0023	0.9977	6.109	2.472	0.186	0.42	0.04
5	8	2055	0.0039	0.9961	7.983	2.825	0.27	0.66	0.12
10	21	2730	0.0077	0.9923	20.86	4.567	0.33	1.10	0.44
0.3	8	4169	0.0019	0.9981	7.906	2.81	0.13	0.32	0.06
7	29	4785	0.0061	0.9939	29.01	5.386	0.225	0.84	0.38

Mutation frequency for controls = 0.0032 … calculated from Ogura

THERE HAVE NEVER BEEN ANY SCIENTIFICALLY VALID STUDIES SUPPORTING THE LNT. THOSE CLAIMING TO SUPPORT IT SHOW STATISTICAL BIAS, DATA LUMPING AT LOW DOSES TO HIDE LOW DOSE EFFECTS, LACK OF DOSE-RESPONSE DATA, CIRCULAR REASONING, FAILURE TO CORRECT FOR CONFOUNDING VARIABLES, AND/OR BAD EXPERIMENTAL DESIGN.

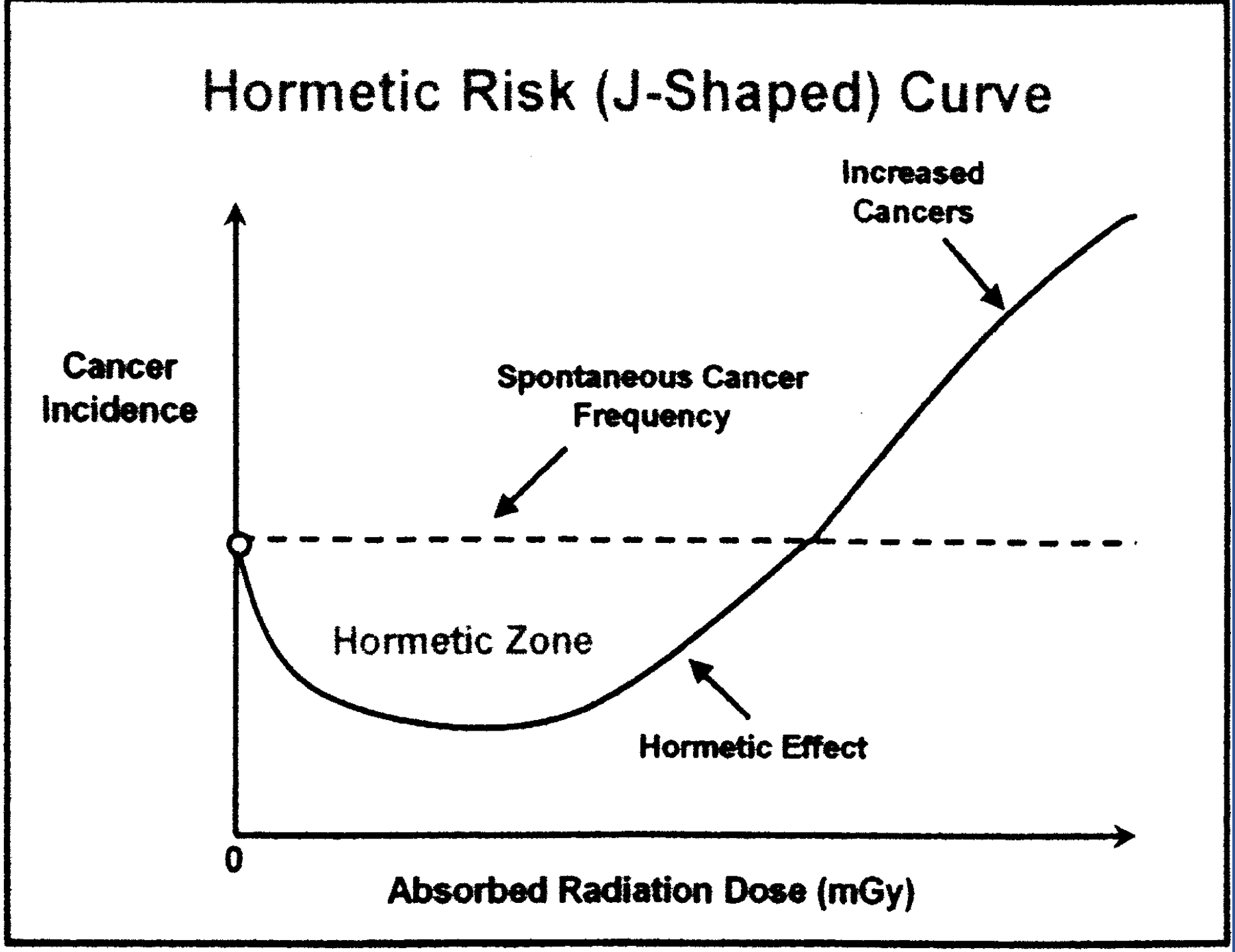
LET US NOW EXAMINE REPAIR MECHANISMS.

THERE ARE THREE GENERAL CLASSES OF REPAIR; (1) ANTIOXIDANT *PREVENTION,* (2) ENZYMATIC *REPAIR* OF DNA DAMAGE, AND (3) *REMOVAL* OF DNA ALTERATIONS BY APOPTOSIS, DIFFERENTIATION, AND THE IMMUNE SYSTEM.

THESE REPAIR SYSTEMS SEQUENTIALLY REDUCE DNA DAMAGE FROM ABOUT 10^6 ALTERATIONS/ CELL/DAY TO ABOUT 1 FIXED DAMAGE (MUTATION)/CELL/DAY. THESE MUTATIONS IN STEM CELLS ACCUMULATE FOR A LIFETIME, WITH PROGRESSION OF DNA DAMAGE THAT IS ASSOCIATED WITH AGING AND CANCER.

THESE REPAIR SYSTEMS ARE NON-SPECIFIC AS TO DAMAGE SOURCE. THEY NOT ONLY REPAIR DAMAGE CAUSED BY RADIATION, BUT DAMAGE CAUSED BY OXYGEN METABOLISM, OTHER POISONS, AND TOXINS. THE IMPORTANT POINT IS THAT ONCE THE REPAIR SYSTEMS ARE STIMULATED BY LOW DOSE AND LOW DOSE RATE RADIATION, THEY REPAIR MUCH MORE DAMAGE THAN WAS CAUSED BY THE RADIATION.

THIS PHENOMENON IS CALLED HORMESIS, IN WHICH LOW DOSES OF PROCESSES OR CHEMICALS WHICH ARE DELETERIOUS AT HIGH DOSES ARE BENEFICIAL AT LOW DOSES. THIS IS A VERY COMMON PHENOMENON. FOR EXAMPLE, LOW DOSES OF IRON ARE NECESSARY FOR LIFE, BUT HIGH DOSES MAY BE FATAL. THE SAME IS TRUE OF VITAMINS. IF YOU APPLIED LNT AND ALARA TO IRON AND VITAMINS YOU WOULD BECOME ANEMIC AND VITAMIN DEFICIENT. WHEN YOU APPLY LNT AND ALARA TO RADIATION, YOU ARE DEPRIVED OF VALUABLE DNA REPAIR. LNT AND ALARA APPLIED TO RADIATION ARE NOT ONLY WRONG, THEY ARE DELETERIOUS. THEY ARE CERTAINLY NOT "CONSERVATIVE".


Hormetic Risk (J-Shaped) Curve
Increased Cancers
Cancer Incidence
Spontaneous Cancer Frequency
Hormetic Zone
Hormetic Effect
0
Absorbed Radiation Dose (mGy)

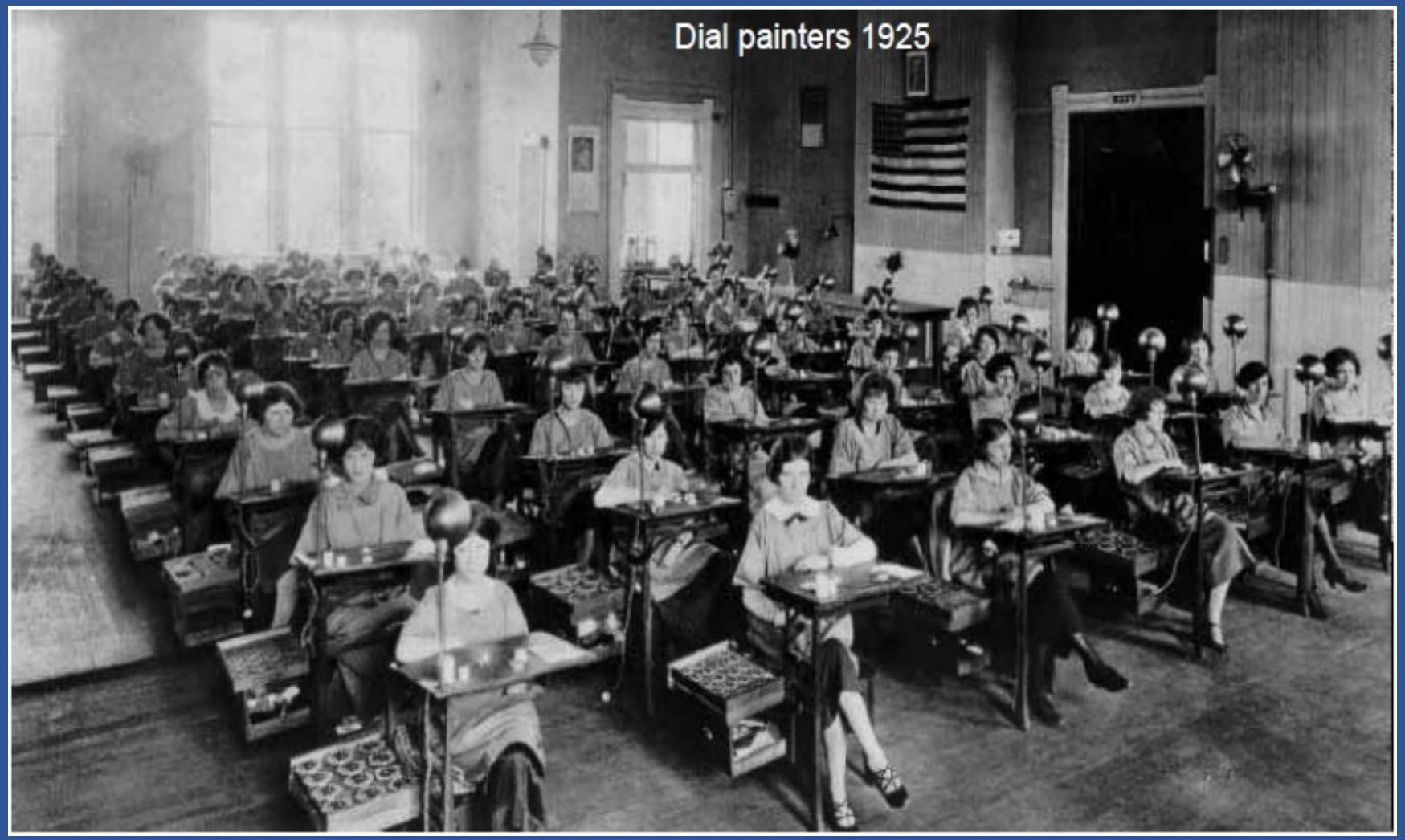
LOW DOSE RADIATION HORMESIS IS PERVASIVE, HAVING BEEN FOUND IN:

MICROORGANISMS
ALGAE
PLANTS
INSECTS
INVERTEBRATES
VERTEBRATES
MAN

THIS IS NOT SURPRISING, GIVEN THE EVOLUTIONARY PRESSURE TO SURVIVE IN AN ATMOSPHERE WITH POISONOUS OXYGEN (A WASTE PRODUCT OF PHOTOSYNTHESIS) AND BACKGROUND RADIATION LEVELS 5-7 TIMES HIGHER THAN TODAY.

IT IS IMPORTANT TO POINT OUT THAT WE DO NOT NEED HUMAN EPIDEMIOLOGIC DATA TO DISPROVE THE LNT. BIOCHEMICAL, CELLULAR, AND ANIMAL DATA ARE SUFFICIENT. HUMAN EPIDEMIOLOGIC DATA ARE USEFUL, BUT THERE ARE OFTEN ISSUES SUCH AS BACKGROUND RADIATION DOSES AND MEDICAL RADIATION DOSES THAT ARE UNKNOWN IN THE PEOPLE INVOLVED, AND IN THE LOW DOSE RANGE THIS CAN BE AN ISSUE.

4133 IDENTIFIED RADIUM DIAL PAINTERS IN USA



BONE CANCER THRESHOLD AT 10 GY OR 1000 RAD OF RADIUM ALPHA RADIATION

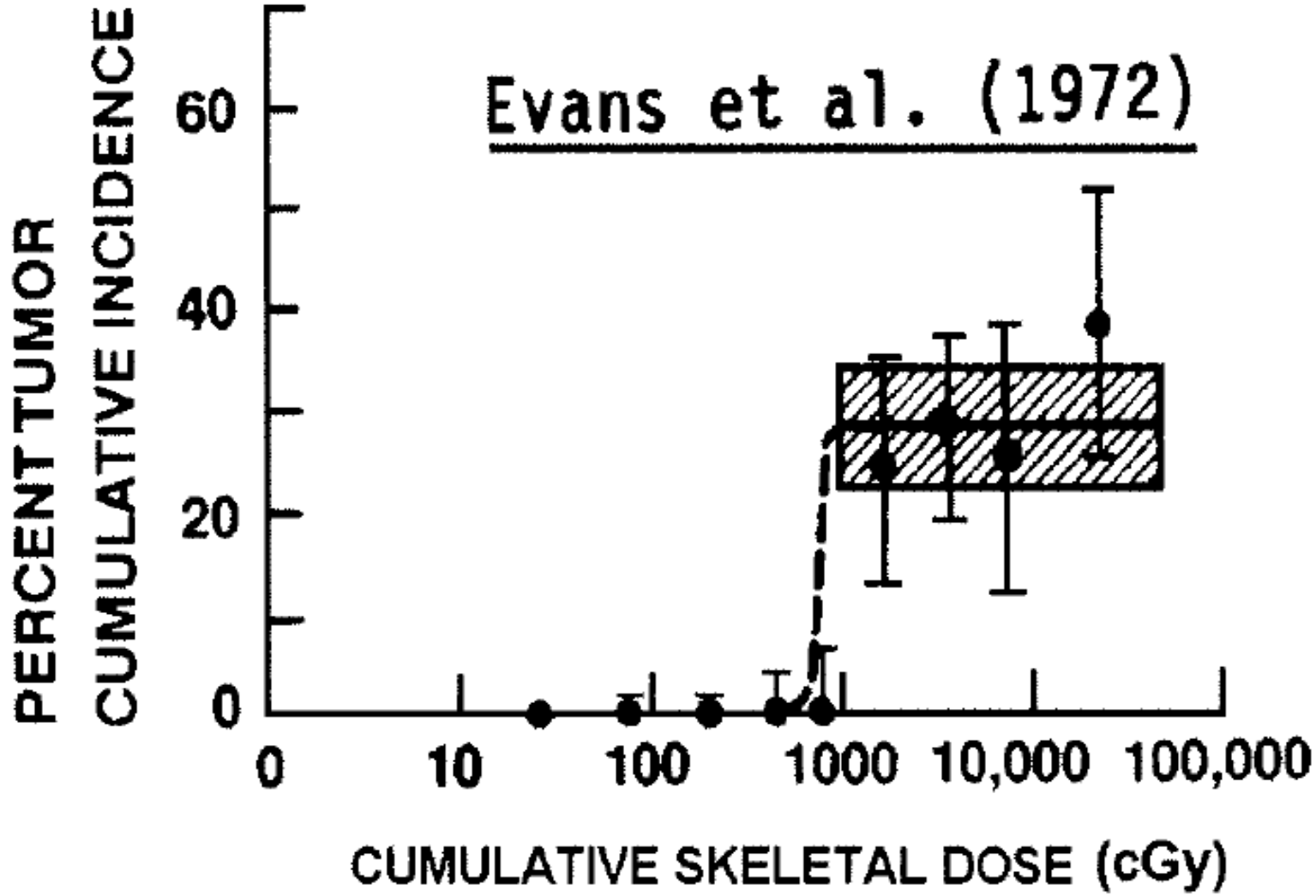
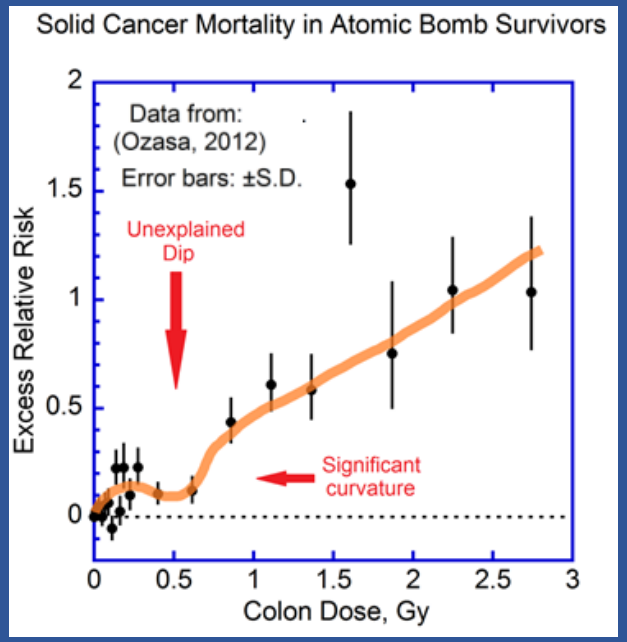


Fig. 11. Cumulative bone sarcoma incidence in people exposed to ^{226}Ra as a function of cumulative dose to the skeleton as reported by Evans et al. (1972).

ONE OF THE MOST IMPORTANT STUDIES OF HUMAN ACUTE RADIATION EFFECTS CONCERNS THE SURVIVORS OF THE ATOMIC BOMBINGS OF HIROSHIMA AND NAGASAKI

LINEARITY IN THE ATOMIC BOMB SURVIVOR DATA (AFTER THE LATEST UPDATE IN 2012)



(Ozasa et al, 2012

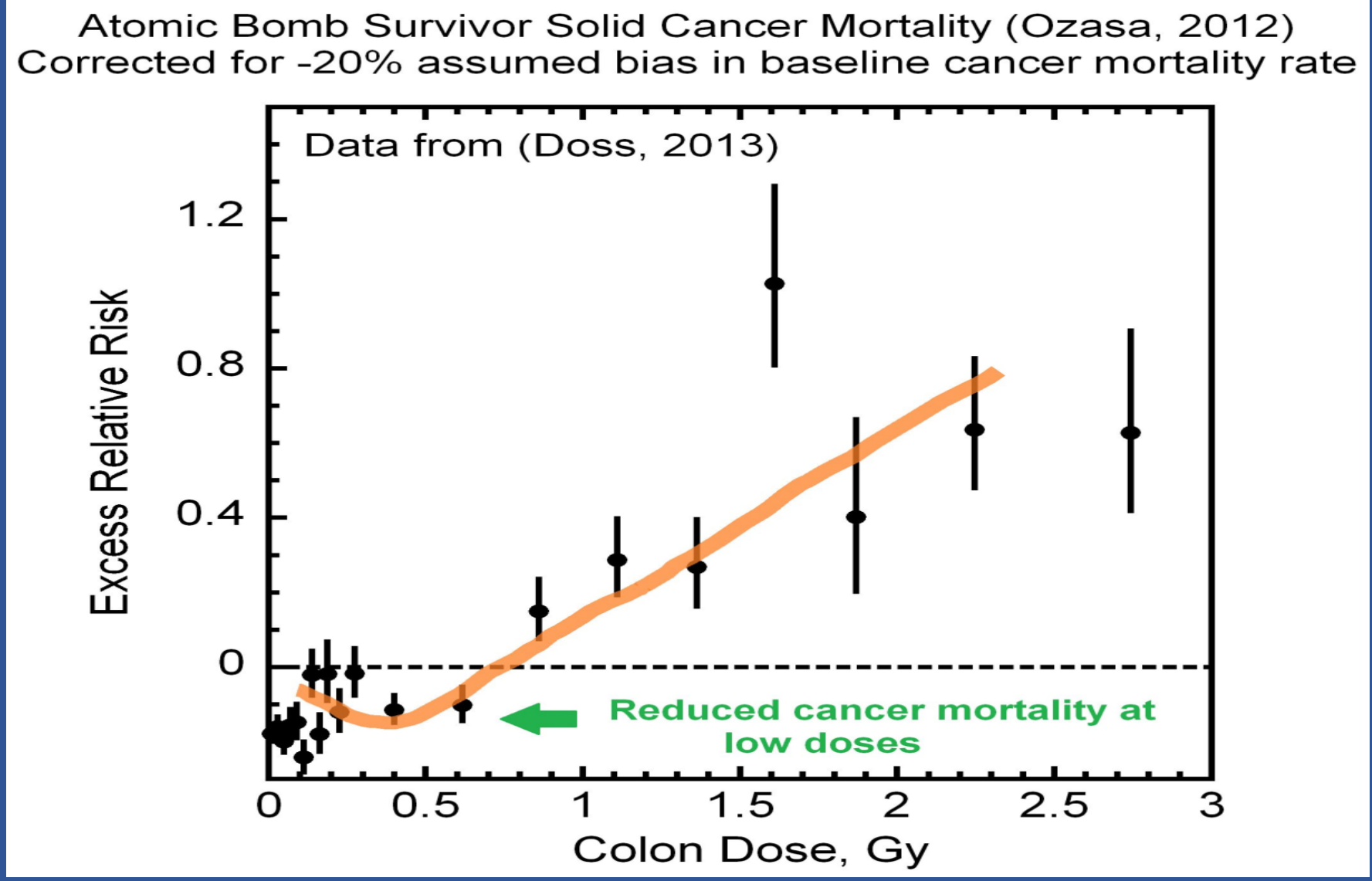
Although the linear model provided the best fit in the full dose range, statistically significant upward curvature was observed when the dose range was limited to 0–2 Gy ($\theta = 0.81$, $P = 0.02$) (Tables 6 and 7). The curvature over the 0–2-Gy range has become stronger over time, going from $\theta = 0.20$ for the period 1950–1985 to 0.81 for 1950–2003, and has become significant with longer observation (Table 7).

Oz

or for the dose range 0–2 Gy (Fig. 5). The apparent upward curvature appears to be related to relatively lower than expected risks in the dose range 0.3–0.7 Gy (Fig. 4), a finding without a current explanation. A recent paper (*24*)

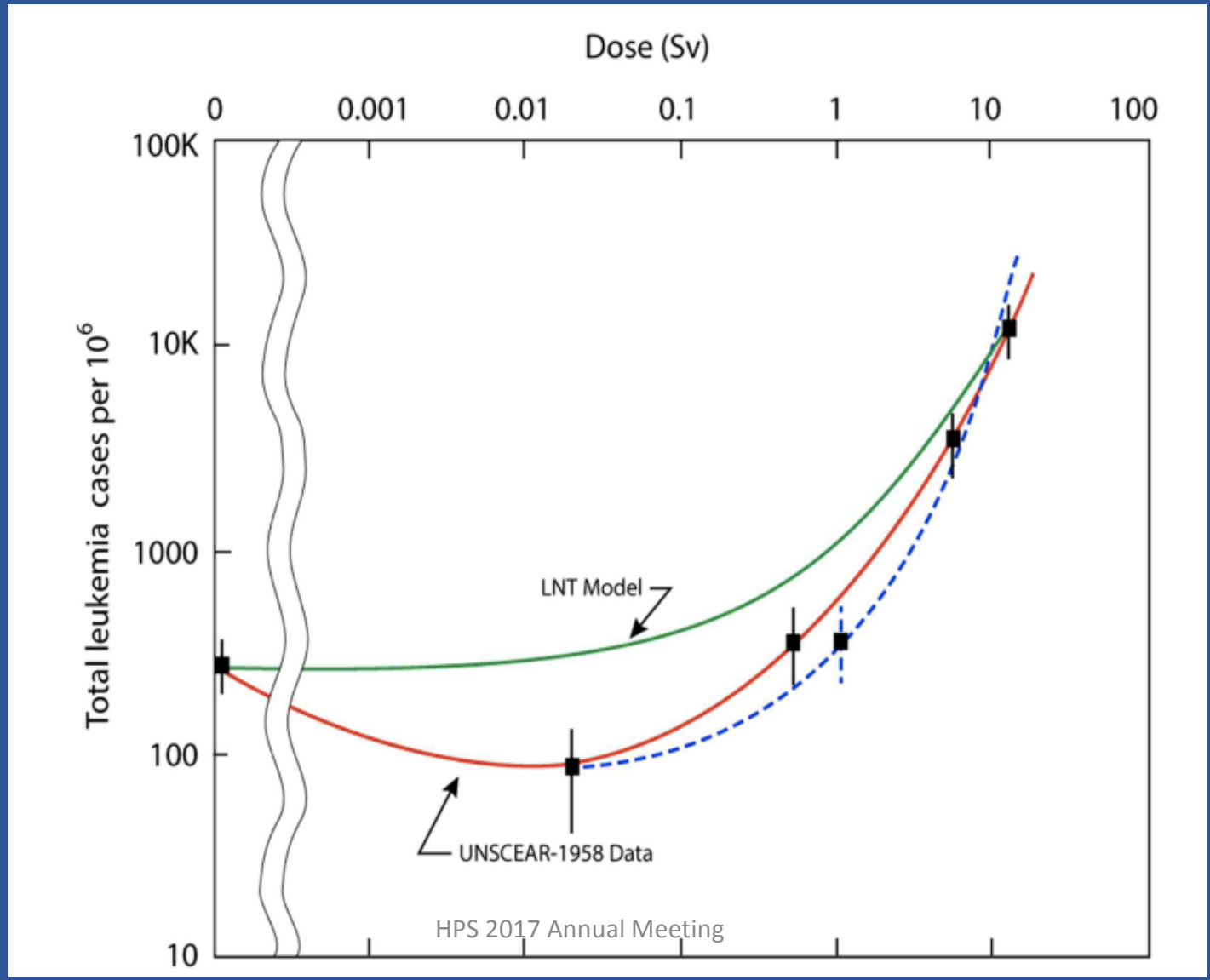
ATOMIC BOMB SURVIVOR DATA NO LONGER HAVE A LINEAR DOSE-RESPONSE.

EXCESS RELATIVE RISKS FOR LOW DOSES NEAR ZERO WOULD BE LOWER DUE TO ADAPTIVE PROTECTION. SINCE THESE ERRS EXTRAPOLATED TO ZERO DOSE WERE USED AS BASELINE CANCER RATES IN THE FITTING PROCESS FOR DETERMINING THE ERRS BY OZASA ET AL, THE BASELINE CANCER RATES WOULD HAVE A NEGATIVE BIAS.



THE SHAPE OF DOSE-RESPONSE CURVE, WITH THE CORRECTION FOR THE NEGATIVE BIAS IN THE BASELINE CANCER RATE, IS CONTSISTENT WITH THE CONCEPT OF RADIATION HORMESIS.

1958 UNSCEAR LEUKEMIA DATA IS INCONSISTENT WITH LNT



BEIR VII report (COMMITTEE OF THE NATIONAL ACADEMY OF SCIENCES) IGNORED DATA CONTRARY TO LNT

- **OCCUPATIONAL RADIATION STUDIES**
- **"IN MOST CASES, RATES FOR ALL CAUSES AND ALL CANCER MORTALITY IN THE WORKERS WERE SUBSTANTIALLY LOWER THAN IN THE REFERENCE POPULATIONS."**
- **"BECAUSE OF THE UNCERTAINTY IN OCCUPATIONAL RISK ESTIMATES … THE COMMITTEE HAS CONCLUDED THAT THE OCCUPATIONAL STUDIES ARE CURRENTLY NOT SUITABLE FOR THE PROJECTION OF POPULATION-BASED RISKS."**

28,000 NUCLEAR SHIPYARD WORKERS EXPOSED TO ~36 MSV HAD A 24% LOWER DEATH RATE

Int. J. Low Radiation, Vol. 1, No. 4, 2005 463

Nuclear shipyard worker study (1980–1988): a large cohort exposed to low-dose-rate gamma radiation

- **NEUTRON-ACTIVATED CO-60 WAS DEPOSITED IN PIPES AND VALVES OF REACTOR COOLING SYSTEM.**
- **MEAN DOSE 8 MSV/Y**
- **AGE-MATCHED, JOB-MATCHED CONTROL GROUP ELIMINATED HEALTHY-WORKER BIAS.**
- **1991 REPORT EXCLUDED 24% LOWER DEATH RATE FINDING.**
  - **SUBMITTED TO DOE 3 YEARS AFTER STUDY COMPLETION**
  - **NOT PUBLISHED**

STUDIES OF NUCLEAR POWER PLANT WORKERS IN MULTIPLE COUNTRIES HAVE ALSO SHOWN LOWER CANCER RATES. THE LNT BELIEVERS BLAME THIS ON THE "HEALTHY WORKER EFFECT". THIS IS THE ASSUMPTION THAT ONLY HEALTHY PEOPLE GO INTO RADIATION WORK, AND THAT THEY HAVE A NATURALLY LOWER INCIDENCE OF CANCER ANYWAY.

BUT THIS DOESN'T MAKE ANY SENSE. RADIATION WORKERS DO NOT GET PHYSICAL EXAMS TO DETERMINE WHETHER THEY ARE HEALTHY ENOUGH TO WORK WITH RADIATION. AND, THERE IS NO EVIDENCE THAT HEALTHY PEOPLE GET LESS CANCER THAN UNHEALTHY PEOPLE. INDEED, HEALTHY PEOPLE LIKELY GET MORE CANCER THAN UNHEALTHY PEOPLE. HALF OF ALL CANCERS OCCUR IN PEOPLE OVER THE AGE OF 65. YOU HAVE TO BE HEALTHY TO GET OLD ENOUGH TO GET CANCER!

MOST PEOPLE GET INTO RADIATION WORK IN THEIR TWENTIES OR THIRTIES. MOST PEOPLE ARE HEALTHY AT THIS AGE. UNHEALTHY PEOPLE AT THIS AGE DIE YOUNG. PEOPLE WITH JUVENILE ONSET DIABETES DIE RELATIVELY YOUNG OF INFECTIONS, RENAL FAILURE, AND HEART ATTACKS. PEOPLE WITH HYPERLIPIDEMIA DIE VERY YOUNG WITH HEART ATTACKS. PEOPLE WITH CYSTIC FIBROSIS DIE OF INFECTIONS. THESE UNHEALTHY PEOPLE DON'T LIVE LONG ENOUGH TO DIE OF CANCER.

THE “HEALTHY WORKER EFFECT” IS A BASELESS MYTH INVENTED BY PEOPLE WHO ABSOLUTELY DON’T WANT TO ADMIT THAT THE LNT IS WRONG AND THAT HORMESIS EXISTS.

1983 20,000 TONS OF CO-60 CONTAMINATED STEEL IN 200 BUILDINGS IN TAIWAN.

7,271 TAIWAN APARTMENT DWELLERS EXPOSED TO ~400 MSV OVER 10 Y HAD FEWER CANCERS

CANCERS OBSERVED 95
CANCERS EXPECTED 115
…PLUS 35 LNT-PREDICTED CANCERS 150

LNT DISCREPANCY = (150 - 95) / √150
= 4.5 STANDARD DEVIATIONS

PROBABILITY {LNT IS TRUE} ~ 7-IN-A-MILLION.

CANADIAN TB FLUORO STUDY

31,710 FEMALE PATIENTS WITH TUBERCULOSIS IN CANADIAN SANATORIUMS FROM 1930-1952 WERE SUBJECTED TO MULTIPLE FLUOROSCOPIES TO MONITOR THEIR DISEASE STATUS. OF THESE PATIENTS, 26.4% RECEIVED RADIATION DOSES TO THE AFFECTED SIDE OF 10 CGY (10 RADS) OR MORE, AND THEREFORE MOST RECEIVED LOWER DOSES. THE RELATIVE RISK OF BREAST CANCER WAS STUDIED IN THESE PATIENTS.

PATIENTS WHO RECEIVED A TOTAL RADIATION ABSORBED DOSE IN THE RANGE FROM 5-30 CGY (5-30 RADS) HAD A BREAST CANCER INCIDENCE UP TO ONE THIRD LESS THAN THE BACKGROUND INCIDENCE. ONLY AT DOSES ABOVE 50 CGY (50 RADS) DID THE CANCER INCIDENCE BEGIN TO INCREASE ABOVE BASELINE.

IN LIGHT OF THESE AND MANY OTHER STUDIES, WHY IS THE LNT STILL THE BASIS OF RADIATION PROTECTION REQUIREMENTS?

1) THOUSANDS OF REGULATORS WOULD LOSE THEIR JOBS IF LOW DOSES WERE ADMITTED TO BE HARMLESS OR BENEFICIAL.

2) THOUSANDS OF RSOS WOULD LOSE THEIR JOBS AS WELL. THEY MAINLY COLLECT USELESS PAPERWORK FOR INSPECTORS TO INSPECT.

3) MANY LAWYERS WOULD NO LONGER MAKE A LIVING FROM RADIATION DAMAGE LAWSUITS.

4) MANY SCIENTISTS WOULD LOSE THEIR GRANTS, GRADUATE PROGRAMS, AND GOVERNMENT RELATED IMPRESSIVE CONSULTANT POSITIONS.

5) MANY POLITICIANS WOULD NO LONGER BE ABLE TO USE RADIATION HYSTERIA TO GAIN VOTES.

“IT IS DIFFICULT TO GET A MAN TO UNDERSTAND SOMETHING, WHEN HIS SALARY DEPENDS ON HIS NOT UNDERSTANDING IT.” (Upton Sinclair)

THEREFORE IT IS NOT HARD TO UNDERSTAND WHY THE LNT HAS BECOME VERY MUCH LIKE A RELIGION.

DID YOU EVER TRY TO TALK SOMEONE OUT OF A RELIGION?

SO WE CONTINUE TO HORRIBLY OVERREGULATE IONIZING RADIATION TO THE TUNE OF $2.5 BILLION PER THEORETICAL (USING THE LNT) LIFE SAVED, AND THAT LIFE ISN'T EVEN REAL.

WE CONTINUE THE NONSENSE OF ALARA, IN WHICH LOW DOSES WHICH ARE HARMLESS OR BENEFICIAL MUST BE LOWERED TO DOSES WHICH ARE ALSO HARMLESS BUT LESS BENEFICIAL. IS THIS REASONABLE? WHY DO IT?

SO WHERE DO WE GO FROM HERE?

1) MEDICAL PEOPLE NEED TO LEARN THE TRUTH, AND INSIST THAT THEIR PROFESSIONAL ORGANIZATIONS ACTIVELY FIGHT LNT AND ALARA BASED REQUIREMENTS.

2) MEDICAL PEOPLE NEED TO INFORM THEIR PATIENTS OF THE TRUTH. DON'T BE AFRAID TO TELL THEM THAT THE GOVERNMENT IS LYING. MOST PEOPLE DON'T BELIEVE THE GOVERNMENT MUCH ANYWAY.