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Review

Physics Essentials Enable Deeper Understanding in Signaling and Crosstalk of the Carcinogenesis Paradigm "*Epistemology of the Origin of Cancer*"

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Abstract
Radioactivity and radiation-induced mutations are believed to be primary causal examples of cancer-initiating events (stimulus). The assumption that an increase in cancer risk develops from any amount of radiation gave rise to the linear no-threshold model. This also led to the assumption that cancer is caused by somatic mutations as described by the somatic mutation theory. Against this backdrop, in actuality only ~5%–10% of cancers result from somatic mutations or its various modifications, while ~80% of cancers are still termed as 'sporadic', meaning that their cause is unknown. Therefore, both the linear no-threshold model and the somatic mutation theory have resulted in an incongruity in thinking. Decades of molecular and clinical research since 2012 led to the development of the cancer paradigm, "*Epistemology of the origin of cancer*", which explains why the majority of cancers originate as a result of a six-step sequence of events. An understanding of the essentials of physics helps to explain the interconnections between physics and the biology of cancer. This allows for a much-needed reconciliation of past errors and leads to a deeper understanding of carcinogenesis.

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Introduction

Radioactivity in the form of ionizing radiation can induce mutations in DNA and is believed to be the primary causal example of a cancer-initiating event. The Linear No-Threshold (LNT) model was created based on the assumption that any amount of radiation had some detrimental genetic effects in the form of DNA damage that could then lead to cancer, i.e. a zero-threshold assumption or that there is no radiation dose that is without an incremental quantifiable increase in cancer risk. This was the basis for the belief that cancer is caused by mutations as described by the somatic mutation theory (SMT). In fact, only a small proportion of cancers (~5%–10%) have been shown to result from mutations over the past 100 years and the majority (80%) of cancers are therefore still referred to as 'sporadic', meaning that their cause remains unknown [1-14].

Decades of molecular and clinical research led us in 2012 to the development of the cancer paradigm *"Epistemology of the origin of cancer"*, with a complex six-step set of events published in open-access format [9]. This paradigm explains why the majority of cancers originate after this sequence of events, namely (1) a pathogenic stimulus (biological or chemical) followed by (2) chronic inflammation, from which develops (3) fibrosis with associated changes in the cellular microenvironment. From these changes, (4) a pre-cancerous niche develops, which triggers the deployment of (5) a chronic stress escape strategy. When this condition fails to resolve, (6) the transition of a normal cell to a cancer cell occurs. The initial concept was realized between 2014 and 2016 including the original cancer paradigm and five papers [9-11, 15, 16]. This was followed by critical analyses of available knowledge five years after the paradigm was first published [17-26].

To date, the assessment of the contributions of physics to the process of carcinogenesis has been missing. Physics is of much greater significance in cancer research than is generally perceived. The essentials of physics provide a deeper understanding of how and why the LNT is invalid and thus gives an impetus for further critical thinking and analyses to more completely understand carcinogenesis, which describes the complex, incompletely understood process by which changes in cells/tissues/organs lead to the disease that we refer to as cancer (see also Supplementary Material – for all supplementary material see www.cellphysiolbiochem.com).

Radioactivity

For their joint discoveries, Antoine Henri Becquerel (1852–1908) (spontaneous radioactivity from uranium salts), and Marie (1867–1934) and Pierre Curie (1859–1906) (identification of polonium), received the Nobel Prize in Physics in 1903. Marie Curie reported on radium between 1898 and 1907 [27-33], and Pierre Curie and his student Albert Laborde measured continuous emissions from radium in 1903 [32]. More detailed information about the discoveries of radiation and in Physics is provided in the Supplementary Material (see also Fig. 1-10 in Supplementary Material).

Background radiation

Background radiation consists of approximately 82% natural and approximately 18% man-made radiation, which is mainly due to medical X-rays (58%), nuclear medicine (21%), consumer products (16%), occupational sources (2%), atomic bomb fallout (2%), and nuclear fuel cycles (1%) [34]. Exposure to ionizing radiation is a consistent occurrence for all life on Earth. Approximately 90% of the annual radiation dose "*for a person living in the US comes from natural sources such as cosmic radiation and radioactive rocks*" ([35], reviewed in [36]). Cosmic radiation originates from the sun and distant galaxies [37].

According to the International Atomic Energy Agency (IAEA) of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) report in 1993, natural background radiation comes from "*cosmic radiation, external radiation from radionuclides in*

the earth's crust and internal radiation from radionuclides inhaled or ingested and retained in the body" [38]. In summary, "*exposures due to cosmic rays, terrestrial gamma rays and ingestion vary only slightly with time, so they can be regarded as the background exposure to natural sources.*"

Radiation exposure in people is influenced by multiple factors. Geographic location is one such factor, as cosmic radiation increases with elevation above mean sea level. Background radiation also depends on local geology, and here preexisting radon is of importance, as radon sources affect exposure. In 1993, the UNSCEAR sought to establish a representative approach describing radiation exposure as follows: the determination of "*radiation exposures from various sources consists of presenting the collective dose to the world population received or committed (a) from the end of 1945 to the end of 1992 (47 years) for discrete events and (b) for a period of 50 years at the current rate of practice or exposure for all other sources, including natural sources.*" This approach was deemed to be reasonable for a period of 50 years (25 years before and after the present), although it has been stated that it is "*likely that this assumption overestimates the future doses from practices that are not rapidly expanding, because improved techniques and standards of protection will reduce the doses per unit of practice*" but it was not clear, how doses are affected by practice.

The worldwide average annual effective radiation dose in adults from all natural sources was estimated to be 2.0 mSv [39] in 1982, with a later estimate of 2.4 mSv (range: 1–10), consisting of 0.9 mSv (37.5%) from external exposure (cosmic rays: 0.4 mSv [16.7%]; terrestrial gamma rays: 0.5 mSv [20.8%]) and 1.5 mSv (62.5%) from internal exposure (inhalation [primarily radon]: 1.2 mSv [50%]; ingestion: 0.3 mSv [12.5%]) [40, 41]. The dosage levels are listed in Table 1 [modified according to 34] (see also Supplementary Material, Section 'measurement parameters'). One's exposure depends on several variables. For example, cosmic ray dose rates depend on altitude, with exposure rates being five-fold higher at higher altitudes compared with average rates at sea level [38]. Terrestrial γ-ray doses depend on local geology and residential ventilation such that some communities may have an exposure rate that is 100-fold higher than average due to the presence of certain types of naturally occurring radioactive minerals.

While the global average human exposure to natural background radiation is 2.4 mSv/a (270 nSv/h avg) [40, 41], there are large geographic variations [42]. For example, the average natural background radiation in Finland is ~8 mSv/a (~900 nSv/h avg) versus 90 μSv/h (800 mSv/avg) on a monazite beach near Guarapari, Brazil [43]. A Finish nationwide register-based case-control study on the Chernobyl fallout revealed that "*Overall, background gamma radiation showed a non-significant association with the OR of childhood leukemia (OR 1.01, 95% CI 0.97, 1.05 for a 10-nSv/h increase in average equivalent dose rate to red bone marrow)*" [44]. No accumulation of dose with age was found.

Table 1. Units of dose (modified from [34])

	Unit	Symbol	Conversion factor
Quantifying radioactive decay	Becquerel (SI)	Bq	1 disintegration/s = 2.7 x 10^{-11} Ci
	Curie	Ci	3.7 x 10^{10} disintegrations/ s = 3.7 x 10^{10} Bq
	activity of substances are expressed as activity per weight or volume e.g., Bq/g or Ci/L)		
Quantifying exposure and dose	Gray (SI)	Gy	1 J/kg = 100 rad
	Rad	rad	0.01 Gy = 100 erg/s
	Sievert (SI)	Sv	1 J/kg = 100 rem
	Rem	rem	0.01 Sv

High background radiation (HBR) exposure

Depending on the geographic location, different effects of high background radiation exposure have been observed. For example, people living in mountainous areas can be exposed to high levels of natural background radioactivity because they live in so-called HBRAs (high-background-radiation areas) containing high concentrations of thorium and uranium [42, 45] (see also Supplementary Material, Section 'nuclear fission and atom splitting'). However, to date no increases in cancer rates have been observed in HBRAs, such as China [46] or in Poland, and an even lower cancer death rate has been observed in these countries [47]. Moreover, the prevalence of thyroiditis and hypothyroidism have not been shown to be correlated with natural radiation exposures in Karunagapally, India, which is a HBRA [48].

Interestingly, higher rates of unscheduled DNA synthesis have been reported for people living in HBRAs compared with the control areas of Enping and Taishan Counties, China, without an increased all-cancer mortality rate. More specifically, rates for leukemia, breast cancer, and lung cancer, which are thought to be influenced by radiation, are not higher in HBRAs: "*respective average annual doses are about 330 and 110 mR/yr, in the HBRAs in Yangjiang County approximately 90% of the annual radiation dose.*" The above-mentioned areas showed nominally lower cancer mortality rates, although the differences were not statistically significant [49]. This finding agrees with various investigations: seeds from a given plant species do not exhibit phenotypic changes when exposed to radiation at high altitudes with correspondingly higher levels of cosmic rays [50], and data revealed that HBRAs did not have increased leukemia rates [51].

Furthermore, background radiation has not been demonstrated as a significant predictor of leukemia mortality rates when data were examined without regard to age [52]. A negative lung cancer correlation was found in three Rocky Mountain states, which have a 3.2-fold-higher natural background radiation level than three Gulf Coast states, and a strong negative correlation between lung cancer and natural radon levels has also been observed [53].

The Life Span Study (LSS) revealed that at doses below 0.1 Gray, cancer incidence is negligible; however, the cancer incidence increases to 29.5% at 1 Gray and to 61% at 2 Gray (hinting at a linear dose-response). However, in strongly irradiated survivors, such levels were observed for less than 10% of the survivors of the A-bomb [54]. Thus, 2 Gray (2 J/kg) is the amount of radiation necessary to produce the same effect on living organisms as 1 Gray of high-penetration X-rays, which is equal to 2000 mSv (2 Sv). There is no evidence of radiation effects for doses below about 500 mSv (0.5 Sv) [55]. It has been shown that a low LET radiation dose of 0.1 cGy per year results in an average of approximately 10^{-7} mutations per cell per day [56] but this is not just a very low number but also a number that does not take DNA repair, an integral component of all living organisms, into account.

Further detailed information on background radiation is also given in the Supplementary Material, section 'background radiation'.

Hiroshima and Nagasaki 1945

Between 1939 and 1945, the Manhattan Project at the Los Alamos Scientific Laboratory in New Mexico, United States, revealed that plutonium was more toxic to humans than radium, but less hazardous in practical terms (see also Supplement, Section 'quantum age'). These findings led to the development of nuclear bombs, with their use to devastating effect in 1945 [57, 58]. Following the first nuclear explosion on 16 July 1945 (Trinity test), the first atomic bombs were detonated on 6 August 1945 at 08:15 AM on Hiroshima and on 9 August 1945 at 11:02 AM on Nagasaki. The bombs were different in that the Hiroshima bomb contained uranium whereas the Nagasaki bomb contained plutonium as discussed elsewhere in this paper (see also Supplementary Material, Section 'electromagnetic radiation'). Although reports vary, the direct casualties were devastating. Approximately 170,000 citizens died immediately [Hiroshima: 90,000–120,000; Nagasaki: 60,000–80,000] [59]

due to the extreme heat and pressure of the blasts, which resulted in an extensive firestorm emanating from the hypocenter (explosion site). Ionizing radiation was emitted, and nearly all people within 1.5 km of the hypocenter were killed [54, 59, 60].

Both bombs exploded before reaching the ground (Table 2) (according to [34, 55, 61-63]); thus, the fission products were dispersed into the atmosphere and spread over a large area.

Table 2. Atomic bombs detonated at Hiroshima and Nagasaki [34, 55, 61, 63]

Variable	Hiroshima	Nagasaki
Date, time	6 Aug 1945, 08:15 AM	9 Aug 1945, 11:02 AM
Atomic bomb designation	L-11, Little Boy	F-31, Fat Man
Atomic bomb material	Uranium-235, 238	Plutonium-239
Isotope mass	64 kg	6.2 kg
Burst height	1.903 ft (600 m)	1.650 ft (503 m)
Wind	8 knots at 170 grad	1-knot head wind
Head wind spread	0	1
Yield (uncertainty)	15 kt (20%)	21 kt (10%)
Outside range	12–18 kt	18.9–23.1 kt

The perception at the time was that radiation from atomic bombs resulted in health effects such as leukemia and other cancers as well as a high risk of genetic malformations. However, the results of long-term studies do not support this view, particularly regarding the assumed genetic effects. The first study with a defined objective (not a report of one or multiple cases) was published in 1953: "*There is no indication from this study of any 'unusual' sensitivity of human genes to irradiation*" ([64], reviewed in [54]).

However, this perception remained and many long-term studies of the survivors were conducted. In 1947, the United States founded the Atomic Bomb Casualty Commission, which was later restructured as the Japanese Radiation Effects Research Foundation, financed by the United States and Japan. Since 1955, such investigations have been performed in a systematic manner, and the LSS began, which has follow-up data covering approximately 60 years for cohorts of individuals recruited between 1951 and 1953. This study includes approximately 120,000 individuals (54,000 within 2.5 km of the hypocenter [relatively high radiation doses], 40,000 2.5–10 km outside the hypocenter matched with regard to city, age, and sex [low/negligible radiation doses], and 26,000 unexposed residents) and approximately 77,000 children born between 1946 and 1984 with at least one parent who was exposed ([65], reviewed in [54, 60]). It was assumed that the LSS cohort included approximately 50% of survivors who were alive five years after the bombings ([66], reviewed in [54]).

The 1986 report on atomic bomb radiation dosimetry in Hiroshima and Nagasaki (in regard to the dosimetry system DS86) raised concerns about the calculated and measured values of thermal neutron activation of cobalt-60 (^{60}Co), particularly because it was assumed that the neutron dosages were underestimated in this study ([67, 68], reviewed in [69]). The new dosimetry system, DS02, suggested improving the dosimetry estimates at the Radiation Effects Research Foundation (RERF) by using tools such as the Geographical Information System (GIS) which resulted in 5% to 10% reductions of house and body shielding transmission factors for neutrons.

Linear No-Threshold (LNT) Model

The LNT model assumes that any amount of radiation has a detrimental effect in terms of mental health, genetic effects, and cancer, i.e. a zero-threshold assumption or put differently, that there is no radiation dose that is without an incremental quantifiable increase in cancer risk. Some have attempted to use this model to establish regulatory dose limits (Nuclear Regulatory Commission, NRC) although the model has not been verified as predictive (Fig. 1a and 1b). Furthermore, the LNT model is used to assess non-stochastic (deterministic) effects, but in actuality no response is seen until a threshold dose is exceeded. Contradictory findings have been observed in one of the most important cases of manipulated data in science, which gave rise to the dogma of the LNT model in the first instance [60, 70-73] and the LNT subsequently led to another dogma, the Somatic Mutation Theory or SMT used to explain the critical element in carcinogenesis [11]. An exploration of the data illustrates

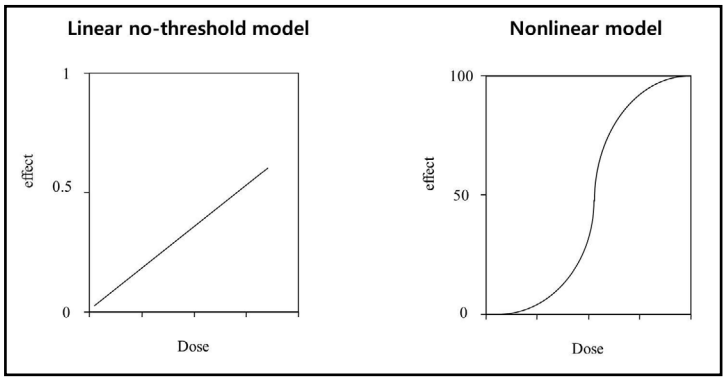

Fig. 1. Radioactivity and cancer risk (effect) models. (A) Linear no-threshold model with the assumption that that any amount of radiation has some detrimental genetic effects in the form of DNA damage that could then lead to cancer, i.e. a zero-threshold assumption or that there is no radiation dose that is without an incremental quantifiable increase in cancer risk. (B) Non-linear model: this model applies to non-stochastic (deterministic) effects: no response is seen until a threshold dose is exceeded. In this model non-stochastic effects are postulated and in this model, a defined minimum dose must be exceeded before the effect (diseases) occurs.

how the LNT and the later, the SMT, achieved widespread acceptance in the absence of strong supporting data (see also Supplementary Material, Section 'nuclear fission and atom splitting').

Herman Joseph Muller (1890–1967) irradiated *Drosophila melanogaster* (fruit flies) and observed lethal mutations within the F2 generation (88 lethal mutations in 758 cultures versus 1 lethal mutation in 947 cultures in the control group). However, in the F4 generation, hardly any mutations were observed [74-77]. Muller received the Nobel Prize in Physiology or Medicine in 1946. At that time, the atomic bombs had recently been detonated, and fears regarding radiation were substantial leading to the LNT model. Edward Butts Lewis (1918–2004), Professor of Biology at the University of California, San Francisco, supported the linear, no-threshold hypothesis as a model for radiation protection standards and afterwards the committee endorsed the LNT during the hearings of the Joint Committee on Atomic Energy Hearings at the end of the 50s, [78].

Science published an anonymous article in 1956 with the following conclusion: "*The basic fact is - and no competent persons doubt this - that radiations produce mutations and that mutations are in general harmful…..We ought to keep all of our expenditures of radiation as low as possible….From the point of view of genetics, they are all bad"* [79]. This statement was reported on the front page of the New York Times in an article entitled "*Scientists term radiation a peril to future man*" with the subtitle "*Even small dose can prove harmful to descendants of victim, report states*" [80], reporting on the LNT model. In 1957, Edward Butts Lewis (1918–2004), published observations that radiation caused leukemia in *Science*, [81] and he received the Nobel Prize in Physiology and Medicine in 1955 for his contribution to evolutionary developmental biology. Criticized by scientists [73], Lewis' leukemia paper reported on heritable effects based on the LNT model and cancer induction in terms of the SMT. The SMT has been previously subjected to an exhaustive review [11].

The situation became worse over time, with the NAS Radiation Committee still promoting the LNT model as recently as in 2006 [34]: *"LNT has also been applied to chemical carcinogens: the smallest amount of a carcinogen is hazardous without a threshold for positive excess risk*" [72] (see also Supplementary Material, Section 'radiation in living organism').

The LNT and the SMT are based on models, not data, and have had unbelievable consequences for cancer research and oncology for the past 70+ years in that (1) use of a false radiation exposure model (LNT) resulted in "*the road to linearity*" (in regard to [73], and (2) a complete scientific molecular branch (carcinogenesis) was directed on the wrong path with the SMT being touted as the basis for the majority of cancers [11].

When the International Congress of Radiology was held in 1925 in London, an International X-ray Unit Committee was founded. The Second Congress in Stockholm, Sweden, took place in 1928, named the International X-ray and Radium Protection Committee (IXRPC). This

meeting was followed by meetings in Paris (1931), Zurich (1934), and Chicago (1937). In 1950, the organization was named the International Commission on Radiological Protection (ICRP) (reviewed in [82-84]). In that year, the ICRP indicated "*the dose limit from tolerance dose to maximum permissible dose.*" There are now multiple societies and committees that determine radiation protection policies, such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the Committee on the Biological Effects of Ionizing Radiation (BEIR) of the National Research Council (NRC) of the United States. UNSCEAR and BEIR suggest ICRP recommendations to regional committees/institutions, such as the World Health Organization (WHO) and the IAEA, and industries, which result in national regulations (Fig. 1, reviewed in [84] - not provided here).

In 1950, the ICRP was not in the position of making firm recommendations regarding the maximum permissible amounts of radioactive isotopes [85, 86]; however, the committee recommended 300–600 mrem per week for skin, blood, gonads, and eyes in 1954 [87] and as a genetic dose in 1958 [88]. In 1956, the National Academy of Sciences (NAS), which is the highest scientific authority in the U.S., with its 'The Biological Effects of Atomic Radiation (BEAR) committee' adopted and wrongly recommended the LNT on 12 June ([89], reviewed in [73, 90]). According to the LNT, even the smallest amount of radiation is hazardous to human health. However, the LNT model is not based on solid data, but is instead a product of mathematical assumptions resulting in considerable uncertainty. If the LSS data had not been underestimated, the cancer risk would not have been overestimated. Currently, it is clear that the actual human data published in the LSS does not support the LNT model.

Today, we know that an ideologically driven decision based on unverified assumptions resulted in the genesis of the LNT. In 1977, the ICRP stated [91] that the induction of malignant tumors was a major risk based on the LNT model in terms of the SMT for carcinogenesis. In 1990, the Committee declared that even small radiation doses may produce deleterious health effects, as DNA changes would result in mutations and consequently cancer (reviewed in [82]), completely ignoring the role of DNA repair enzyme systems. However, their report stated that "*the extent to which these diseases would increase with a given increase in the mutation rate have for the most part not been demonstrated directly in any organism*" [91], an important caveat that has been ignored to date.

Another mistake was when rodent (mouse) studies were directly extrapolated and applied (1:1) to humans. We know that mouse studies cannot be automatically extrapolated to humans, especially if such investigations have not been performed for ages comparable to those of humans in terms of signaling pathways (Table 3) (adapted from [92]). In addition to the need to identify signaling pathways, although mice are the most commonly used animal model in cancer research, data reproducibility from these studies enables <8% of mice data to be successfully extrapolated from animal models to clinical cancer trials [93]. Mouse models are also primarily used because of the inherent genetic mutability in mice.

Only germline mutations can pass on characteristics (positive or negative) to the progeny. However, somatic mutations are those genetic changes that occur in non-germline cells and, in addition to not being passed down to progeny, also do not adequately describe the majority of cancers as is widely perceived (see also Supplementary Material, Table 1). Furthermore, we know that gene functions change in response to their environment [11, 15]. Epigenetics is the study of this phenomenon, where environmental factors determine whether a gene is activated (with subsequent effects on proteins/RNA) or whether a gene remains unactivated during a defined time. In experiments, genes are fixed (by a rigid definition) in a certain direction to elucidate

Table 3. Age equivalents in mice and humans and representative age ranges (adapted from [92])

Mouse / months	Human / years
1	10
2	15
3	20
4	25
5	30
6	35
9	40
12	40
15	65
18	70
21	75
24	80
27	85
30	90
33	95
36	100

parts of their function or study interactions. Rather, in biology, genes over multiple generations are responsible in for an organism's ability to adapting to changes in its environment. Recent developments in cancer biology support a strong role for the tumor microenvironment and stroma in determining tumor progression [9, 94, 95].

It has been stated that "*some somatic effects are stochastic; of these, carcinogenesis is considered to be the chief somatic risk of irradiation at low doses and therefore the main problem in radiation protection*" [91]. In 1998, studies on genetic susceptibility to cancer were part of the official IRCP mission [96], suggesting that the ICRP directly supported and promoted the SMT. These studies were primarily based on mice or cell lines *in vitro*, such as investigations of p53 mutation accumulation in organs of mice irradiated with low-dose X-rays [97, 98].

Today, experiments still produce inconclusive results with equivocal evidence [93]; thus, it is no accident that UNSCEAR stated in 2012: "*the Scientific Committee does not recommend multiplying very low doses by large numbers of individuals to estimate numbers of radiation-induced health effects within a population exposed to incremental doses at levels equivalent to or lower than natural background levels*" [99]. Also, it is believed that radiation may be influenced by the presence of reactive oxygen species (ROS) and other free radicals [100]. This viewpoint is quite interesting as the cell nucleus is almost anoxic and approximately 90% of oxidation in the cell occurs inside the mitochondria [101], thus the short-lived free radicals would not be proximate to where the DNA resides inside the nucleus of the cell.

Researchers have sought to establish radiation-induced histone modifications [102-105] as an alternative mechanism to yield double-stranded DNA breaks (dsDNA). In this respect, three observations may be relevant: (1) the anthracycline drug, doxorubicin, induces substantial epigenetic changes in cultured cardiomyocytes *in vitro* with histone-3 acetylation [106]; (2) Histone modifications are mediated independently of ROS [99]; and (3) ionizing radiation induces locus-specific changes to histone modification enrichment in zebrafish and Atlantic salmon in generation F1, but not in subsequent generations [107]. Thus, changes in histone modifications in the investigated targets were not retained in a multi-transgenerational effects, in contrast to histone modifications that persist in transgenerational memory over 14 generations in *Caenorhabditis elegans* [108]. For this species, it has been shown that "*Exposure to high temperatures [in Caenorhabditis elegans] led to expression of endogenously repressed copies of genes—sometimes called "junk" DNA*," which "*persisted for >10 generations of worms.*" The relevance of such findings cannot be extrapolated to humans, based on available data.

Although studies in cell lines and mice can be valuable, the reality is shown by clinical observations, which are too often underestimated. Out of 10,929 solid-cancer deaths within the LSS, only 527 (4.8%) were radiation-related ([109], reviewed in Table 4311 in [110]).

A 10-year follow-up of 1,292 children exposed *in utero* to radiation from atomic bombs in Hiroshima and Nagasaki showed no increase in malignant cancers [111], which is consistent with other reports [112]. No significant differences in mutation rates at microsatellite loci were reported, with an estimated mean mutation rate of 0.39×10^{-2} in the exposed group [(7 + 4)/2,789)] compared to 0.35×10^{-2} in the control group [113, 114], and which contradicts other reports [115]. However, *in utero* exposure to radiation seems to be considerably lower than early childhood exposure [116]. As discussed below, data from the Chernobyl nuclear plant accident affirms this phenomenon.

Chernobyl nuclear power plant accident

The 1986 Chernobyl nuclear power plant accident is the most serious radiation exposure accident since WWII [41]. However, there is no scientific evidence to indicate that this accident increased the overall cancer incidence over that of the general United States population with regard to thyroid cancer: "*National trends in cancer incidence rates for the nation of Ukraine are comparable to those observed in its neighbor country, Belarus, and are*

mostly comparable to those of the United States." Moreover, the "*...calculated average annual percent change for thyroid cancer incidence rates in the nation of Ukraine from 1999 to 2016 was 4.2%, which was not particularly different from the 3% to 4% observed in the United States Surveillance Epidemiology and End Results (SEER) registry over a similar time interval*" [117].

Most recently it was shown by whole-genome sequencing of 130 children, born between 1987-2002 to parents exposed to ionizing radiation from the 1986 Chernobyl disaster, that "*...no elevation in total germline de novo mutations regardless of cumulative preconception gonadal paternal (mean = 365 mGy, range = 0-4,080 mGy) or maternal (mean = 19 mGy, range = 0-550 mGy) exposure to ionizing radiation*" was observed [118].

The question, scientists need to pose is "*Why are no trans-generational effects observed after ionizing radiation, especially as this is still being promoted as the so-called prime example for initiating carcinogenesis*?"

Evaluation of the LNT model

Overall, radiation health effects (excluding physical/heat from the blasts) were due to γ-rays and neutron radiation from the atomic bomb blasts, for which dosages could be reconstructed based on the distance from the hypocenter.

It has long been believed that there exists a linear dose–response relationship between health effects and radiation exposure (dose). This belief is based on findings in *Escherichia coli* and *D. melanogaster* [75, 119-123], although it is also known that "*the time rate of mutation varies greatly among different types of normal cells, representing different stages in the germinal cycle*" [121]. Thus, several factors influence the results. "*The results from Drosophila and from Tradescantia demonstrate that in the low-dose range, neutrons are much more efficient in the production of two-break chromosome aberrations than X- and γ-rays*" [124].

Linear energy transfer (LET)

A small fraction of the dose absorbed by the Japanese atomic bomb survivors was due not to γ-rays but to fast neutrons. Directly ionizing particles are charged particles such as high-energy electrons, protons, α-particles, or fast heavy ions [34]. Indirect ionization occurs by uncharged rays, such as X- or γ-rays, which include fast neutrons.

LET is defined as the average energy lost by a particle due to electronic interactions per unit length along its trajectory, expressed in kiloelectronvolts per micrometer (keV/μm). High-energy electromagnetic radiation, such as X- or γ-rays is rarely ionized because in tissue it releases fast electrons with a low LET. The major energy transfers result from the photoelectric process, Compton scattering, and pair production. In tissues, the photoelectric process dominates at low energies (< 0.1 MeV), and most of the photon's energy is imparted to the ejected electron as kinetic energy. At intermediate photon energies (0.5–3.5 MeV), Compton scattering is the most probable event, and the energy of the incoming photon is converted into the kinetic energy of an electron and a second ("scattered") photon (with less energy). Pair production can occur at energies greater than 1.02 MeV. In this case, the photon energy is converted into a positron and electron after the radiation interacts with the atomic nucleus, and in turn, other molecules can be ionized.

The overall fraction of dose absorbed by atomic bomb survivors due to neutrons was small, approximately 2% in Hiroshima and 0.7% in Nagasaki ([125], reviewed in [34]). Here, it is important to note that small neutron doses can have large effects. Neutron energies reach up to millions of electron volts, which is higher than the energy of protons. Thus, high local concentrations produce far more clusters of ionization than low-LET photons, and result in more DNA damage [34]. The resulting recoil protons produce the maximum cellular damage per unit energy imparted ([126], reviewed in [34]).

The relative biological effectiveness (RBE) is the ratio of biological effectiveness of one type of ionizing radiation to another. The RBE of neutrons is about 12 compared to a γ-ray dose of 1 Gy (reviewed in [34]) (see also Supplementary Material, Section 'radiation in living organism'). Using rats, Boerse and Gerber showed that 4 mGy of fast neutrons produced as many mammary neoplasms as 0.4 Gy of X-rays, implying an RBE of 100 ([127], reviewed in [34]). The experiments by Wolf in 2000 showed that a neutron dose of 20 mGy in Sprague–Dawley rats was equivalent to an acute 1-Gy X-ray dose, meaning that the neutron RBE is 50 versus a value of 1 for X-rays [128]. Approximately 70-80% of low-energy radiation-DNA interactions do not result in dsDNA breakages, a necessity to make DNA repair systems ineffective as there is no template to repair the damaged DNA. The more typical low-energy radiation-DNA interaction that results in DNA damage is primarily single-stranded DNA breaks (ssDNA), with only 0.5%–1.4% observed as dsDNA [129, 130] and these ssDNA are easily repaired as there is an intact strand to use as a template by the repair mechanisms [131-133]. However, dsDNA are believed to contribute to radiation-induced cancers. This assumption is also based on investigations in cell lines *in vitro* (reviewed in [134, 135]). However, as discussed, the reality in humans is different as only some 4.8% of solid-cancer deaths were causally shown to be radiation-related [109].

The Nagasaki atomic bomb produced low-LET radiation, resulting in a large number of ssDNA and consequently showed an S-shaped dose–response for leukemia. This is because DNA repair enzymes can use the intact strand as a template to repair the ssDNA damage as discussed above. Similar findings have been reported for most non-carcinogenic chemicals and/or pharmaceuticals (reviewed in [135, 136]).

Thus, agents that primarily produce dsDNA breaks are more relevant because repair enzymes have no template for repairing the damaged DNA [137] as occurred with the high LET radiation from the atomic bomb dropped on Hiroshima unless one has defective DNA repair enzymes. Such a condition occurs in children with the rare autosomal recessive condition, Xeroderma pigmentosum [11, 26, 138, 139].

It has long been known that many variables influence radiation resistance, such as age [140-143], gender [144, 145], and environment [146-148]. It was shown in 1937 that neutrons are approximately 5- to 6-fold more effective in inducing mutations than X-rays, which was confirmed in 1964 [149-151]. These findings led to the expectation that a dose–response effect would be found for neutrons [150].

Linear energy transfer (LET) and its effects

The above discussion explains why the dose–response curves differ in high- and low-LET radiation exposures and for acute versus chronic exposure. High-LET curves are typical for fissile reactions while low-LET curves are typical for X-rays, γ-rays, and tritium β-rays, as shown in Fig. 2. In this figure, the dashed curves for chronic exposure differ in both cases (high- versus low-LET) compared with single acute exposures. This figure was modified from the original presented by Straume and Carsten (1993) [152], which was based on earlier publications [153-163]. Only agents capable of dsDNA breakage become clinically relevant unless one has defective DNA repair enzymes, e.g. as in children with Xeroderma pigmentosum.

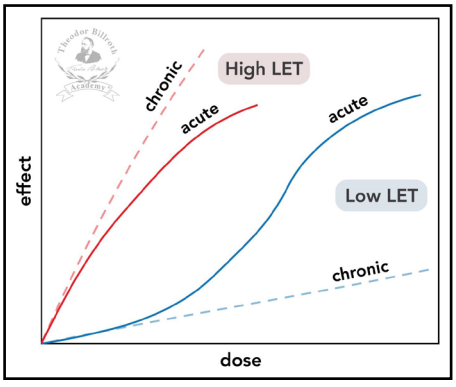

Fig. 2. Linear energy transfer (LET) and its effects. Observed differences in acute versus chronic effects for high versus low LET [this figure was modified from 152-163].

Somatic mutation theory (SMT)

As a result of the mathematically constructed but data-deficient LNT, the SMT grew in popularity to become the prime explanation for how the majority of cancers begin. Researchers have consistently tried to force fit the SMT, which holds true for only a minority of cancers by applying various changes and modifications [164, 165], such as introducing the concepts of driver and passenger mutations [166] and the hypermutation theory [167]. The so-called 'bad luck' paper was the latest such attempt to generate a mathematical explanation for the occurrence of carcinogenesis and it was based on the theory that somatic mutations cause cancer with a constant risk for a given number of cell divisions [168]. Furthermore, the statement that 66% of cancers would be explained by the SMT [168] was proven to be incorrect [169]. As the SMT can only be applied for some 5 to 10% of cancers, it is obvious that this is an untenable model that cannot be applied to explain the majority of cancers. Here, it is helpful to read the primary literature beyond the original papers [170-172] and none of the above papers cited the original publications.

Findings were simply combined into one box, reflecting biased thinking, without acknowledging the known significant differences between animal or cell line experiments and humans. It is known that the expression levels and composition of DNA repair genes differ considerably between humans and mice ([173, 174] reviewed in [175]). The same group investigated germline and somatic mutation rates in humans and mice [175]. Detecting mutations is not as easy as one may think. Germline mutations can be observed in all somatic cells, while post-zygotic somatic mutations are measurable only if a large fraction of the cell population is sampled. Thus, measured somatic mutations do not provide a direct estimate of the actual somatic mutation rate. Somatic mutation frequencies in single cells are based on investigating reporter loci whereas surrogate genes "*cannot be considered as representative for the genome overall*" [175] as "*the high error rate of current high-throughput sequencing platforms (0.1%–1%) effectively masks low-abundance mutations*" [176].

To overcome this challenge, the identification of clonally amplified mutations in most cells might provide more reliable results; however, this approach requires that one finds the same mutation in multiple independent reads from the same gene locus. Thus, whole genome amplification (WGA) has been suggested as a more accurate approach. When a reference sequence is aligned, "*mutations are detected as differences between the amplified single-cell genomic DNA and the reference sequence normalized to the non-amplified genomic DNA of the mother cell population*" [177]. Gundry et al. suggested sequencing the genomes of multiple single cells from *D. melanogaster* (S2 cells) and mouse embryonic cells (mouse embryonic fibroblasts, MEF), after treatment with the mutagen N-ethyl-N-nitrosourea to estimate the agent's mutagenicity. It has been stated that this approach could provide "*a direct measure of exposure to mutagenic agents and for assessing genotypic heterogeneity within tissues or cell populations*", but not much in this regard has been published.

Somatic mutation frequency "*cannot be determined by sequencing total genomic DNA due to the very low abundance of such mutations, which are unique to individual cells*" [175]. The frequencies of germline and somatic mutations in humans and mice are different: after adjusting for the number of mitosis cycles, a median germline mutation rate of 1.2×10^{-8} mutations per base pair (bp) per mitosis was calculated for humans, with a value of 5.7×10^{-9} mutations per bp for mice. As these differ significantly, findings in mice cannot easily be transferred 1:1 to humans in this regard. Furthermore, the mass of mutations have very small effects [178]. To fully elucidate radiation effects, we must explore radiation effects in living organisms in greater detail.

Radiation effects

The effects of radiation include damaging changes in the bases and polynucleotide chains of DNA as single- and double-stranded breaks. This damage is influenced by many variables. Cells in the mitotic and G2 phases are the most sensitive, while cells in the S phase are the most radiation-resistant. The tissue of origin influences the results, as rapidly proliferating cells such as those from the skin mucosa or bone marrow reveal effects within a few weeks while slow or non-proliferating tissues such as nerves, muscles, and bones can reveal adverse effects months or years post-exposure [179-181]. Knowledge of embryogenesis and fetogenesis, as well as the process of differentiation of the three germ layers into various tissues, is required to understand the different effects of radiation (see Supplementary Material, Table 1, and for further details see also Supplementary Material, Section 'radiation in living organism').

Franklin Paine Mall (1862–1917) attempted to classify embryology in 1914 [182-184] and founded the "*Carnegie Collection*" in 1887 (officially announced in 1902) (see also Supplementary Material, sections 'radiation in living organism' and 'development during embryology'). Approximate Carnegie stages are delineated based on the development of structures in mice and rats according to Nishimura [185] based on Streeter [186-189], Nishimura [190, 191], Olivier and Pineau [192], Iffy [193], Jirásek [194], and O'Rahilly and Müller [195]. These stages were also reviewed in Yamada [196] and in terms of various irradiation dates in regard to rats [197-199] and mice [200, 201] (Fig. 3).

LD50/30

According to the United States Nuclear Regulatory Commission (USNRC), a radiation dose of 4–5 Sv is expected to cause death in 50% of an exposed population within 30 days (lethal dose [LD] 50/30) [202]. By comparison, flight attendants are subjected to an annual dose of 1.5–1.7 mSv [203], and a chest X-ray, mammogram, and a single abdominal computed tomography scan corresponds to an exposure of 0.1 mSv (range: 0.05–0.24), 0.4 mSv (range: 0.1–0.6), and 8 mSv (range: 3.5–25) [204]. Although an increase in some cancers have been reported in flight crews compared to the general population, the results should be interpreted in light of self-reported health information and a cross-sectional study design. A more equivocal finding was reported in Swedish cabin crews [205].

The total-body lethal radiation dose that causes death in 50% of individuals (LD50) is about 3–4 Gy [206, 207].

Time of radiation exposure

Many variables influence radiation-induced cancer risk, such as direct dose-time exposure/ radiation fallout/ingestion, time of exposure (prenatal, postnatal, or early childhood, late life), and time of prenatal exposure (embryogenesis or fetogenesis) (see also Supplementary Material, section 'radiation in living organism'). These factors may explain some of the contradictory findings regarding decreased cancer risk for the majority of Japanese atomic bomb survivors in comparison to ongoing excessive thyroid cancer risk associated with childhood exposure to radiation [116, 208]. Observations of varying cancer incidences during the pre-implantation period versus *in utero* irradiation during embryogenesis (blastogenesis versus organogenesis) versus fetogenesis were reviewed by Lena Einhorn in 1991 (reviewed in [209]). The Zeitgeist culture of most of discoveries as well as important content to take into account are enabled in the Supplementary Material, section 'Time in context European Vision'.

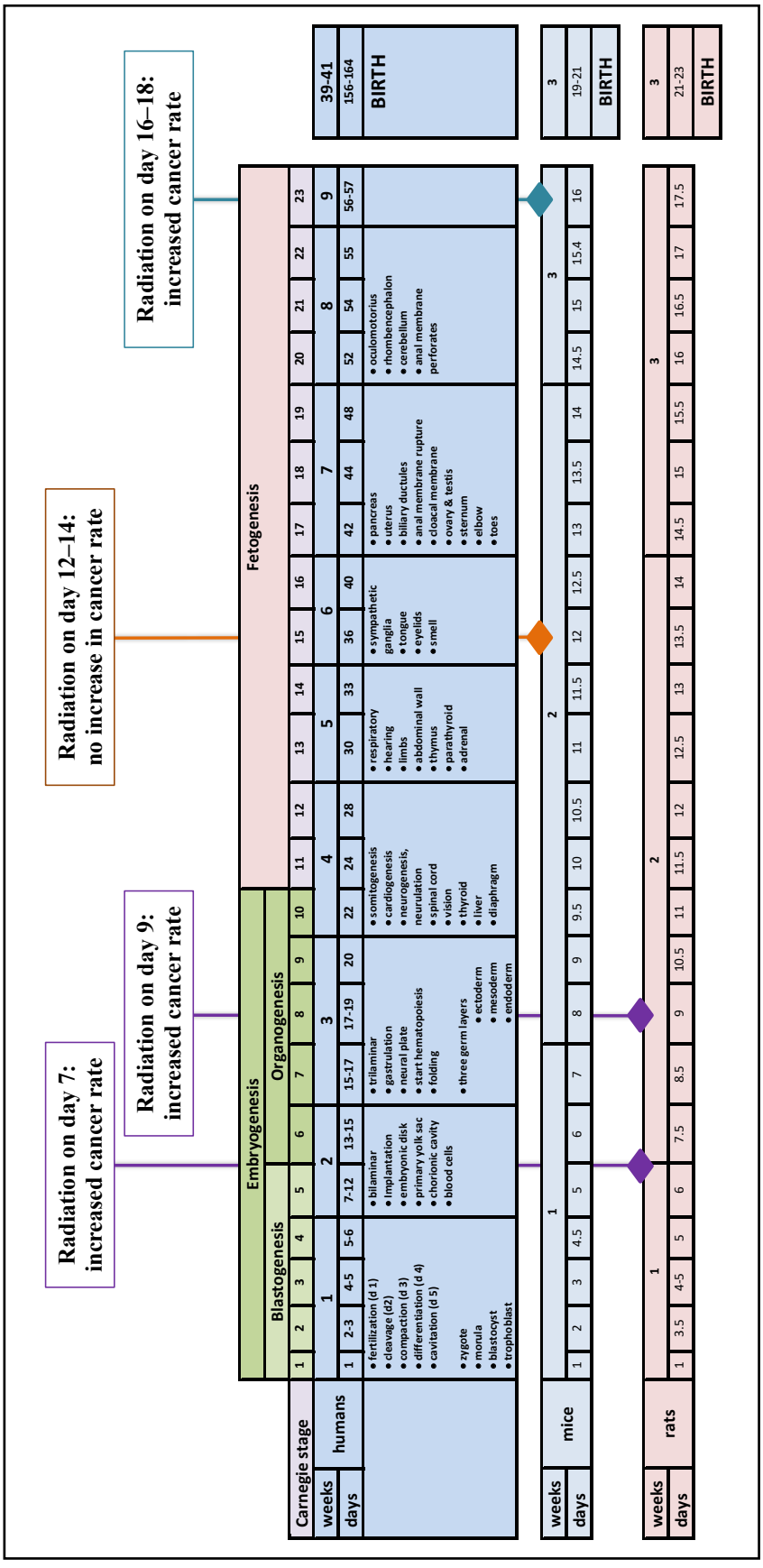

Fig. 3. Radiation effects and cancer response during development according to Carnegie stages in humans, mice, and rats. Approximate Carnegie stages delineated through the development of structures, modified according to [185-195]; also reviewed in [196]. Results are presented for various irradiation dates in rats [197-199] and mice [200, 201].

Conclusion

Only some 5 to 10% of cancers are proven to be caused by mutations. The continuous use of radiation as the origins of mutation-induced cancer is not valid as discussed for the majority of cancers. These erroneous inferences are all redicated on the LNT and SMT models as detailed above. From a scientific point of view, we should ask "*Why are no trans-generational effects observed after ionizing radiation, especially as this is still being promoted as the so-called prime example for carcinogenesis?*" The cancer paradigm "*Epistemology of the origin of cancer*" with its sex-step process for carcinogenesis includes signaling, as well as anti- and pro-inflammatory regulatory mediators or mechanotransduction, precancerous niche and cell transition that together enable a deeper understanding of the mistakes and incongruity in events that lead up to the development of cancers. Since 2019, the literature supporting this paradigm is being published with some regularity [210-249]. By this, both the essential principles of physics and the cancer paradigm provide insights to the puzzle of carcinogenesis and serve as an impetus to further critical thinking and analyses. The outcome could be new concepts and cognition in science for mankind and especially for cancer patients.

Abbreviations

BEIR (Committee on the Biological Effects of Ionizing Radiation); BIPM (Bureau international des poids et mesures (International Bureau of Weights and Measures)); CIPM (Comité international des poids et mesures (International Committee for Weights and Measures)); dsDNA (double-stranded DNA breaks); GIS (Geographical Information System); Gy (Gray); HBR (High background radiation); HBRAs (high-background-radiation areas); IAEA (International Atomic Energy Agency); ICRP (International Commission on Radiological Protection); ICRU (International Commission on Radiation Units and Measurements); IXRPC (International X-ray and Radium Protection Committee); LD50 (lethal dose for 50% of an exposed population); LD50/30 (lethal dose of radiation which is expected to cause death in 50% of an exposed population within 30 days); LET (linear energy transfer); LNT (linear no-threshold model); LSS (Life Span Study); MEF (mouse embryonic fibroblasts); NRC (Nuclear Regulatory Commission); RBE (relative biological effectiveness); RERF (Radiation Effects Research Foundation); ROS (reactive oxygen species); SEER (United States Surveillance Epidemiology and End Results registry); SI (Système international [d'unités] (International System of Units)); SMT (somatic mutation theory); ssDNA (single-stranded DNA breaks); Sv (Sievert); UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation); USNRC (United States Nuclear Regulatory Commission); WGA (whole genome amplification); WHO (World Health Organization).

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Disclosure Statement

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