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Review Article

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On the genetic effects of low-dose radiation

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ABSTRACT

There is a discrepancy between the reportedly significant elevation in a minisatellite DNA mutation rate in the children of parents, who had been exposed to radiation from the Chernobyl accident, and absence of significant inherited genetic effects found among the offspring of atomic bomb survivors. At the same time, average doses received by the residents of the contaminated areas, where the studies of the children of exposed parents were performed, had been comparable to those from the natural radiation background. Several publications exaggerating medical consequences of elevated radiation background were discussed earlier. The following limitations can be found in such papers: Interpretation of spontaneous conditions as radiation-induced, indication of radioactivity or dose levels without confrontation with the natural radiation background, conclusions about incidence increase of certain conditions without an adequate comparison with a control. In conclusion, arguments in favor of inapplicability of the linear non-threshold theory to the radiation doses, comparable to those from the natural radiation background, are discussed.

KEY WORDS: Chernobyl, ionising radiation, minisatellite loci, mutation, semipalatinsk

INTRODUCTION

Several publications exaggerating medical consequences of the elevated radiation background were discussed earlier [1-4]. Another example is provided by the paradox discussed in [5-8]: Statistically significant increase in the minisatellite (junk) DNA mutation rate in the children of parents who had been exposed to radiation from the Chernobyl accident [9-13], while contradicting studies found no significant inherited genetic effects among the offspring of atomic bomb survivors [5,6]. In particular, the results reported in [14,15], based on the observations among the A-bomb survivors in Japan, indicate that a single acute exposure of spermatogonial cells in humans does not give rise to discernible effects on mutation induction at minisatellite loci. Although this finding appears to be in line with the results for mice [16,17], "Dubrova's studies indicate the opposite, namely that spermatogonial cells are the sensitive cells for this type of mutation after either acute or chronic exposure [11,18]" [15]. The elevated levels of minisatellite mutations were interpreted by Dubrova as "sensitive reporters of radiation-induced mutation in the human germline" [9] i.e., possibly associated with medical consequences for humans.

However, as far as whole body doses are concerned, the six million residents of the areas deemed contaminated after the Chernobyl accident received average individual effective doses for the period 1986-2005 of about 9 mSv, which is a minor increase over the dose due to background radiation during the same period-around 50 mSv [19]. The Mogilev region (oblast) of Belarus (not the most contaminated one), Zhitomir and Kiev regions of Ukraine, where the studies [10,13] were performed, generally belong to this category. According to the calculations using the data from the UNSCEAR 2000 report [20], the average individual whole-body doses received during the period 1986-1995 by residents of Mogilev, Zhitomir and Kiev regions amounted approximately to 17.8, 14.9 and 6.8 mSv respectively. For the last two regions, the approximate values 14.9 and 6.8 mSv were obtained by division of the total collective effective doses for residents in rural areas with different levels of contamination by the total numbers of those inhabitants. Exposures after the Chernobyl accident in rural areas were considerably higher than in towns [20]. For comparison, annual individual doses from the natural radiation background are expected to be within the range 1-10 mSv but can be higher [21,22].

DISCUSSION

In the author's reply [23], it is written: "The author also makes a very serious accusation stating that 'statistics with unknown levels of significance' was used in our publications [13,24]. I would like to stress that the main result of these two studies, showing significantly elevated mutation rate in the germline of irradiated parents, was verified by means of the most conservative statistical test-Fisher's exact test." To start with, the references in the corresponding sentence from the letter [8] were [9,13], not [13,24]. The arguments below pertain to [9]. The following was written in the letter [8]: "A negative correlation between the mutation rate and a paternal year of birth among inhabitants of Semipalatinsk area is stated without giving the value of the correlation coefficient and its level of significance." Considering the configuration of the diagram

in [9], this correlation may be insignificant. Nevertheless, a discussion is led on its basis, e.g.,: "Most importantly, this correlation provides the first experimental evidence for change in human germline-mutation rate with declining exposure to ionizing radiation and therefore shows that the Moscow treaty banning nuclear weapon tests in the atmosphere (August, 1963) has been effective in reducing genetic risk to the affected population [9]." [8] In any case, the Fisher's exact test is not used for evaluation of the level of significance of the correlation coefficients. Furthermore, the dose comparisons concerning Chernobyl accident in [8] were left without comment, and it was concluded: "Another of the author's statements that the doses used in our mouse studies 'were more than 100 times higher than average individual doses' for the irradiated families is not correct." [23] The doses received by the residents of the contaminated territories, where the studies [10,13] were performed, are discussed above. These dose levels agree with the data from [25] cited in [23]. In the mouse studies by Dubrova's group [26], 1 Gy of acute X-rays was administered to the mice. Possibility of higher effectiveness of acute exposure to low-linear energy transfer radiation compared to protracted exposure [27,28] should be taken into account as well. In a recent study, no evidence for mutation induction at pre-meiotic male germ cells following gamma-irradiation with the doses 0.5 and 1 Gy was found [29]. No evidence for minisatellite mutation induction has been found in humans after radiotherapy [30-32].

Furthermore in the author's reply [24], the argument was repeated: "Existing estimates of doses for the residents of contaminated areas around the Chernobyl nuclear power plant reflect external and internal exposure to caesium-137 and caesium-134 [26]. As discussed in [14,33], these estimates are often at odds with those obtained by retrospective biodosimetry, which may reflect the initial external and internal exposure to the short-lived radionuclides." However, the individual doses to the residents of the contaminated areas after the Chernobyl accident, discussed above, are below the resolution level of biodosimetry [34,35]. According to the UNSCEAR 2008 report [19], accuracy and precision of biodosimetric methods are insufficient for epidemiological studies at low radiation doses. Furthermore, it was pointed out in [8] that the share of the short-lived radionuclides in the population exposure after the Chernobyl accident must have been lower than that after the atomic explosions in Japan, where no significant increase in the minisatellite mutations was detected [14,15]. After a nuclear power plant accident, predominantly those radionuclides are released into the environment, which had been accumulated in the reactor, i.e., relatively long-lived ones; whereas during an atomic explosion both short- and long-lived radionuclides are generated and can exert their biological action. This argument was dismissed with the remark: "Author's belief that the 'share of short-lived isotopes in the population exposure must have been lower than that after the atomic explosions in Hiroshima and Nagasaki' is totally groundless" [23].

With regard to the Semipalatinsk nuclear test site it is written in [23] that "according to the results of numerous studies, the doses for the families living in the Semipalatinsk District of Kazakhstan have been estimated as 0.5 Sv and higher" with a reference to [36]. However, in the abstract of this latter article it is written: "The village of Dolon, in particular, has been identified for many years as the most highly exposed location in the vicinity of the test site. Previous publications cited external doses of more than 2 Gy to residents of Dolon while an expert group assembled by the WHO in 1997 estimated that external doses were likely to have been <0.5 Gy." [36], which was cited inaccurately. The single historical measurement in the village of Dolon was likely performed at the axis of the radioactive trace [36]. Accordingly, the dose estimates based on this measurement are considered as possible maximum external dose rather than the average dose for the residents of this village [37]. Dolon was identified as the most exposed village in the vicinity of the Semipalatinsk test site [36,37]. Dubrova *et al.* [24] collected material in the rural areas around the Semipalatinsk nuclear test site, where, considering the above considerations, the average individual doses must have been lower than "0.5 Sv and higher" as per [23].

Several publications exaggerating medical consequences of the elevated radiation background were discussed earlier [1-4]. The following limitations can be found in some studies: Interpretation of spontaneous conditions as radiation-induced, indication of radioactivity or dose levels without comparison with the natural radiation background, conclusions about incidence increase of certain diseases without an adequate comparison with a control. The publication bias should be also mentioned: Studies reporting positive or significant results are more likely to be published [38]. Some experiments in which no effects were seen among animals exposed to radiation were excluded from databases [39]; studies with lesser or no negative impacts of radiation have remained not cited in certain reviews [40] etc. There is an opinion that Chernobyl accident has been exploited for the worldwide strangulation of nuclear energy production [41], which seems to be a continuation of the soviet-time intellectual effort aimed at exaggeration of radiation-related genetic risks connected among others with the name of Dubinin *et al.* [42-44]. The concept he advocated, further commented in the next paragraph, can be characterized by the following citations (from Russian): "Any minimal radiation dose causes damage to heredity"; "there are no genetically inefficient low doses of radiation"; "genetic harm of low radiation doses is considerable if large populations are exposed" etc., [42]. After the Chernobyl accident, the renowned scientist wrote that "contamination of the territory with long-lived radionuclides after the Chernobyl accident was comparable to that from 200 to 300 Hiroshima bombs" [44], which can create a biased impression about medical consequences of the nuclear accident, where the doses, dose rates and number of exposed people are of foremost significance. Dubrova's place in the Dubinin lineage might lead others to think that he continues working in the same direction. Insufficient development of atomic energy has contributed to higher prices for fossil fuels. Moreover, the doubling dose estimates (the amount of radiation necessary to double the naturally occurring rate of mutation) was printed in the article [43] without references: 180 mGy for dominant visible and 300 mGy for recessive mutations in mice, these figures being, according to [43], accepted for

humans. These values are relatively low compared to those from the international literature. Neel reached after approximately 50 years of research that the doubling dose of an acute gonadal exposure is approximately 2.0 Sv, which on his opinion was a conservative estimate, meant to preserve the safety of future generations from genetic risk in the form of mutations [7,45]. Obviously this issue needs further research.

Finally, the linear non-threshold theory (LNT), which provided a theoretic basis for the concept of damage to heredity from minimal radiation doses [42], should be commented. The history of the LNT and controversies around it were discussed in [46]. According to the LNT, the linear dose-effect correlation, proven to some extent for higher doses, can be extrapolated down to the minimal doses. Applicability of the LNT to ionizing radiation has been broadly discussed [47-50]. The LNT is corroborated by the following arguments: The more particles hit a cell nucleus, the more DNA damage would occur and the higher the risk of malignant transformation would be. Reducing the dose reduces the number of tracks and, correspondingly, the frequency of the effect [27,51]. This concept does not take into account that DNA damage and repair are normal and permanent processes, which are in dynamic equilibrium. There is probably an optimal level of background radiation, as it is the case for other factors normally present in the environment: Light and ultraviolet radiation, temperature, atmospheric pressure etc., where deviation in either direction from the optimum is harmful. Any living organism would be best adapted by the natural selection to those radiation levels that occur naturally. For ionizing radiation this concept is confirmed by experimental and epidemiological evidence in favor of hormesis i.e., beneficial effect of low-level exposure [52,53], as well as by the lacking evidence of increase of the cancer risk in areas with elevated natural background radiation [22], leaving apart the separate topic of radon and lung cancer at a cumulative exposure level of about 250 mSv [54]. Natural selection is a slow process; adaptation to a changing environmental factor must lag behind its current value. Therefore, actual adaptation would probably correspond to some average of previous levels, which might be especially the case for such an ancient mechanism as the DNA repair. Natural background radiation has probably been decreasing during the time of life existence on the Earth, mainly due to the radionuclide decay on the Earth's surface and oxygen accumulation in the atmosphere, resulting in formation of the ozone layer, protecting against ultraviolet and partly against Roentgen radiation. Moreover, accumulation of oxygen with its relatively high molecular weight has probably caused more effective absorption of cosmic radiation. Fewer radionuclides were brought to the surface due to the decreasing volcanic activity. Changing the orientation of the Earth's magnetic field and magnetic poles caused displacements of the intensity maximums of cosmic radiation on the surface. These maximums were during some periods farther from the geographical poles thus affecting more living organisms. Temporarily weakened magnetic field of the Earth during its reversals was accompanied by increasing intensity of cosmic radiation, etc. Accordingly, living organisms must have been adapted to a higher background radiation level than that existing today; more details are in [1,55]. The character of the dose-response relationship at the dose level close to the natural radiation background can be predicted on the basis of general considerations. There are many carcinogenic factors. The lower would be the level of environmental radioactivity, the less would be the contribution of the radioactive contamination compared to the natural radioactive background, and the less would by the role of radioactivity in general compared to other carcinogens and spontaneous carcinogenesis. According to the considerations delineated above, the dose-effect curve would progressively deviate from linearity with a decreasing dose. The dose-effect dependence can even become inverse in accordance with the hormesis phenomenon. A corresponding graph, plotted on the basis of experimental data, with a sagging of the dose-effect curve below the background cancer risk due to hormesis within the dose range 0.1-700 mGy, is depicted in the review [53]. Considering the above, the LNT concept is not applicable to radiation doses comparable to those received from the natural background.

CONCLUSION

In conclusion, dose-effect relationships after low-dose exposures should be clarified in animal experiments with exactly known doses and dose rates. Animal studies can provide reliable information; whereas dose reconstructions in Chernobyl and Semipalatinsk areas are inexact and, as discussed above, partly comparable with those received from the natural radiation background. Outstanding data, for example, that "above doses of 50-100 mSv (protracted exposure) or 10-50 mSv (acute exposure), direct epidemiological evidence from human populations demonstrates that exposure to ionizing radiation increases the risk of some cancers," [51] or four-fold increase in the incidence of thyroid cancer in children linked to an estimated thyroid dose of 90 mGy [56] should be verified by experiments. The same applies to the data on the excess radiation-related cancer deaths occurring at doses below the current occupational limits [57]. Although the value of animal experiments for extrapolation to humans, in particular, in predicting the effectiveness of treatment strategies in clinical trials, has remained controversial [38], for such universal biological mechanisms as mutation and DNA repair the extrapolations must be, in the author's opinion, largely admissible. Further work in this direction, parsing of extensive studies on relative biological effectiveness of radiation in different animal species [58], would better quantify radio sensitivity of the species thus enabling more precise extrapolations to humans.

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