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Review article

Hormesis: are low doses of ionizing radiation harmful or beneficial?

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Abstract. A review is provided of the literature on radiation hormesis, hormesis being any physiological effect that occurs at low doses and which cannot be anticipated by extrapolating from toxic effects noted at high doses. Epidemiological studies suggesting beneficial effects are considered, and experimental evidence for the existence of hormesis is then appraised. In the latter context, there are possible low-dose effects at the molecular level, at the cellular level and on the organism as a whole. It is concluded that while it is difficult to analyse the effects of low-dose radiation with statistical significance, the concept does permit the reconsideration of the validity of currently accepted notions.

Key words: Hormesis – Ionizing radiation – Epidemiological studies – Experimental studies

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Introduction

Since its discovery ionizing radiation has captured the imagination of the public. Initially it was thought to be healthy in all doses, leading to unusual applications such as ladies corsets containing radium and radium drinking cups. But as time passed it became clear that there was an upper limit to the presumed beneficial effects. Undesired side-effects caused by relatively high doses of radiation led to the belief that radiation was harmful at all doses. Later, the concept of the threshold dose was introduced to explain the fact that negative effects were observed only above certain dose levels. Furthermore, it was suggested that low doses of radiation might actually have beneficial effects on organisms. Results of experiments that pointed in this direction were attributed to a process named "hormesis" [1].

Hormesis is *any physiological effect that occurs at low doses and which cannot be anticipated by extrapolating from toxic effects noted at high doses* [2]. Hormetic effects are normally beneficial but may co-exist with toxic effects. Hormesis may be characterized as a process whereby low doses of an otherwise harmful agent may result in stimulatory or otherwise beneficial effects. The word originates from the Greek word *hormaein,* which means "to excite", and refers to a much broader spectrum of phenomena including many toxicological observations. According to Stebbing [3] the term was probably first coined in a publication dating from 1942 describing the growth stimulation of fungi by a naturally occurring antibiotic, which at higher concentrations suppressed fungal growth. There are many examples in nature of processes that follow a hormetic model. A striking example is vitamins, widely accepted to be very beneficial at certain doses, but known to be toxic at higher doses. Hormetic models of ionizing radiation suggest that it behaves in a similar way. A schematic representation of the models illustrating the presumed beneficial and harmful effects of ionizing radiation is shown in Fig. 1. The hormetic model is clarified in Fig. 1C, which illustrates the concept that at lower doses the effects of radiation are beneficial. In the diagrams effects are shown to be either harmful or beneficial as the radiation dose is increased. The point at which the radiation has no overall effects is referred to as the "zero equivalent point" [cf. 24].

In this article we shall review the literature that has appeared on this subject. Subsequently epidemiological and experimental evidence will be brought forward to elucidate the arguments in favour of radiation hormesis. This paper will be concluded by highlighting some criticisms raised against hormetic models.

Epidemiological evidence suggesting beneficial effects of radiation

Literature data on radiation hormesis describe the observed beneficial effects at dose levels between 1 and 50 cGy [cf.18]. Many epidemiological studies have been performed to investigate whether threshold dose of ionizing radiation exists. Obviously, it is difficult to find a situation in which a large group of subjects is exposed to

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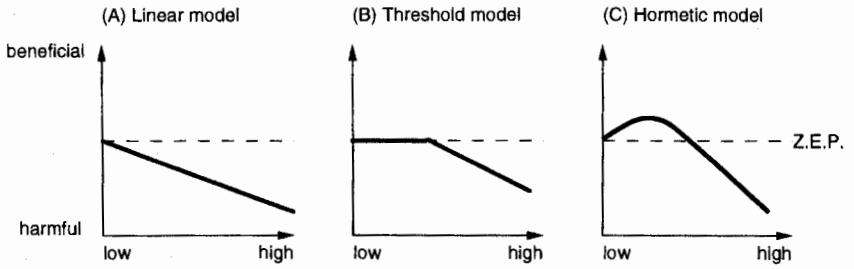

Fig. 1A–C. Representation of the effects of low-level ionizing radiation on living organisms. On the x-axis the overall effect of the radiation is represented, on the y-axis the level of radiation received is represented. **A** shows the established linear model, in which it is presumed that the effects of radiation are unfavourable at all doses above zero. **B** shows a threshold model, in which the adverse effects start at some point above zero. The hormetic model is demonstrated in **C**; in this model the effects of radiation at lower doses are beneficial. *Z.E.P.*, Zero equivalent point at which radiation has no overall effect

ionizing radiation, allowing accurate assessment of the dose. As a consequence of this, beneficial effects may be difficult to quantify. Nevertheless, several epidemiological studies have come to the conclusion that such beneficial effects really exist. These reports are summarized in the following paragraphs.

In a Canadian study [4] the mortality due to cancer at nuclear power stations was reported to be 58% lower than the national average. One reason for this could be the strict medical tests that the nuclear power workers are subjected to before being offered a job. However, workers in the non-nuclear power industry who underwent comparable medical tests have a mortality due to cancer which amounts to 97% of the national average. It is therefore unlikely that this marked drop in cancer mortality is due to "the healthy worker effect" alone, as equally "healthy" workers in the non-nuclear power industry do not have this lower mortality. An epidemiological study of cancer frequency and mortality in nuclear power workers has also been carried out in Britain [5]. Also in this study it was found that cancer frequency amongst nuclear power workers was lower than the national average, but no definite conclusions were reached.

In a Chinese study [6], two groups of people were epidemiologically compared. The first (74,000 people) lived in an area with a relatively high background radiation (2.28 mGy per year), while a second (control) group (78,000 people) lived in an area with less radiation (0.95 mGy per year). The first group had a lower mortality due to cancer. Cancer mortality in the first group was 48.8×10^{-5} (±2.3) per person per year. Cancer mortality in the control group was higher 51.1×10^{-5} (±2.2). The difference is not statistically significant, but if only an older age category is compared (40–70 year olds) a significant difference is observed. The cancer mortality in the first group is 144×10^{-5} (±8.0) per person per year, whereas the control (lower background radiation) group shows the higher rate of 168×10^{-5} (±9.0) per person per year. The justification for only comparing these higher age groups is that this part of the population has received a higher total life radiation dose, causing enough difference in dose between the groups for a hormetic effect to be observed. The chance that this difference would occur at random is 2.3%. One must, of course, be aware that other factors such as dietary habits may have caused this difference in cancer mortality.

In an U.S. energy department study [7], the workers at three facilities were exposed to plutonium and other radioactive substances. The purpose of the study was to measure adverse health effects caused by the exposure. The plutonium exposure was mainly by inhalation. It appeared that the standard mortality ratio due to lung cancer was only 14% of the national level and all cancers in general appeared to be 70% of the national level. These figures are too extreme to be caused only by "the healthy worker effect". It was also observed that the number of smokers amongst the studied group was comparable with the national average, eliminating this factor as a source of error.

In a study looking at the effects of a high background radiation in various cities in India [8] it was observed that in areas with a high background radiation level the cancer incidence/mortality was significantly less. Five cities were studied and the higher the level of radiation, the lower the rate of various forms of cancer. Bombay, Nagpur, Bangalore, Pune and Madras were chosen for this investigation. Whereas the radiation levels in Bombay and Pune were much lower (<400 μSv/year, compared to 600–800 μSv/year in Bangalore and Madras), cancer incidence and mortality were higher. The reduction occurs at the rate of 0.03 per μSv/year (per 100000 people) in the Indian population. In the United States, Hickey et al. [9] have also measured the effects of differing levels of background radiation in different areas. From this study it was concluded that total cancer mortality is inversely correlated with background radiation dose with a statistical significance level of 0.05, but the Indian data are based on a larger population. In addition the authors mention that, due to a low degree of industrialization, carcinogenesis is less influenced by the environment than in other countries.

A Japanese study looking at cancer incidence/mortality in atomic bomb survivors looked at the dose response within the low dose range [10]. In this study it was difficult to evaluate the data and not really possible to establish the existence of hormesis by statistical analysis. Another Japanese study [11] looked at 290 male A-bomb survivors who had been exposed to 50–149 cGy of radiation. These showed significantly lower mortality from non-cancerous diseases than unexposed males but higher rates of cancer. It is evident that epidemiological studies amongst atomic bomb survivors are difficult to carry out, as received doses are difficult to ascertain. To date no really conclusive evidence for hormesis has been found in this type of study.

Cohen and Colditz [12] looked at the effects of radon exposure on cancer risk in U.S. homes. It has been suggested that radon in U.S. homes is responsible for about 10000 fatal lung cancers each year (BEIR 1988) [13]. This number is, however, based on extrapolations of data on miners who have been subjected to high radon concentrations. This study found that lung cancer rates decreased with an increase in radon levels. Smoking prevalence may have influenced the results, but this was corrected for. Many other confounding factors are considered and dealt with, such as socio-economic variables and geography. Nonetheless, a very strong negative correlation was found between lung cancer mortality rates and mean radon levels. A British study came to similar conclusions [14]. Both these studies support hormetic models for lung cancer mortality.

A study involving 700,000 shipyard workers (108,000 of whom were nuclear shipyard workers) by the Johns Hopkins Department of Epidemiology, School of Public Health and Hygiene [15] concluded that both the nuclear workers receiving more than 500 mR and those receiving less than 500 mR had significantly lower mortality (0.76 and 0.81, respectively) from all causes of death than the non-nuclear workers. Non-nuclear shipyard workers' mortality rates were similar to non-shipyard workers, therefore eliminating the healthy worker effect as a bias. This is consistents with other studies of populations in states with higher background radiation (approximately 1 mGy per year more than states with lower background radiation) that demonstrated increased longevity and a 15% reduction in overall mortality [16–19].

A study of 31,710 Canadian female tuberculosis patients who underwent fluoroscopy [20] concluded that the breast cancer risk increased with received radiation dose. According to this report, which comprised examinations performed in the period between 1930 and 1952, a theoretical lifetime excess of 900 deaths due to breast cancer would occur in a hypothetical group of one million women having received 0.15 Gy. The report used a linear model to calculate the hypothetical increased risk at this low dose of radiation. A more recent analysis of the data by Pollycove [21] applying an empirical polynomial function demonstrated that for this dose, 10,000 deaths per million would be prevented rather than 900 excess deaths being induced (better than 99% confidence limit).

Experimental evidence

Further evidence for the existence of hormesis has been obtained from results emanating from experiments designed to demonstrate low-dose effects at the molecular level, the cellular level and on an organism as a whole [22].

Effects at the molecular level

At the molecular level hormesis has been explained by both DNA repair and detoxification of free radicals.

DNA repair. It is an established fact that the extent of DNA damage is proportional to the radiation dose received [23]. However some experiments indicate that this relationship may not be totally linear. Low-dose radiation might cause an adaptation whereby cells become resistant to the mutagenic effects of subsequent high-dose exposures. These low doses may induce the production of proteins that are involved in DNA repair. Experiments showing the induction of adaptation to ionizing radiation have been carried out on human lymphocytes using low levels of radiation-incorporated tritiated thymine followed by higher doses of X-rays [24]. It was found that the number of chromatid breaks induced by the X-rays was lower than expected. It was later found that this adaptive effect could also be induced by exposure to very low doses of X-rays before the higher doses were given [25]. Another interesting observation was that the effects could only be induced using a fairly narrow range of doses [19]. This may be an explanation for the fact that hormetic models have not come to light earlier. In this laboratory test it appeared that, once the effect was induced, it lasted for the relatively long duration of three cell cycles. It was also found that these phenomena were only fully existent after 4–6 h, suggesting the involvement of a repair enzyme. Electrophoresis experiments reinforce this idea that proteins (enzymes) are involved and have determined the presence of a 30- to 35-kDa protein, thought to be responsible for DNA repair [26].

Free radical detoxification. Free radicals are known to cause DNA damage. Ionizing radiation causes a temporary increase in intracellular free radical concentration. It is suggested that protective mechanisms are activated, leading to longer term protection against DNA damage. Feinendegen et al. [27] have investigated the effect of low-level radiation and the subsequent increase in intracellular free radical concentration on DNA synthesis. It was found that DNA synthesis was temporarily inhibited, this inhibition reaching its maximum in 5 h. The

decrease in DNA synthesis was accompanied by an increase in the concentration of the free radical scavenger gluthionine. This temporary inhibition of DNA synthesis gives the cell time to carry out the DNA repair process. By temporarily inhibiting crucial intracellular activities and inducing the production of free radical scavengers, the low-level radiation has the effect of inducing a degree of protection against the harmful effects of further exposures to radiation and the detrimental effects of subsequent free radical attacks.

Effects at the cellular level

At the cellular level hormetic effects include immunostimulation and fertility enhancement. Some authors believe that radiation is essential for life and the preservation of the species. Luckey [28] hypothesized that a base amount of radiation is essential for cell growth. Several studies have been carried out to look at effects on the cell, as detailed below.

Immunostimulation. High doses of radiation are known to suppress the immune system, but at low levels radiation may induce the generation of a haematopoietic growth factors. In a Chinese study [29] the effects of low dose radiation on the immune system were studied using mice. The reactivity of thymocytes to interleukin-1 was shown to be depressed at radiation doses ranging from 0.025 to 0.25 Gy, but there was an increase in cell number in the thymus between 0.025 and 0.10 Gy, resulting in an improvement of the reaction of the whole organ. In these experiments the reaction of the organ to interleukin-1 was measured by counting cells in thymocyte suspensions made after exposure to varying degrees of radiation: the greater the cell count, the better the reactivity [30, 31]. Studies of the immune system of A-bomb survivors [32] showed some results which may not rule out hormetic enhancement of the immune system but failed to come up with conclusive evidence for immunostimulation.

Fertility enhancement. In a Belgian/French study [33] male and female mice were exposed to 10 mrad/h for different lengths of time. Female fertility was decreased and male fertility increased relative to a control group. This increase in male fertility may be an example of radiation hormesis. Female fertility was reduced due to the high sensitivity of the oocytes to radiation. Cytological and histological studies of the testes did not reveal any difference between the exposed and unexposed organs, suggesting that the increase in fertility occurs in an indirect way via physiological effects. Human studies also suggest an increase in fertility as a result of low levels of radiation [34].

Experiments at the cellular level. At the cellular level experiments have been performed using unicellular organisms. Background and chronic low levels of radiation have been found to increase the growth rate of the aquatic protozoans, *Paramecium caudatum* and *Paramecium tetraurelia* [35]. Using groups that were shielded from background radiation, groups exposed to low levels of gamma radiation and control groups, it was found that radiation could stimulate proliferation of these single-cell organisms. The stimulatory effect occurred only in a limited range of doses and disappeared at doses above 50 mGy/year. Experiments were also done in space onboard the space shuttle Challenger [36] to measure the effects of cosmic radiation on paramecia; however, results were inconclusive due to the combined influence of cosmic radiation and low gravity.

Cellular experiments were also done by Fabrikant [37]. His experiments demonstrated changes in the proliferative characteristics of tissues under continuous low-dose radiation. Cell population kinetics were measured for rapidly and slowly dividing cell types. Data were collected on immunohaematopoietic tissues, regenerating liver tissue, intestinal epithelium and seminiferous epithelium. Adaptive changes to the irradiation were observed in the cell populations, the cell cycle being accelerated so as to replace damaged cells. Cells that normally divide more rapidly showed a better response, replacing damaged cells at a higher rate.

Effect on the organism as a whole

In animals and humans low-level radiation presumably leads to an increase in life span. This increased longevity has been attributed to two factors: (1) an initial production of free radicals (which are thought to be involved in ageing [38]) as a result of low-level radiation leading to a feedback reduction of intracellular free radical levels; (2) the fact that these phenomena resemble caloric intake restriction effects [39] (caloric intake restriction has been found to increase life span [40]). Low-level radiation is known to produce oxygen radicals, which affect endocrine balance. This is interpreted by the body as an increased food intake, thus lowering appetite and therefore caloric intake, which in turn increases longevity.

Animal experiments. Theories on hormesis have been tested by performing experiments on mammals. Congdon [41] reviewed some of these with interesting results. Starting in the 1940s, experiments at the National Cancer Institute (USA) led by Lorenz exposed mice, guinea pigs and rabbits to varying degrees of radiation. A group of mice was exposed to 0.11 R per 8-h day until natural death. The experimental group had a longer mean survival rate (nearly 2 months compared to the control group). There was also an increased body weight in the irradiated animals: animals exposed to 0.11 R had an average weight increase of 50% over the controls after approximately 69 weeks of exposure.

In another study [42] young adult beagles were injected with graded activities of radioactive substances and were observed for the entire remaining portion of

their life. The main part of the radiactive dose was due to α particles. The rate at which bone sarcoma appeared in these animals increased fairly linearly with dose and no evidence for hormesis whatsoever was found.

Observations in humans. In 1987 Matanoski etal. [43] published a study on the mortality amongst radiologists in comparison to other medical practitioners. Radiologists who started practising before 1940 experienced an increased rate of death due to cancer as well as other diseases. This is in contrast to the mortality found in a group of radiologists who started practising after 1940: amongst younger radiologists the mortality appeared to be lower than that among other medical specialists of the same age group. This observation has been attributed to the fact that the younger radiologists received a lower overall dose of radiation and that due to greater precautionary measures in more recent years the average yearly radiation dose received by radiologists is less. The authors suggest a protective effect, which disappears in later life when the cumulative dose becomes too high.

Concluding remarks

Although the issue of radiation hormesis has been investigated by a number of authors, it appears that relatively few articles have been published on this subject since its so-called discovery. This is surprising as radiation hormesis is undoubtedly of interest from a scientific standpoint and may even have social consequences. It is obvious that many radiobiological studies have concentrated on the effects of high doses of radiation and that the reports on hormesis with low doses have often led to the passionate exchange of views [44, 45, 46]. Criticism comes down to general recognition that it is difficult to analyse the effects of low-dose radiation with statistical significance [47]. The cumulative results as expressed in this article may not really prove the existence of hormesis but they do allow one to challenge the paradigms. On the other hand it should be noted that some authors are undesirably enthusiastic to prove the theory and unintentional selective scientific blindness may occur. In science, self-fulfilling prophesies are not uncommon and often negative results are not published and create false ideas.

After reading through the existing literature on radiation hormesis, however, we believe that one should not necessarily agree or disagree with the concept. It rather opens the possibility to reconsider the validity of currently accepted notions.

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