RADIATION HORMESIS - A REMEDY FOR FEAR

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ABSTRACT

Personal reflections on radiation hormesis for the past fifty years are presented. The causes of ignoring and rejections of this phenomenon by international and national bodies and by radiation protection establishment are analyzed. The opposition against nuclear weapons and preparations for nuclear war was probably the main factor in inducing the concern for adverse effects of low doses of ionizing radiation, a byproduct of activism against the nuclear weapon tests. UNSCEAR was deeply involved in preparation the scientific basis for cessation of nuclear test, and contributed to elaboration of the LNT assumption, which is in contradiction with the hormetic phenomenon. However, this authoritative body recognized also the existence of radiation hormesis, termed as "adaptive response". The political and vested interests standing behind exclusion of hormesis from the current risk assessment methodology are discussed.

Key Words: hormesis, radiation, adaptive response, hormetic, linearity, risk assessment

I began working with ionizing radiation in 1953, as a medical doctor - radiotherapist at the Institute of Oncology in Gliwice. At that time my colleagues and I were not interested in protecting ourselves from radiation. Our main concern was to cure our patients by irradiating their tumors with high doses while protecting their healthy tissues outside the tumor volume against harmful collateral effects. This approach resulted in a permanent loss of papillary lines on my fingers, and on those of my colleagues. I estimate that my body must have absorbed a dose of some 600 mGy from such professional and from subsequent medical exposures. Perhaps this is why at the age of 82 years I am still active in winter and summer outdoor sports (I must however admit that the very persistence in such activity might be the real cause of its duration). In the early 'fifties at the Institute of Oncology we treated some advanced cases of leukemia with fractionated whole body or hemi body irradiations, up to a total dose of 2 grays, exposing both neoplastic and healthy tissues. The palliative results were positive. I believed that this effect was partly due to the stimulation of the defense system of the patients' healthy tissues, but I did not think of this as being a "hormetic effect". In fact, the term "hormesis" had been coined ten years earlier (Southam and Erlich, 1943) but was not widely used. Hormetic effects were known to exist since the end of the 19th century(Calabrese et al., 1999), and while after World War II they were mentioned in some 20 articles each year (Brucer, 1987), they were clearly out of the mainstream interest of radiologists. Whole- and hemi-body radiotherapy were soon forgotten at our Institute, due to the exaggerated fear of irradiating healthy tissues even with small doses, only recently to regain some recognition (Wojcik et al., 2002).

It was the Cold War period with its massive production and incessant testing of nuclear weapons. Strontium-90 and caesium-137 fallout from atmospheric tests polluted the whole planet and, together with the terrifying prospect of a global nuclear war, induced worldwide radiophobia. People were quite rightly scared of large lethal doses of radiation from local tropospheric fallout, deposited over distances of hundreds of kilometers from the sites of nuclear explosions. But later they also became scared of small doses of radiation arising from the global stratospheric fallout of nuclear tests in the atmosphere. The fear of lethal doses was a highly cherished element of the deterrence value of nuclear weapons, loudly voiced by their owners. One of the more important examples was the excellent handbook of Glasstone, demonstrating the disastrous effects of atomic weapons, published by the United States Department of Defense and the Atomic Energy Commission (Glasstone, 1957). But it was the leading physicists responsible for inventing the nuclear weapons, having realized how dangerous were their inventions, who instigated the fear of small doses. In their noble, wise and highly ethical endeavor to stop preparations for atomic war, and the "hysterical" amassment of enormous arsenals of nuclear weapons, they were soon followed by many scientists from other fields. The general strategy was to attack the crucial component of military nuclear efforts of the time – atmospheric nuclear testing. Later on, this developed into opposition against atomic power stations and all things nuclear. Although the arguments of physicists and of their followers were false, they were effective: atmospheric tests were stopped in 1963 (Rusk et al., 1963), only to be moved underground. However, this was achieved at a price –a terrifying specter of small, near zero radiation doses endangering all future generations had emerged. This specter became a long-lived and worldwide societal affliction, nourished by the linear non-threshold (LNT) assumption, according to which any dose, even that close to zero, would contribute to the disastrous effect. Radiation hormesis is an excellent remedy for this affliction, and it is perhaps for this reason that this phenomenon has been ignored and discredited over the past half century. What happened fifty years ago still influences the current thinking of the decision makers and of those who elect them. Therefore, let us dwell upon it for a while.

In March 1950, over a year before the first American H-bomb explosion on May 8th 1951, Albert Einstein estimated that "*radioactive poisoning of the atmosphere* (by H-bombs) *and hence annihilation of any life on earth, has been brought within the range of technical possibilities*" (Einstein, 1950). In the same year Hans Bethe, the former head of the Theoretical Physics Division of the Manhattan Project, and a major contributor to the development of the Hiroshima- and Nagasaki-type fission nuclear weapons, warned on television that H-bomb clouds *"could annihilate life on earth"* (Anonymous, 2005).

Similar statements were later repeated in innumerable publications, and captured in popular books and movies of the 1950s, such as *On the Beach, Fail-Safe,* and *Dr. Strangelove.* I demonstrated that such statements were unjustified (Jaworowski, 1999). If the whole global nuclear arsenal at its peak of 50 000 warheads and 13 000 megaton explosive power were to be exploded over a few days, the average individual would have received a life-time (70 year) radiation dose of about 55 mSv ensuing from the worldwide fallout, a far cry from the short-term dose of 3000 to 5000 mSv that will most likely kill a human or induce an epidemic of chronic post-irradiation diseases.

Eight years later, Linus Pauling, the chemistry Nobel laureate, virtually repeated what Einstein and Bethe had said, by stating that merely the preparation for thermonuclear warfare (and not the war itself) would destroy most of the planet's living creatures (Pauling, 1958). In a telegram of 1st March 1962 to President J.F. Kennedy, on the effects of nuclear tests, he estimated the genetic effects of small radiation doses from fission products and carbon-14 dispersed by nuclear tests: "*I state that nuclear tests .... would seriously damage over 20 million unborn children, including those caused to have gross physical or mental defect, and also the still births and embryonic, neonatal and childhood death*". Pauling's telegram started with a question: "*Are you going to give an order* (to continue the tests) *that will cause you to go down in the history as one of the most immoral men of all time and one of the greatest enemies of the human race?*" Perhaps the impact of this telegram was reflected in President Kennedy's statement: "*Today every inhabitant of this planet must contemplate the day this planet may no longer be habitable*". For this social activism, four years later Pauling received his Nobel Peace Prize.

Interestingly, two inventors of nuclear weapons were also honored with peace rewards. Andrey Sakharov, the father of the Soviet H-bomb, was awarded the Nobel Peace Prize in 1975. In 1978, Samuel Cohen, inventor of the neutron bomb, was awarded the Peace Medal by Pope Paul VI. In the same year, the next Pope, John Paul II congratulated him: "*Mr. Cohen, I trust you are working for peace*" (Cohen, 2005).

On the other side of the Iron Curtin the Soviets were competing with Americans in mass production and testing of fission and fusion weapons. They also built vast arsenals of conventional weapons, preaching worldwide peace at the same time. In the midst of this arms race in 1958, Andrei Sakharov, the father of the first Soviet H-bomb (1953) and of its next more sophisticated and more powerful version (1955), published an astonishing paper in Russian (Sakharov, 1958). After eleven years this paper was re-published in English in Moscow (Sakharov, 1969), and 32 years later - in the United States (Sakharov, 1990).

Most certainly publication of Sakharov's paper in the Soviet Union would not have been possible without prior consent or instigation of the highest authorities, perhaps as a Soviet peace stage in the Cold War drama. Sakharov's paper revealed two important messages on the hydrogen bomb. The first was a description of the fundamental fusion reactions occurring during the explosion of such a bomb (available for the first time in the open literature of the Soviet block, one year after their declassification by Glasstone), of its neutron flux and of the rate of the ensuing radiocarbon (^{14}C) production in the atmosphere. The second message was the calculation of radiation dose from globally dispersed carbon-14 (0.375 mSv per caput). Assuming a future global equilibrium population of 30 billion people, Sakharov estimated a "collective dose commitment"[1], truncated to 8000 years (i.e. to the approximate life-time of ^{14}C), from radiocarbon and other radionuclides produced or dispersed in the atmosphere by nuclear tests up to about 1958. Sakharov concluded that the dose commitment from the weapons tests would result in 500,000 to one million victims of serious hereditary disorders and cancers. In his calculations Sakharov used the LNT principle, with a risk factor for hereditary effects based on data from *Drosophila melanogaster* fruit fly experiments (Muller, 1954). These and similar data were based on high dose X-, gamma- and beta-ray irradiations, ranging between 2.7 and 43.5 Gy (Oliver, 1930; Muller, 1946), which after extrapolation to zero dose, became a basis for the assumption that mutation frequency increases linearly with dose without any threshold. This assumption was adhered to in many later genetic experiments (Sankaranarayanan and Sobels, 1976; UNSCEAR, 1962).

However, the linearity assumption was not confirmed by early epidemiological surveys of Hiroshima and Nagasaki survivors (UNSCEAR, 1962), nor by later studies (UNSCEAR, 2000; UNSCEAR, 2001), in which no hereditary disorders were found in the progeny of highly irradiated parents. For estimation of carcinogenic radiation effects, studies of somatic cells are more relevant than those on germ cells. The results of early experiments with *Drosophila* male germ cells irradiated with X-rays do not agree with new findings in which somatic mutations in the *Drosophila* clearly showed a threshold around 1 Gy (Koana et al., 2004). Koana et al. also found a threshold (below which no increase in mutation frequency is detected in spermatocytes and spermatogonia) between 0.2 and 10 Gy (Koana et al., 2007; Koana et al., 2004). In the 0.2 Gy dose group and at low dose rate of 0.05 Gy/min these authors observed hormetic effects (40% less lethal mutations than those in sham-irradiated flies).

Over several decades the early experiments on mice carried out at Oak Ridge National Laboratory formed the basis for genetic risk estimates, for which the doubling dose for mosaic mutations was believed to be 1 Gy. Reevaluation of the Oak Ridge data demonstrated that in these experiments the frequency of spontaneous mutations was underestimated. The true doubling dose ranged in fact between 5.4 and 7.7 Gy. As the doubling dose increases, estimates of hereditary risk decrease. Therefore, the estimate of risk to humans based on old experiments using mice is probably at least 5 times too high (Selby et al., 2004; Selby, 1998). After perusal of Selby's revision the United Nations Scientific Committee on the Effects of Atomic Radiation decided that "*the prudent way forward is*

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[1] Four years later UNSCEAR defined the dose commitment to the world's population as a sum of radiation doses from a practice (for example, a series of nuclear tests) over endless generations and an infinite time period (UNSCEAR, 1962). I argued that this speculative concept, as well as that of collective dose, both related to LNT, have no biological meaning, and obliterate information required for realistic risk assessments (Jaworowski, 1999).

to abandon the use of an entirely mouse-data-based doubling dose estimate" (UNSCEAR, 2001). The Committee cited also the doubling dose in humans as ranging between 3.4 and 4.5 Gy, this being estimated from the Hiroshima and Nagasaki data (a strange conclusion, since Japanese data had shown no adverse genetic effects of bomb irradiation). Yet, the Committee decided that it "*will use the round figure of 1 Gy in risk estimation*".

However, at the time when Pauling and Sakharov announced their estimates of thousands and millions of genetic victims of nuclear tests, UNSCEAR, after three years of deliberation, did a more balanced and competent job in its first report, published at the end of 1958 (UNSCEAR, 1958). It accepted the possibility of zero increase in leukemia incidence – assuming a threshold, and that 150 000 cases would ultimately occur for non-threshold calculations. The Committee's estimation of the ultimate genetic defects was between 2500 and 100 000 cases (UNSCEAR, 1958).

UNSCEAR was established in 1955 by a resolution of the General Assembly of the United Nations. The Committee reports directly to the General Assembly, and its formal terms of reference are strictly scientific. Over its following five decades the Committee had diligently strived at estimating the effects of small radiation doses from all kinds of sources, and became an unquestionable authority on the matter of radiation effects in humans and their environment. However, as appears from the general conclusions of its 1958 report, the Committee was concerned mainly with the effects of nuclear tests, fulfilling a political task: to help in "*the cessation of contamination of the environment by explosions of nuclear weapons*". The effects of high radiation doses in nuclear war were never a subject of UNSCEAR studies. Later the emphasis of the Committee's work was on other types of exposure, and its publications became a foundation for the international radiation protection recommendations and national regulations.

In 1958 the Committee presented an ambivalent approach to LNT, which reflects the mixed opinion of its members on this subject. This is exemplified by conflicting statements such as: on theoretical grounds, if one ionization suffices to cause the effect, then "*this sort of effect has no threshold – which means that any dosage, however small, is effective in producing some alteration. On the contrary, if several ionization events are needed, the dose effect curve is sigmoid. In this case there is a threshold*". For mutational hazards the Committee was less prone to accept a threshold, stating that "*biological effects will follow irradiation, however small is amount*". However, it acknowledged that "*the studies of mutations in bacteria, Drosophila, and mice do not extend as low as the background radiation, and much uncertainty remains*".

The cautious approach of the Committee is best seen in the general conclusions of the 1958 report, among which one can read that "*Many effects of radiation are delayed; often they cannot be distinguished from effects of other agents; many will develop once a threshold dose has been exceeded...*", or "*the possibility cannot be excluded that our present estimates exaggerate the hazards of chronic exposure to low levels of irradiation*". Support for the LNT approach was most strongly worded in a *votum separatum* of the Soviet delegation (UNSCEAR, 1958). The criticism of LNT in this document was less explicit, but not among some of its authors. Professor W.V. Mayneord, one of the leading radiologists and head of the British delegation at the first session of UNSCEAR in March 1956, stated later "*I have always felt that the argument that because at higher values of dose an observed effect is proportional to dose, then at very low doses there is necessarily some 'effect' of dose, however small, is nonsense*" (Mayneord, 1964).

A similarly cautious approach was evident in the next 1962 UNSCEAR report. While stating that "*the relationship between dose and effect at cellular and subcellular levels does not give any indication of the existence of threshold doses and leads to the conclusion that certain biological effects can follow irradiation, however small the dose may be*", the Committee also observed that "*When dose effect relationships are studied at higher levels of organization, ... it is now being increasingly realized that the situation may be more complex, since many factors play a part between the occurrence of the primary event and the final manifestation of radiation damage*" and that therefore "*a simple mathematical relationship is unlikely to apply*".

In its first report of 1958 the Committee noticed adaptation and the possibility of repair of genetic material, but had not discussed these effects. In that document hormesis is clearly evident in a figure presenting survival times of gamma-irradiated mice and guinea pigs at dose rates of 5 mGy per week (page 162), and also in a table showing leukemia incidence in the Hiroshima population, which was lower by 66.3% in survivors exposed to 20 mSv, compared to the unexposed group (p. 165). This evidence of radiation hormesis was not commented upon. Since then, the standard policy line of UNSCEAR and of international and national regulatory bodies over many decades has been to ignore any evidence of radiation hormesis, and to promote LNT philosophy.

I tried to understand the reasons why was such a policy continued long after its original aim, i.e. stopping atmospheric tests of nuclear weapons, has been achieved. It seems to me that the driving force was (and still is) the vested interests of the radiation protection establishment and of the antinuclear power lobby, both concerned that demonstration of the beneficial effects of small radiation doses, and thus of the existence of a threshold for harmful effects occurring near this dose region, will destroy their *raison d'etre*. Refraining from studying or even acknowledging the existence of the phenomenon of hormesis may be regarded as non-scientific and political influences in the field of radiological sciences (Taylor, 1980); (Weinberg, 1972; Weinberg, 1985).

Ionizing radiation is very widely used in many walks of life. Only in its medical applications, some 330 million people are being exposed every year at low doses for radiodiagnostic purposes, and another 5 million undergo radiotherapy at high doses (UNSCEAR, 2000). Since its discovery until 1992 there were only 402 fatal victims among medical professionals (Molineus et al., 1992), and between1944 and 2001 only 134 fatalities occurred in all radiation accidents (Toohey, 2002). This indicates that radiation is a rather innocuous and not very lethal agent, a fact that the public is not aware of well enough.

Major human activities, including nuclear incidents, increase the radiation exposure of the global population to very low levels above natural background, well beyond those at which any hormetic effects may be apparent. For example, in the record year of 1963, the maximum average annual radiation dose to the global population from nuclear test fallout was 0.113 mSv (UNSCEAR, 2000). Until 1982 in its reports to the General Assembly, for comparing radiation exposures from the most important man-made and natural sources, instead of radiation dose units, the Committee used "units of days equivalent exposure to natural sources". I protested many times against this practice, and finally radiation units were used, but never in graphic form. Years ago I prepared a figure comparing these exposures in sievert units, based exclusively on data from UNSCEAR documents (Figure 1). At several sessions I proposed that the Committee publish such a figure in its report to the General Assembly, but to no avail. The official reason for rejection was the difficulty in making this figure understandable to laymen, but the real explanation offered to me on the side was: "*Visual perception is the most effective, and such a figure may make the politicians at the UN General Assembly think that the vast effort and resources spent on radiation protection of the population are excessive, and the very existence of UNSCEAR might be at stake*".

Reluctance to demonstrate clearly how unimportant is any radiation hazard to population from nuclear industry, the Chernobyl accident, nuclear explosion tests and medical irradiation, in relation to the broad range of natural radiation exposure, at which no adverse health effects were ever observed, reflects a "vested group interest" approach. However, what is published, are staggering and terrifying values of "collective doses" from these same sources (for example 2 330 000 man Sv per year from X-ray medical examinations – UNSCEAR, 2000), which are meaningless results of multiplying of innocuous tiny individual doses by 5.8 billion people. A "collective dose" of 14 000 000 man Sv per year from natural sources is not given for comparison and balancing in the public's mind of millions of man-made man-sieverts.

I was disappointed that the phenomenon of hormesis was ignored in all UNSCEAR documents since its first report. Therefore, in 1980, as chairman of the Committee, I suggested that it was the duty of UNSCEAR to peruse the large body of publications on radiation hormesis, some 1200 articles, published since the beginning of the century, to assess whether this phenomenon is real, and if so, how might it influence the methodology of risk estimates. A large review on this literature had already been published by then (Luckey, 1980), and the Committee had it in its library. The proposal was supported only by the delegation of Poland, and UNSCEAR rejected it. Every following year I repeated this proposal in vain, until after the Chernobyl accident of 1986, in 1987, it finally gained support, first from the representatives of France and Germany, and then from other delegations. Seven years later UNSCEAR published a report, rubberstamping the existence of the phenomenon of radiation hormesis, termed as "adaptive response" (UNSCEAR, 1994).

It was difficult for the Committee to overcome its own prejudices on radiation hormesis, and to produce a balanced report. Along the way, the Committee rejected two rather one-sided drafts of the report, prepared by the late Dr. Hylton Smith, the Scientific Secretary of ICRP, a body which strongly supported LNT and rejected hormesis. However, working for a few years on the report, Dr. Smith changed his initially negative approach to radiation hormesis, and finally produced an excellent, unbiased treatise on this yet unfathomed matter, demonstrating his scientific integrity. When the Committee finally endorsed the report, from the rostrum came this comment of UNSCEAR's Scientific Secretary: "*We are now in total disarray!*". During the Committee's 1995 session, the IAEA observer, Dr. Abel J. Gonzalez, reacted in a more vehement mood, scorning UNSCEAR for publishing its 1994 report, and arguing that this report contradicted the freshly issued Agency's Interim Edition of the "International Basic Safety Standards" (IAEA, 1994). My answer was that UNSCEAR is an independent body, our terms of reference being not regulations but science. I continued that scientific integrity of the Committee and its separation from non-scientific influences are essential for preserving UNSCEAR's role as the objective authority on the matter of ionizing radiation, and that it is not the role of IAEA to instruct UNSCEAR on its duties.

UNSCEAR's 1994 report had a considerable impact on science, reflected among others in the BEIR VII (BEIR-VII, 2005), and French Academy of Sciences - National Academy of Medicine (Tubiana et al., 2005) documents, supporting research on radiation hormesis. It also influenced regulatory bodies, as reflected by publications of the former ICRP chairman (Clarke, 1999) and by his proposals of scrapping some standards and principles based on LNT, such as "*Collective dose*", presented at the 10th International Congress of IRPA at Hiroshima in 2000. These proposals were rejected by the Congress (Webb, 2000), although many speakers supported them, claiming that LNT assumption is incorrect in view of the hormesis phenomenon (Anonymous, 2000). But the implications of hormesis for radiation protection include more issues than were discussed at this Congress, such as dose additivity, tissue weighting factors, radiation weighting factors, the sievert definition of effective dose and dose rate effectiveness factor (DDREF) and ALARA, all closely intertwined with the LNT approach (see e.g. (Cook and Calabrese, 2006; Mitchell, 2006).

During the fourteen years which had elapsed since the UNSCEAR report on adaptive response was issued, several new professional scientific journals and societies have emerged, covering the rapidly developing field of hormetic science. Important new information on radiation hormesis has also appeared in a great number of peer-reviewed publications. At the 2007 session of UNSCEAR the Polish delegation proposed that the Committee should critically review this new matter, which is of vital importance for the philosophy and practice of radiological protection. As in the past, the Committee did not agree to include such a study in its current program of work. I hope that, as in the past, the Committee will soon reconsider this issue.

Threshold or no threshold - that is the question, posed in the UNSCEAR 1958 report, and still unresolved. The no-threshold principle, seemingly simplifying radiation protection procedures (or its bureaucracy), has not only enormously increased their cost, but most importantly, is the culprit who created the universal fear of low levels of ionizing radiation. Among the disastrous consequences is the present lack of public acceptance of nuclear energy, the only realistic means of satisfying the future needs of humanity.

Proponents of the no-threshold philosophy often claim that one can never, with any finite experiment, prove that a given environmental factor is totally harmless. Thus, even if no effect is observed, such as is the case with hereditary disorders in Hiroshima and Nagasaki, one can only state that there is a certain probability that in fact there is no effect. Then the precautionary principle is invoked, and unrealistically low exposure standards are coined. To claim this position with a clear conscience, LNT protagonists should first falsify the elementary model of Feinendegen-Polycove (Feinendegen, 2005) which provides a logical and mathematical basis for radiation hormesis.

The hormesis concept transcends that of a dose threshold. In the absence of hormesis, the existence of a true threshold might be impossible to demonstrate rigorously because of the statistical difficulty of absolutely proving equality of effect in an epidemiological study. If however a deficit is observed in the irradiated population, as is the case in hormesis, there may be a statistically significant difference at an acceptable confidence level (Webster, 1993). The very existence of radiation hormesis phenomenon proves the existence of radiation thresholds and falsifies LNT. This is why hormesis is the best remedy for the mass psychological affliction called radiophobia, and, by the same token, this is why it is ignored by the influential part of the radiation protection establishment, against a vast factual evidence and the benefit of society.

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FIGURE 1.

Exposures of global population from major radiation sources, and of inhabitants of regions highly contaminated by radioactive fallout after Chernobyl accident. After (UNSCEAR, 1988; UNSCEAR, 2000).