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J Strzelczyk
University of Colorado at Denver, Radiology, Denver, CO, USA

W Potter
Nuclear Engineering Consultant, Sacramento, CA., USA

Z Zdrojewicz
Medical Academy, Wroclaw, Poland

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RAD-BY-RAD (BIT-BY-BIT): TRIUMPH OF EVIDENCE OVER ACTIVITIES FOSTERING FEAR OF RADIOGENIC CANCERS AT LOW DOSES

J. Strzelczyk □ University of Colorado at Denver, Radiology, Denver, CO., USA

W. Potter □ Nuclear Engineering Consultant, Sacramento, CA., USA

Z. Zdrojewicz □ Medical Academy, Endocrinology, Wroclaw, Poland

□ Large segments of Western populations hold sciences in low esteem. This trend became particularly pervasive in the field of radiation sciences in recent decades. The resulting lack of knowledge, easily filled with fear that feeds on itself, makes people susceptible to prevailing dogmas. Decades-long moratorium on nuclear power in the US, resentment of "anything nuclear", and delay/refusal to obtain medical radiation procedures are some of the societal consequences. The problem has been exacerbated by promulgation of the linear-no-threshold (LNT) dose response model by advisory bodies such as the ICRP, NCRP and others. This model assumes no safe level of radiation and implies that response is the same per unit dose regardless of the total dose. The most recent (June 2005) report from the National Research Council, BEIR VII (Biological Effects of Ionizing Radiation) continues this approach and quantifies potential cancer risks at low doses by linear extrapolation of risk values obtained from epidemiological observations of populations exposed to high doses, 0.2 Sv to 3 Sv. It minimizes the significance of a lack of evidence for adverse effects in populations exposed to low doses, and discounts documented beneficial effects of low dose exposures on the human immune system. The LNT doctrine is in direct conflict with current findings of radiobiology and important features of modern radiation oncology. Fortunately, these aspects are addressed in-depth in another major report—issued jointly in March 2005 by two French Academies, of Sciences and of Medicine. The latter report is much less publicized, and thus it is a responsibility of radiation professionals, physicists, nuclear engineers, and physicians to become familiar with its content and relevant studies, and to widely disseminate this information. To counteract biased media, we need to be creative in developing means of sharing good news about radiation with co-workers, patients, and the general public.

1. INTRODUCTION

The world looks so different after learning science

—Feynman (1968)

1.1 Benefits of scientific literacy and consequences of lack of knowledge

As individuals and as a society, all of us have a stake in scientific literacy. It enables us to use scientific principles and processes when making

Address correspondence to Jodi Strzelczyk, Associate Professor, Radiology, Health Sciences Center, University of Colorado, Denver, CO, USA. Phone 720-848-6603; Jodi.Strzelczyk@UCHSC.edu

personal and professional decisions, and in discussions of issues that affect society. It allows us to better comprehend the natural world and strengthens many skills that we use every day, such as solving problems creatively, thinking critically, and using technology effectively for the benefit of mankind. Yet, large segments of the world population lack a knowledge of basic scientific facts and processes. Such deficiencies have serious implications for an individual as well as at the societal level: inability to evaluate validity of various claims, susceptibility to being a subject of scams, diminished interest of a young generation in science and technology careers, and lack of support for research among them.

1.2 Recent changes in the society's level of scientific literacy

Recent surveys conducted by the National Science Foundation (NSF) show little improvement in the public's scientific literacy in the United States; the ability of respondents' to answer science questions has remained essentially unchanged since the 1990s. However, a positive trend is noted in the prestige of science and technology occupations in the past few years; since 2002, more people have expressed confidence in the leadership of the scientific community than in any other profession except the military. While there is considerable variation in science knowledge across countries in Europe, the recent *Eurobarometer* survey shows improvement in most surveyed countries; Belgium, Germany, Ireland, and the Netherlands record double-digit increases in the percentage of correct responses comparing results of 1992 and 2005 surveys. Americans, on the other hand, appear to have more positive attitudes about the benefits of science and technology compared with others. In recent surveys, 84% of Americans, compared with 52% of Europeans and 40% of Japanese, agreed that benefits of scientific research outweigh any harmful results (NSF 2006).

1.3 Scientific literacy and *radiophobia*

These generally positive changes in scientific literacy are likely, and hopefully soon, to include an improvement in the public's basic understanding of radiation and processes involved in the health effects of low-level radiation exposure. The widely spread irrational fear that any level of ionizing radiation is dangerous has lead to serious consequences such as the decades-long moratorium on nuclear power in the United States, and global resentment of anything nuclear. It has been a culprit in patients' refusal of or delay in obtaining medical radiation procedures. It is time for *radiophobia* to be eliminated.

2. HISTORICAL DEVELOPMENT

We live in an unscientific age in which almost all the buffeting of communications and television—words, books, and so on—are unscientific. As a result, there is a considerable amount of intellectual tyranny in the name of science

—Feynman (1968)

2.1 Reasons for *radiophobia*

The principal reason frequently given for the fear of low-level radiation is the psychological aftermath of detonations of nuclear weapons in Japan in 1945 and of subsequent weapon testing. The devastating physical results of these events and health effects of high-dose irradiation are unquestionable and well documented. However, epidemiological studies thus far fail to show causal association between low-level exposure to ionizing radiation and cancer. Nevertheless, such inferences are commonplace in numerous sources of information including some that are published in scientific journals. Thus it would appear that an even more important reason for *radiophobia* is the ambiguous, confusing, and even alarming manner in which cancer risks are presented. Presentations of this kind can be attributed not only to anti-nuclear activists; they can readily be found in the advisory and regulatory documents having to do with radiation protection.

2.2 Cancer risk estimated by radiation advisory organizations

2.2.1 Linear extrapolation of risk from high-dose observations

In the early 1990s, the International Commission on Radiological Protection (ICRP 1991) and the National Council on Radiation Protection and Measurements (NCRP 1993) specified the risks of fatal cancers, to be used in radiation protection as $5x10^{-2}$ Sv^{-1} (0.05 per 100 rem) for a population of all ages, and $4x10^{-2}$ Sv^{-1} (0.04 per 100 rem) for an adult population occupationally exposed to radiation. These judgments were based on the risks observed in populations exposed to high dose radiation: the Lifespan Study of the A-bomb survivors up to 1985 by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 1988); on the ICRP analysis of five distinct populations and the Biological Effects of Ionizing Radiation (BEIR) V Report (NAS 1990).

2.2.2 Acceptance of the linear no-threshold (LNT) hypothesis

The acceptance of the LNT hypothesis by the ICRP as a philosophical basis for radiological protection dates back to 1959; the decision was based on the first report of the newly formed UNSCEAR (1958). A large

part of the original report was dedicated to a discussion of linearity and the threshold dose for adverse radiation effects. The committee's stand almost 50 years ago was formed after an in-depth debate, but not without the influence of the political atmosphere; Soviet and Egyptian delegations to UNSCEAR in particular strongly supported the LNT assumption, using it as a basis for the recommendation to cease all nuclear test explosions. The prevailing, at the time, "target theory" and the results of genetic experiments with fruit flies irradiated with high doses at high dose rates, also influenced this debate (Jaworowski 2000). The UNSCEAR report stated that contamination of the environment by nuclear explosions increased radiation levels all over the world, posing new and unknown hazards for the present and future generations, and that *"even the smallest amounts of radiation are liable to cause deleterious genetic, and perhaps also somatic, effects"*. As noted by Professor Zbigniew Jaworowski, Member and former Chairman of UNSCEAR, the latter statement has had an enormous impact in the next decades, being repeated in a plethora of publications, and even now taken as an article of faith by the general public (Jaworowski 2000).

Throughout the report (UNSCEAR 1958), the committee's view of the LNT remained ambivalent. For instance, the committee accepted a dose of 4 Sv (400 rad) as a threshold for leukemia, but at the same time, based on the LNT model, suggested the use of a risk factor for leukemia of 0.52% per Sv (0.0052 per 100 rad). This difficulty was quite openly presented (page 42), showing that the continuation of nuclear weapon testing in the atmosphere was estimated to cause 60,000 leukemia cases worldwide if no threshold is assumed, and zero cases if a threshold of 4 Sv exists. In conclusion, this controversy is explained as follows: "*Linearity has been assumed primarily for purposes of simplicity*" and *"There may or may not be a threshold dose. Two possibilities of threshold and no-threshold have been retained because of the very great difference they engender"*.

No such controversy appears in any of the ICRP or NCRP reports; LNT is arbitrarily assumed. Over the years, this working assumption came to be regarded as a scientifically documented fact by mass media, the public, and even some scientists. The LNT model, however, belongs to the realm of administration and is not a scientific principle.

3. LOW-DOSE RADIATION AND CANCER

Science is the belief in the ignorance of experts . . . it teaches the value of rational thought as well as the importance of freedom of thought; the positive results that come from doubting that the lessons are all true

—Feynman (1968)

3.1 Misrepresentations of the LNT

The use of a linear no-threshold relationship between radiation dose and carcinogenic effect by extrapolating from high doses to low and very low doses, all the way down to zero – an artificial point with no radiation exposure and no risk of cancer – deserves a great caution. Such a relationship implies that any dose of radiation, no matter how small, and how it is delivered, is *harmful*, and that the mathematically derived risk is *cumulative*. Another serious misconception stems from the implication that there is a high *biological* risk of cancer due to some injury to all cells from a small amount of radiation, when what is actually relevant is the substantially lower physical risk of any one cell receiving a local dose large enough to produce serious injury (Bond and Sondhaus 1987). The appropriateness of this approach has been questioned in many debates over the past 30 years.

3.2 Recent advances in radiobiology and their impact on the LNT doctrine

With regard to the dose-effect relationship, the main contribution to progress has come from biological research. Enormous advances in defining the details at the molecular level of cellular responses to ionizing radiation occurred in the last two decades. The so-called "molecular revolution" enhanced our ability to probe into the functioning cells, their interactions with tissues, and their response to external stressors, including ionizing radiation. New techniques allowing DNA manipulation and the assessment of gene functions are largely responsible for this progress. Their impact on advances in the field of radiation biology has been ably depicted in a recent review article published in *Radiation Research* (Bedford and Dewey 2002).

3.2.1 Levels of organization and responses of living organism to genotoxic agents

Living organisms, human species in particular, are complex systems with well-defined levels of organization, starting with the basic physical/chemical level, followed by the cellular level, the tissue-organ level, up to the whole organism. The components within each level and among the levels, interact functionally with one another via intricate intra- and intercellular signalling processes (Feinendegen et al. 1995). These net-

work links seem to operate in concert to maintain the competence of proper functioning of the system's structures in their microenvironment even when the homeostatic balance is affected by a physical or chemical insult (Barcelos-Hoff and Brooks 2001). An amazing capacity for maintaining the system's integrity is accomplished through complex and efficient defense mechanisms against genotoxic agents at the level of the cell (DNA repair and apoptosis), of the tissue (the role of neighboring cells), and of the total organism (immunosurveillance).

3.2.2 Factors that influence cell and tissue responses to radiation

While radiation induced DNA damage increases with dose, a cell is not passively affected by the accumulation of the lesions; it reacts by at least three mechanisms: by fighting against reactive oxygen species (ROS), by eliminating injured cells, and by stimulating a repair of DNA damage.

There is a general agreement among scientists that cellular responses to low doses of radiation are not readily predictable by extrapolation of responses observed at high doses. At least two reasons for this unpredictability are apparent. First, energy absorbed by a biological tissue exposed to low doses of penetrating radiation is not distributed evenly throughout the tissue. The stochastically distributed particle tracks in the tissue generate along their paths ionizations and excitations, and create ROS with low density (ICRU 1983; Feinendegen 2002). Second, the biological tissue microenvironment contains numerous compounds that are likely to influence the cellular response to low-dose radiation. In addition to endogenous and environmental toxins present in the tissues, there is an abundant constant metabolic generation of ROS. DNA damage in the form of double strand breaks (DSB) due to endogenous ROS is three orders of magnitude more frequent than due to ROS arising from exposure to natural background radiation (Rothkamm and Lobrich 2003; Pollycove and Feinendegen 2003). Living organisms depend on some compounds in the microenvironment of the tissue to suppress destructive ROS. These include endogenous antioxidant enzymes such as superoxide dismutase (SOD), as well as antioxidants gained through diet. The oxidative stress that may be induced by radiation is responsible for stimulating the enzyme system to detoxify the microenvironment as well as for activating numerous signalling pathways.

These signals can profoundly alter the fate of the DNA lesions and responses depend on the nature of cellular damage. Modern transcriptional analysis of cellular genes using microarray technology reveals that, without modification of the genome, numerous genes are activated or inhibited following doses much lower than those required for mutagenesis (Mercier et al. 2004). Additionally, depending on the dose, dose rate and the LET of radiation, not the same genes are transcribed. Different types of DNA damage lead to the activation of different families of genes (Bishay et al. 2001;

Amundson et al. 2005). The signals modulate the action of proteins involved either in a cell cycle control (the interruption of which promotes repair), in DNA repair, or in triggering apoptosis (the elimination of cells that may be mutated or unstable). Intracellular signalling systems are not triggered below a few mSv (a few hundred mrem) and the damaged cells die (Collis et al. 2004). This inactivation may reflect one strategy by which the cells avoid accumulating mutations as a result of error-prone DNA repair.

While mechanisms by which the cells within a tissue coordinate their responses are not exactly known, their properties are becoming clearer with new progress in radiobiology research. The traditional opinion that DSBs and cellular survival or damage are inseparably linked, and that radiation effects could be defined as a function of DNA DSBs, is being challenged by the results of numerous studies. These studies demonstrate indirect (non-DNA related) effects and coordinated tissue responses (Mothersill and Seymour 2005). Radiation-induced signals from cells not directly hit (bystander effects) appear to be responsible for coordinating the responses (Lorimore and Wright 2003). It appears then that, at low doses, more cells than those actually hit directly will respond to heterogeneously distributed energy deposition events. This may lead to a concern that the risk of late effects from DNA damage, such as cancer, will be higher, but the same argument applies to bystander-induced adaptive responses. As shown by Professor Feinendegen (2005), the probability of radiation-induced lethal cancer by a dose of 1 mGy (100 mrad) of low LET radiation such as 100 kV X-rays is extremely small, about 10^{-11} to 10^{-12}. *Thus an opinion that even one DSB poses a risk of lethal cancer has no basis.*

Recent advances in biological research show that at equal doses, the mutagenic effect varies significantly with the dose rate. The mutation frequency, after having passed through a minimum (hormesis?) sharply increases as the dose rate increases (Vilenchik and Knudson 2000). When the number of lesions is low such as is the case when radiation is delivered with low dose rates, a reversible arrest of the cell cycle is observed; it enhances DNA repair. On the other hand, the presence of a high number of lesions prolongs the cell cycle arrest, which can lead to apoptosis (Vilenchik and Knudson 2003).

Apoptosis, a process of programmed death and removal of cells with a damaged or misrepaired genome, can be initiated by doses as low as a few mSv (a few hundred mrem). Its efficacy depends on radiation dose, the cell line and the tissue. While high effectiveness of this process reduces the probability of neoplastic transformation, it also depletes the pool of cells that are able to proliferate, stem cells in particular. However, when a large number of cells in the same tissue are killed or damaged, repair and proliferation mechanisms are triggered in order to protect the integrity and functioning of the tissue. The system reacts to the insult in an integrated response that involves immunosurveillance (Feinendegen 2005).

4. CONCLUSION

Science is the result of the discovery that it is worthwhile rechecking by new direct experience, and not necessarily trusting the . . . experience from the past

—Feynman (1968)

A large body of recent radiobiological data, only a small sample of which was considered here, clearly undermine the validity of the LNT doctrine. As discussed in-depth in the Joint Report of two French Academies, of Sciences, and of Medicine (Tubiana et al. 2005), the incidence of mutations does not increase linearly with dose; it is shown to be greater at high doses and high dose rates. The efficient biosystem of prevention, removal and repair sequentially reduces DNA damage from about one million DNA alterations/cell/day to about 1 "mutation"/cell/day. For comparison, low LET background radiation of 1 mGy/y (100 mrad/yr) produces 1 DNA alteration/500 cells/day (Feinendegen 2005). Contrary to the opinion expressed in BEIR VII Report (NAS 2005), the data indicate that the probability of DNA repair varies with both radiation dose and dose rate. In summary, there are no convincing data from epidemiological studies or radiobiology research that would demonstrate the existence of carcinogenic effect of doses below 100 mSv (10 rem).

As radiation professionals, we have a responsibility to question unreasonable applications of the LNT dogma and to rebut its biased representations. This requires us to be familiar with the results of relevant current research, and to continue working on the means of disseminating them and sharing good news about radiation with our co-workers, patients, and the general public.

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