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MEMORANDUM TO: John E. Glenn, Chief
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SUBJECT: EFFECTS OF LOW-LEVEL, LOW LET RADIATION

The attached report recently published by scientists from the U.K National Radiological Protection Board (NRPB)[1] addresses the scientific issues relevant to assessment of risk from low dose and dose rates of low LET (Linear Energy Transfer) radiation. The authors have reviewed the current state of knowledge based on epidemiological investigations, animal studies and mechanistic studies at the cellular and molecular levels. On the basis of the mechanistic studies the authors conclude that "the risk of induced neoplasia rises as a simple function of dose and does not have a DNA damage or DNA repair related threshold like component".

This conclusion is justified by the evidence that a single radiation track (the lowest dose and dose rate possible) has a finite (but small) probability of producing a variety of damage to the DNA including damage which results in a tumor initiating mutations. Thus, for early molecular damage there can be no real threshold in the dose response relationship for any ionizing radiation, and only if this damage is always repaired with total efficiency and accuracy could there be a dose threshold at the cellular level.

Given the considerable evidence of multi-stage process of carcinogenesis the question has arisen if a true dose threshold might exist at other stages. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), has examined this question in detail and concluded in its 1993 Report[2]:

> In view of these many possibilities, it would be difficult to conclude on theoretical grounds that a true threshold

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[1] Stather, J.; Muirhead, C.; Cox, R. Radiation-induced cancer at low doses and low dose rates. National Radiological Protection Board (NRPB)'s Radiological Protection Bulletin (ISSN 0308-4272) No. 167, pp. 8-12, July 1995.

[2] UNSCEAR, Sources and effects of ionizing radiation. 1993 Report to the General Assembly, with annexes, New York, United Nations (1993).

> should be expected even from multi-stage mechanisms of carcinogenesis, unless there were clear evidence that it was necessary for more than one time-separated change to be caused by radiation alone. The multitude of animal and human data showing an increase in tumors after a single brief exposure to radiation and also the occurrence of spontaneous tumors in the absence of radiation, implies that these restrictions do not apply in general. These theoretical considerations cannot preclude the possibility of particular situations where the probability of an effect at low doses may be very small, and even practically negligible, compared with that at higher doses. (page 633)

There is some evidence that low dose and dose rate radiation may produce beneficial effects, the so called hormetic effects or adaptive response. The existence of adaptive response does not contradict the no-threshold conclusion, since in a complex organism both deleterious and beneficial effects can be induced by the same agent.

UNSCEAR in its 1994 Report[3] reviewed the available evidence of adaptive response in cells and organisms and reached the following conclusion:

> However, errors in repair do occur, even during metabolism, such as small base-sequences changes (point mutations), gene deletions or rearrangements, although the overall DNA integrity may be retained. It needs to be recognized, therefore, that the effectiveness of DNA repair in irradiated mammalian cells is not absolute, some fraction of the cells retaining stable mutations. Thus, the same low conditioning doses that result in a adaptive response are likely also to result in malignant cellular transformations by the mechanisms discussed in Annex E, "Mechanisms of radiation onco-genesis" in the UNSCEAR 1993 Report. It would seem important to judge the balance between the fidelity of repair, residual damage and malignant transformations and whether indeed these effects interact with

[3] UNSCEAR sources and effects of ionizing radiation. 1994 Report to the General Assembly, with Scientific Annexes. New York, United Nations (1994).

> each other. The Committee hopes that more data will become available in the near future to address this point. (page 223)

and

> It is to be hoped that better understanding of mechanisms of radiation effects obtained in molecular studies might provide a basis upon which to judge the role of adaptive response in the organism. In the meantime, it would be premature to conclude that cellular adaptive responses could convey possible beneficial effects to the organism that would outweigh the detrimental effects of exposures to low doses of low-LET radiation. The Committee recommends that this research be continued in order to clarify the nature and importance of the effects of radiation-induced adaptive response. (page 224)

Thus, the available scientific evidence points to a conclusion, in agreement with the attached NRPB Report, that any incremental dose of radiation is associated with a finite increase in radiogenic cancer risk. At low doses and dose rates that increase may be practically negligible, but is not zero.

Attachment: As stated

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Radiation-induced cancer at low doses and low dose rates

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The Institut de Protection et de Sûreté Nucléaire (IPSN) is a French public organization carrying out research and expert evaluations in the various matters relevant to the control of radiation risks, safety technology, protection of man and of the environment, management of accident conditions, and security of transport. As an input to its work, IPSN commissioned NRPB to present an updated review of the current state of knowledge in some of the major fields relevant to the assessment of the risk of radiation-induced cancer at low doses and low dose rates for radiation protection purposes[1]. The review considered the results of epidemiological investigations and fundamental studies on the cellular and molecular mechanisms involved in radiation damage and response. Additionally, this information was supplemented by studies with experimental animals which provide further guidance on the form of the dose–response relationship for cancer induction, as well as on the effect of dose rate on the tumour yield. The emphasis of the report, summarized below, was on cancer induction resulting from exposure to radiations with a low linear energy transfer (LET). The conclusions of this report represent the position of NRPB and not necessarily the view of IPSN in each of the matters.

EPIDEMIOLOGY

Epidemiological studies provide a substantial amount of direct, quantitative information on the risks of cancer in man following radiation exposure[2]. The main source of data is the Life Span Study of the survivors of the atomic bombings of Hiroshima and Nagasaki in 1945. This population shows a pattern of increasing risk with increasing dose for both leukaemia and most solid cancers with a significant increase in the risk of cancer at acute doses in the range 200–300 mGy and above. Information on cancer risks is also available from a number of studies of patients irradiated for medical reasons. Many of the patients in these studies received high doses to particular organs, often 1 Gy or more, although some had received much lower doses. Results from pooling several studies have suggested a statistically significant increase in the risk of thyroid cancer at doses down to about 100 mGy (low-LET).

A number of studies provide information on the risk of childhood cancer following exposure of the mother's abdomen during pregnancy. The low background cancer rates in children also improve the ability to detect an elevated cancer risk after irradiation *in utero*. These studies, together with data from the long-term follow-up of those exposed to atomic bomb irradiation, strongly suggest that irradiation *in utero* increases the risk of cancer. In the case of the Oxford Survey of Childhood Cancer, a 40% increase in the childhood cancer rate in children up to 15 years of age has been seen following doses in the range of about 10–20 mGy (low-LET). Similar results have been obtained in a number of other[3] smaller studies of the effects of obstetric radiography. Although there may be some increase in sensitivity to radiation at this

early stage of development, there is no reason to believe the mechanisms involved in tumour induction will be fundamentally different to those in adults.

Direct information on the effects of low dose chronic radiation exposure is becoming available from studies of radiation workers, both in the UK and elsewhere. The quantitative estimation of cancer risks from these studies presents particular problems, however, because of the need for a large study population to detect elevated risks at the low doses involved and the need for a long period of follow-up. Despite this limitation, some studies of occupationally exposed workers exposed to low-LET radiation provide indications of excess cancer risks, notably for leukaemia. Although the data are not strong enough to allow quantitative risk estimates to be obtained, the findings are generally consistent with the risk estimates developed by ICRP in Publication 60[3] and with the assumption of a cancer risk even at low doses.

Studies of the effects of exposure to background radiation and of environmental exposure are subject to the influence of confounding factors and generally lack sufficient statistical power to detect small increases in risk.

Epidemiological studies thus indicate an approximately 40% increase in the risk of radiation-induced cancer in childhood following exposures *in utero* at doses of low-LET radiation of about 10–20 mGy. A statistically significant increase in the risk of cancer has also been observed following exposure of children to doses down to about 100 mGy and to the atomic bomb survivors, generally in the dose range 200–500 mGy.

ANIMAL STUDIES

Studies in experimental animals cannot be used to obtain quantitative estimates of cancer risk to apply to human populations because of differences in sensitivity between species. They can, however, be used for examining the form of dose-response relationships and biological and physical factors that influence the radiation response.

Analyses of a series of studies in mice have shown that the lowest doses at which a statistically significant increase in cancer yield is observed varies between studies, depending on the number of animals in the experiment, the radiation sensitivity of the strain of mouse to specific cancers, and the spontaneous cancer rate, as well as the dose range. In a number of studies, the lowest acute dose to give a significant effect on tumour yield falls in the range between about 100 and 200 mGy (low-LET). This is similar to that found in studies on adult human populations. The lowest dose to give a significant increase in risk following chronic irradiation is generally higher than that for acute exposure because of the reduced effectiveness of low dose rate radiation in inducing cancer. It is concluded that animal studies provide broad support for the results of epidemiological studies of the tumorigenic effects of radiation at low to intermediate doses.

DOSE RATE EFFECTS

Studies at the molecular, cellular, tissue and whole-animal level have demonstrated that radiation damage increases with dose and that, at least for low-LET radiation, at high dose rates it is often greater, per unit of exposure, than at low dose rates. Although the assumption that has frequently been made for radiation protection purposes is that the dose-response curve for cancer induction is linear, with the risk proportional to dose, in practice a dose and dose rate effectiveness factor (DDREF) is commonly used to allow for a reduced effectiveness of radiation in inducing cancer in man at both low doses and low dose rates. There are, however, only limited data on the effects of dose rate on the induction of radiation-induced tumours in human populations.

Analysis of the dose-response data for the combined incidence of leukaemia and

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solid cancers in the Japanese atomic bomb survivors may be used to derive a DDREF of about 1.7 in order to provide an overall estimate of human cancer risks at low doses and low dose rates of ionising radiation. Human data on the induction of thyroid cancer suggest a DDREF of 3 when the effects of acute external irradiation are compared with low dose rate exposure resulting from intakes of iodine-131. There are, however, questions about the contribution of heterogeneity of dose and uncertainties in dose estimates, as well as the effect of age on the overall risk. For female breast cancer, information is conflicting, but comparative data from Canadian provinces indicate a DDREF of possibly 3 for a reduction in effect at low dose rates.

Animal studies and experiments on cell transformation in culture and on somatic and germ cell mutation rates have provided further insight into the likely effects of both dose and dose rate on tumour induction. Studies both on cell transformation *in vitro* and on mutation rates in somatic and germ cells suggest values of DDREF in the range 2–4. A review of relevant animal tumorigenesis studies provides values of DDREF in the range from 1 to 10 or more for dose rates varying by factors from 100 to 1000 or more. Thus, it may be conjectured that at lower dose rates than those experienced by the Japanese atomic bomb survivors, a DDREF greater than 1.5 might apply. Risk estimates derived from limited data on the effects of human exposures at low dose rates do not, however, support the use of high values of DDREF.

Taken together, the available human and experimental data suggest that it is appropriate to apply a low value of DDREF, and a value of 2, as presently recommended by ICRP in Publication 60[3], and a value of less than 3, as recommended by UNSCEAR[2], seem justified.

MOLECULAR AND CELLULAR STUDIES

Increasingly, interpretation of epidemiological and experimental studies at low doses is being influenced by accumulating information on the fundamental nature of the tumorigenic process. Neoplasia in tissues is now seen as a complex, multistage process that can be subdivided into four phases: neoplastic initiation, promotion, conversion and progression. The subdivisions are necessarily simplifications of the overall process, which is, in any event, somewhat variable between different tumour types. However, they do provide a basis from which to interpret the cellular and molecular changes involved[4].

Neoplastic *initiation* encompasses the essentially irreversible cellular damage, which, although not necessarily expressed immediately, provides the potential in cells for neoplastic development. There is good evidence that this initiation process results from damage to DNA leading to gene or chromosomal mutations in single target cells in tissues. It is argued that the critical damage is likely to be coincidental damage to both DNA strands (DNA double strand breaks). Although a proportion of such double strand damage will be repaired, completely error-free repair of such damage, even at low doses, is not expected. It has been suggested that, because of the high level of single strand DNA damage arising spontaneously in cells, the small increment of damage induced by low dose radiation will be insignificant for cancer risk. This argument is not sustainable since it fails to recognise the very low abundance of spontaneous DNA double strand damage and the crucial importance of these lesions and their misrepair for cellular radiobiological response.

Once the necessary gene mutation is present in a cell, further neoplastic development is believed to be highly dependent upon both the intra- and extracellular environment. As a consequence of *proliferational* events, influenced by growth factors in cells, dietary constituents, hormones, or other environmental agents, there may be

an increase in cell proliferation and in some instances interference with communication processes between cells that act to maintain cellular stability in tissues. Neoplastic promotion can be seen as a process whereby initiated cells receive an abnormal growth stimulus and begin to proliferate in a semi-independent manner. *Conversion* of these pre-neoplastic cells to a form in which they are committed to become fully malignant is a central feature of the process of neoplastic development. Such changes are now believed to be driven by further genic mutations accumulating within the expanding population of pre-neoplastic cells. These changes may arise simply as a consequence of the natural rate of spontaneous mutation, although there is evidence that some gene-specific mutations in pre-neoplastic cells also act to destabilise the genetic material, thus accelerating the process of malignant development.

Once the potential for full malignancy has been established, the subsequent *progression* of the disease may depend upon further cellular changes that allow invasion of adjacent normal tissues, the circulation of neoplastic cells in the blood and lymphatic systems, and the establishment of metastases (secondary tumour growths) at other sites in the body. It is this invasive process that provides principally for the fatal effects of most common human tumours.

Two classes of tumour-associated genes have been identified. *Proto-oncogenes* are subject to gain-of-function mutations which result in overexpression or more subtle functional changes in respect of the synthesis in cells of a range of proteins essential for cellular growth and development. The changes in DNA which bring this about range from single DNA base-pair changes to more complex chromosomal damage. *Tumour suppressor genes* act as negative regulators of cellular processes that mediate cell division and development. It is loss, rather than gain, of function of these genes that contributes to the development of neoplasia. This loss of function may result from single DNA base changes, deletions of small regions of DNA, or the loss of whole chromosome segments. The first phase of radiation tumorigenesis *in vivo* can be viewed as the induction of a broad range of genic damage in the cell population as a whole. If damage to a specific subset of proto-oncogenes and/or tumour suppressor genes is not repaired correctly, this can generate gene mutations which create the potential for neoplastic development. Such mutation will not be unique to radiation damage, but will simply add to the 'pool' of mutations in target cells arising either spontaneously or as a consequence of other environmental agents.

Although radiation-induced mutation may in principle affect all stages of the neoplastic process, it is argued that neoplastic initiation is the key stage that is primarily targeted by low doses of radiation. It is also argued, on the basis of evidence from biochemical, cytogenetic and molecular studies on both haemopoietic and solid tumours, that, with very few exceptions, tumours arise from single cells and, by implication, develop from a gene-specific mutation in a single cell in the originating tissue. The growth of a sub-population of cells from this original mutated cell by division then provides preferential targets for full neoplastic change. On this basis, a single mutational event in a critical gene in a single target cell *in vivo* can create the potential for neoplastic development. Thus, a single radiation track (the lowest dose and dose rate possible) traversing the nucleus of an appropriate target cell has a finite probability, albeit very low, of generating the specific damage to DNA that results in a tumour initiating mutation. Following this, and again at a low probability, these initiated cells can develop by multistage processes into an overt malignancy. As a consequence, at the

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level of DNA damage, there is no basis for the assumption that there is likely to be a dose threshold below which the risk of tumour induction would be zero. For radiation protection purposes, it is appropriate therefore to assume a progressive increase in risk with increasing dose, with no threshold.

There is some evidence that low dose radiation may induce or activate cellular DNA repair functions, the so-called adaptive response. The majority of effects seen to date have been essentially short term, and the current consensus is that knowledge of their relevance to neoplastic processes is insufficiently developed and understood to influence current judgements on tumorigenic responses at low doses and low dose rates.

Other tissue and cellular processes may influence tumour development. Programmed cell death (apoptosis), or terminal differentiation of initiated cells to a non-dividing state, is expected to reduce the risk of spontaneous and radiation-induced malignant development, but there are no convincing data to show that such protective effects are specifically enhanced at low doses and low dose rates. Immune surveillance mechanisms may also target and eliminate a proportion of neoplastic cells in tissues but principally those associated with oncogenic viruses rather than those of the common tumours known to be induced by radiation. Other surveillance mechanisms in cells and tissues may play a similar role, but there is great uncertainty as to their efficiency and specificity in respect of non-viral human tumours. There also remains the possibility that, for a few tumour types, development may not be monoclonal in origin. There is some evidence from animal experiments that, for a number of specific tumours, overt tissue damage/fibrosis may be required, and in this instance tumours are likely to require a threshold dose in order that the essential tissue environment is present for their development. Thymic lymphomas and ovarian tumours in mice appear to show this type of response.

CONCLUSIONS

It is concluded, therefore, that data relating to the role of gene mutations in tumorigenesis, the monoclonal origin of tumours, and the relationship between DNA damage repair, gene/chromosomal mutation and neoplasia are well established and broadly consistent with the thesis that, at low doses and low dose rates, the risk of induced neoplasia rises as a simple function of dose and does not have a DNA damage or DNA repair related threshold-like component. Whilst adaptive responses or other protective mechanisms may influence the risk of tumour development, they do not provide a sound basis for judgement that tumorigenic response at low doses and low dose rates of radiation is likely to have a non-linear component which might result in a dose threshold below which the risk may approach zero. These mechanistic studies, in addition to the epidemiological information, indicate that for radiation protection purposes there is little basis for arguing that low radiation doses (about 10 mGy) would have no associated cancer risk and that, in the present state of knowledge, it is appropriate to assume an increasing risk with increasing dose.

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Radiation hormesis – fact or fiction?

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Deriving from the Greek verb *hormein*, which means to stimulate and excite, hormesis literally refers to any kind of stimulation and excitation. As a medical and geomedical term (though of unsettled status) it has a more restricted meaning however, indicating merely the putative or real stimulatory and beneficial effects observed when a biological system is exposed to a low dose of an agent known to be toxic or hazardous at a significantly larger dose. Depending on the type of stimulatory agent, one can speak of chemical or physical hormesis, radiation hormesis being a member of the latter group. The present paper reviews and evaluates the history and origins of the concept of radiation hormesis and its present status – fact or fiction. It is concluded that despite the numerous, sometimes undeniably strong, individual pieces of evidence that have been presented in favour of this phenomenon, the bulk of the evidence is so far not strong enough to establish it as a scientifically proven fact. It is also evident that, instead of speaking of radiation hormesis as an entity, one should pay attention separately to the effects of alpha, beta and gamma radiation, the deleterious and possible beneficial hormetic effects being different in each case.

Keywords: Radon, cancer, geomedicine, medical geochemistry

Introduction

Ever since Henri Becquerel (1852–1908) in 1896 discovered the phenomenon that was later to be called radioactivity by Marie Curie (1867–1934), public opinion concerning its beneficial or hazardous effects on human health has changed many times, some of the changes being rapid swings from one extreme to the other. During the past five or six decades, however, those views have dominated which are based on the 'radiation paradigm' (see Henry, 1961, p. 671), which maintains that all radiation at all doses is harmful. Recently, the attitudes of a growing number of scientists and experts (Loken and Feinendegen, 1993 and the 42 references therein) seem to have started to move away (Sagan, 1989) from the categorically stagnant state imposed by the radiation paradigm, towards recognition and acceptance of a concept known as radiation hormesis, which states that low-level ionising radiation (LLIR) may be beneficial for human health. The current shift of opinion is obviously the result of an increasing number of scientific papers favouring the idea of radiation hormesis (Luckey had already collected some 1,200 references in 1980 and further references can be found in Loken and Feinendegen, 1993) which, among other things, brought to light the fact that there are often net benefits associated with LLIR and that there is often a negative correlation between the incidence of lung cancer, for instance, and the radon content of the ambient indoor or outdoor air (Cohen, 1991; 1993; Plispanen, 1991). On the other hand, reports arriving at diametrically opposite conclusions have also been published (Modan *et al.*, 1989; Wolff, 1989; Henshaw *et al.*, 1990; Upton, 1990; Pershagen *et al.*, 1994), which indicates that opinions differ about the beneficiality of LLIR and that the topic as a whole is controversial. The present paper weighs up and summarises the evidence that favours the idea and also reviews the origin and scientific status of the concept of radiation hormesis in order to help the reader to decide about the validity of the hypothesis. Since the phenomenon (if there is one) is intimately associated with the occurrence and distribution of radioactive elements such as Rn, U, Ra and Th in nature, the topic is in part geochemical in character.

History and Origin of the Concept of Hormesis

Etymologically, hormesis derives from the Greek word *hormein*, which means to stimulate or excite. Literally therefore, it denotes any kind of stimulation or excitation. As a medical and geomedical term, however, it is more restricted in scope and refers merely to the putative and allegedly 'stimulatory or beneficial effect, observed when a biological system is exposed to a low dose of an agent known to be toxic (or hazardous) at significantly larger dose' (Loken and Feinendegen, 1993, p. 446). As far as can be traced back, the term was first used in 1943 by Southam and Ehrlich, who were led to the idea after having observed a stimulatory effect of dilute solutions of red-cedar heartwood extracts on the growth of certain wood-decaying fungi, the same extracts having been deleterious or lethal at higher concentrations (Southam and Ehrlich, 1943).

Depending on the type of stimulatory agent

can speak of chemical and physical hormesis, that described by Southam and Ehrlich being an example of the former. The existence of chemical hormesis (although not by that name) was, in fact, noted prior to Southam and Ehrlich by two nineteenth-century German biologists, Hugo Arndt and Rudolf Schultz, who considered the phenomenon to be universal (Sagan, 1989, p.574). The status of chemical hormesis as a scientific concept today – in contrast to that of radiation hormesis – seems to be firmly established, particularly in pharmacology and toxicology (Laughlin *et al.*, 1981; Calabrese *et al.*, 1987; Furst, 1987; Stebbing, 1987; Totter, 1987; Calabrese and Baldwin, 1993; Loken and Feinendegen, 1993).

Physical hormesis comprises electrical, magnetic and radiation hormesis *etc.*, the latter being subject to further subdivision on the basis of the type of radiation in question. In line with the current practice, radiation hormesis is here, however, dealt with as a single entity and by it is meant the putative beneficial effects of low-level radioactive (alpha, beta and gamma) and X-ray radiation.

Even though the term itself did not exist prior to 1943, the idea of hormesis is rooted far deeper in the past. The ancient Romans, who liked to bathe in the thermal waters of health spas situated in countries now known as Italy (Ischia), Germany (Brambach), France (Sail-les-Bains) and Austria (Gastein, Bad Gastein or Badgastein), can be said to have believed implicitly in hormesis, because they found the baths healthful, stimulative and even efficient as cures for medical disorders which we now know as diabetes, epilepsy, gout, hypertension, infertility, rheumatism, cretinism, melancholy and impotence. It has proved that the waters of many of the spas favoured by the Romans were in fact radon-bearing, which leads one to speculate that if indeed the baths did help, it may have been due to their radioactivity and the phenomenon of radiation hormesis.

One of the first measures towards a scientific clarification of the factors lying behind the alleged curative properties of the waters of the spas, and at the same time one of the earliest steps towards an understanding of these waters, was taken in the 1850s by the German chemist Justus von Liebig (1803–73), who himself believed in the beneficial properties of the water of the famous Austrian Bad Gastein spa. Liebig analysed the water and found it to contain 'dissolved gas with mysterious electrical effects' (Macklis 1990, p. 615). Liebig believed that the pharmacological effects of the baths were due to this mysterious gas, which was later identified as radon. In 1900, after Liebig's time, the gas was recognised as a new element, called 'radium emanation' by German chemist and inventor Friedrich Ernst Dorn. Around 1923 the gas eventually obtained its present name, radon, after having been called 'emanation' and 'niton' during the early part of the present century (Partington, 1964).

At the beginning of this century, shortly after Wilhelm Röntgen (1845–1923) in 1895 and Henri Becquerel in 1896 had discovered X-rays and radioactivity, it was soon realised that, in addition to the harmful effect of causing skin burns (erythemas), radiation was beneficial in destroying tumours and other human or animal excrescences and could thus be used as a tumoricidal surgical weapon for the annihilation of cancerous sarcomas (Stannard, 1988). This discovery led to a common belief that radiation, irrespective of the dose taken, had a stimulatory or otherwise beneficial effect on the human body and health in general. Marie Curie, for instance, firmly believed in the overall beneficial effects of radioactivity (Weart, 1988, p. 50) and one of the elements which she discovered, radium, was regarded by her and many others as a universally blessed healing surgeon's knife which could not and would not have any adverse side-effects. The newspapers' wildest visions concerning the beneficiality of radium and radioactivity went much further, of course, than the moderate visions put forward by earnest scientists. To give an illustrative example, a contemporary newspaper article claimed that radium could even raise the dead, an idea immortalised in the 1935 movie serial 'The Phantom Empire', in which a dead woman was brought back to life in a 'radium reviving room' (Brenner, 1989, p. 75).

Even though scientists and physicians did not expect radium to raise the dead, the common, almost unreserved belief in the beneficial effects of radium and radioactivity resulted in a boom of hospital and institution building for radium therapy or, as it was also called, Curie therapy, which was carried out during the first three decades of the present century by administering heavy doses of radioactive radiation as a tumoricidal weapon or as a general medication against cancer and other disorders. The difficulties involved in the enrichment and separation of the radium necessary for this therapy raised the price of the element sky-high, so that one gram of it cost several thousand times more than one gram of gold (Weart, 1988, p. 48).

The dark side of the therapy, the unexpected adverse side-effects of strong doses of radioactive and X-ray radiation soon made itself apparent, however (Weart, 1988, p.47). Radiation not only killed tumours but caused injuries and gave rise to new tumours and leukaemia (Henry, 1961, p. [illegible]). As early as 1911, physicians in the USA had diagnosed more than 50 cases of cancer causally related to these radium or X-ray treatments (Weart, 1988, p. 47). Marie Curie herself died of leukaemia [illegible]

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(Faure, 1986, p.4), and what raised even more public attention, and was an even stronger impulse in turning public opinion, was that tens of the mostly young females who applied luminous radium-bearing paints to the dials of military equipment and clocks during the First World War in order to make them visible in the dark and who had the habit of trimming the paint brush between their lips, were observed in the 1920s to be suffering from bone marrow cancer (Macklis, 1990, p.615; Macklis and Beresford, 1991, p.351; Loken and Feinendegen, 1993, p.446).

The hazards associated with radiation thus being obvious, radium therapy as such was soon in decline and was replaced after the Second World War by modern radiotherapy, in which radiation was applied in a more orderly way. These modern methods for annihilating tumours have replaced radium with radioactive isotopes of other elements with precisely known activities, energy spectra and other properties which enables the dose to be controlled exactly and the beam of radiation to be aimed precisely at the target, so that the deleterious side-effects can be eliminated or minimised.

Despite the fact that the hazards involved in the use of heavy doses of radiation had already been realised during the first two decades of the present century, another form of radiation medicament, mild radium therapy (MRT), based on an entirely different philosophy, grew beside radium therapy and flourished until 1932 (Macklis, 1990). MRT was rooted philosophically in the late nineteenth century American homeopathic medical movements and was based on an idea that 'mild' doses of radiation could be a cure for certain non-cancerous medical disorders. MRT comprised oral or parenteral administration of microgram quantities of radium and its daughter isotopes and was used primarily to cure rheumatic diseases, hypertension and metabolic disorders. Low level doses of radioactivity were aimed at but, in retrospect, one can see that the doses applied were still too high, as shown by the sad end of Eben M. Byers (described below).

To obtain MRT in its heyday in the 1920s, one could purchase commercial, privately manufactured radium-bearing patent medicines (pills, elixirs and creams) from mail order firms or over the counter in almost any drug-store in the USA. The most famous (and most notorious) among these products were 'Agua (sic) Radium' and 'Radithor', the latter of which contained radium isotopes 226 and 228 in distilled water so that the radioactivity of a half-ounce bottle was as high as 74 kBq (Macklis 1990, p. 614).

The MRT business eventually came to a sudden end in March 1932, when a famous Pittsburgh playboy, sportsman, industrialist and millionaire, Eben M. Byers, died of 'radium poisoning', 'multi-system failure' and cancer of the jaws in March 1932 (Macklis, 1990, p.615). Byers had purchased 'Radithor' from one of the most notorious purveyors of the patent medicines, William J.A. Bailey of East Orange (NJ), and had drunk one or more bottles of it almost daily for four years. His death aroused enormous publicity and caused a sharp decline in business at the same time as the government authorities began to regulate and legislate on the sales of patent medicines in general.

Despite the general pessimistic attitudes of this period towards the use of radiation as a medicament, W.P. Davey seems to have realised that the dose was an essential factor and was decisive in determining whether the effect would be beneficial or adverse. He therefore suggested in 1919 that a *low* level of ionising radiation might stimulate rather than depress biological functions and health. Davey's view was based on experimental work which he had carried out and as a result of which he had been able to verify a prolongation of life in *Pribolium confusum* populations exposed to small doses of X-rays (Davey, 1919). Together with Atkinson, who had even earlier in 1898 made the observation that röntgen-irradiated algae grew faster than their non-irradiated controls (Atkinson, 1898; Webster, 1993), Davey may have been the first to speak in favour of the idea of radiation hormesis.

Evidence Supporting the Idea of Radiation Hormesis

According to Loken and Feinendegen (1993), the idea of radiation hormesis has been gaining an increasing foothold and more numerous supporters, and its significance is emerging in medical practice. As a sign of the rising status of the concept, 'the scientific literature is replete with reports indicative of hormesis in various biological systems after exposure to low doses of ionising radiation' (Loken and Feinendegen, 1993, p. 447). The authors list 42 reports in favour of the idea, and if the roughly 1,200 references listed by Luckey (1980) are also taken into consideration, the number of positive reports is quite impressive. Instead of trying to go through the above references individually here, I will attempt to classify and summarise the evidence, and also refer to some additional papers from my own experience.

Evidence supporting the idea of radiation hormesis can be divided into four broad categories: (1) experiments with plants or animals; (2) human occupational comparisons; (3) regional studies and (4) experiments throwing light on the effect of radiation at the molecular level.

(1) The first pieces of experimental evidence sup-

porting the idea of radiation hormesis derive from the early research of Atkinson (1898) and Davey (1919) referred to above. In more recent times, experiments with animals have been conducted by the (US) National Cancer Institute, for instance. Those carried out in the early 1940s, for example, pointed to a rather unexpected relationship: the irradiated animals had a slightly longer mean life span and greater weight gain than their non-irradiated controls (Henry, 1961, p. 121). Similarly, animal experiments carried out by Lorenz and his associates in 1955 (Henry, 1961, p.122) indicated that exposure of both mice and guinea pigs to 0.11 r per day of radium gamma increased their average life span by about 7 %, whereas exposures of 1.1 r per day slightly reduced it. Summarising the results of a large number of animal experiments, Henry arrived at a positive view of the radiation hormesis hypothesis: "The preponderance of data better supports the hypothesis that low chronic exposures result in an increased longevity than it supports the opposite hypothesis of decreased longevity" (Henry, 1961). Similarly, Sagan (1989), after summarising a large number of animal experiments, including those of Congdon (1987), concluded that "many experimental studies (but not all) have shown that laboratory animals exposed to low doses of radiation outlive unexposed controls".

(2) In addition to animal experiments, Henry (1961) also carried out a statistical study of the life span of radiologists in the UK and the USA. His working hypothesis was that since radiologists as a group are subject to higher chronic exposure to radiation than any other group of physicians, one could expect on the basis of the radiation paradigm to find higher mortality from cancerous diseases in them than among other physicians. The results ran against such expectations, however, and showed a 10 % lowering of mortality among the radiologists. On the other hand, an earlier study carried out by Warren (1956) had indicated an opposite relationship, while Seltzer and Sartwell (1958) had arrived at conclusions in line with those of Henry. A recent report by Tietjen (1987) also supports the idea of radiation hormesis, since it reveals that lung cancer among the highly exposed workers at the US Department of Energy (USDOE) is well below expected levels.

(3) Regional studies carried out in the USA, China, India, Japan and Finland also suggest a negative correlation between cancer and radioactivity. According to recent reports by Cohen (1991 and 1993), lung cancer in the USA is rare in regions with high radon levels. In his most recent paper (1993), Cohen studied correlations between average radon levels in 1600 US counties and mortality rates from various types of cancer. By far the closest correlation was with lung cancer, but as Cohen points out, the sign of the correlation was

Table 1 Statistically significant ($p < 0.001$) Spearman product-moment correlation coefficients between the incidences of various forms of cancer (1–8) and the concentration of uranium in the groundwater in northern Finland (Piispanen, 1991, Table 2).

Spearman coefficient	Type of cancer	Concentration of U
1	Total cancer in males (for details, see Pukkala *et al.* 1987)	-0.49
2	Stomach cancer in males	-0.36
3	Colon cancer in males and females	-0.47
4	Pancreatic cancer in males	-0.27
5	Lung cancer in males	-0.47
6	Lung cancer in females	-0.44
7	Thyroid cancer in females	-0.26
8	Leukaemia in males	-0.34

negative. Even when areal differences in smoking habits are taken into consideration, the correlation remains essentially the same. In China, cancer mortality rates are slightly lower in Guangdong province than elsewhere, although (or because) the natural background radiation level there is three times the national average (Loken and Feimendegen, 1993, p. 447). The same is true in India (Nambi and Soman, 1987) and Japan, where Mifune (1992) demonstrated low mortality rates for cancerous diseases (with 46–54 % reductions) in Misasa, where hot baths in waters having radon activity levels as high as 400 Bq L^{-1} are fashionable. In Finland, I (Piispanen, 1991) observed statistically significant negative correlations between various types of cancer and the concentration of uranium in the groundwater (Table 1), and areas with high radon levels similarly do not coincide with areas with high incidences of lung cancer or leukaemia, a relationship known since 1984 (Castren, 1994). Regional longevity studies carried out in various countries have also produced results which show

Table 2 Summary of claims put forward regarding the putative beneficial effects and mechanisms of operation of low-level ionizing radiation (LLIR). (Modified after Macklis and Beresford, 1991).

LLIR stimulates unscheduled DNA repair.
LLIR induces free-radical detoxification and repair systems.
LLIR is immunostimulatory, HLIR being immunosuppressant.
LLIR is a metabolic catalyst and fertility enhancer.
LLIR selectively inactivates inhibitory or senescent cells in organisms.
LLIR reduces cancer risk in chronically exposed populations.
LLIR extends average life-span in lightly exposed populations.
LLIR is an evolutionary drive (Parsons, 1991).
LLIR functions as a vital force and may be essential (Luckey, 1982).

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higher life spans among peoples living in areas of high natural background radiation (Henry, 1961; Neafsey, 1990; Parsons, 1990).

(4) Kondo (1989) reported that there was an enhancement of immune cell production in patients who had been exposed to LLIR.

By What Mechanism Does Radiation Hormesis Operate?

Assuming that radiation hormesis is a fact, the question arises of the mechanism by which LLIR can bring about its beneficial effect. Answers to this question have been offered by Feinendegen *et al.* (1987), Sagan (1987; 1989), Macklis and Beresford (1991) and Loken and Feinendegen (1993). The proposed mechanisms, together with other claims concerning the beneficial properties of LLIR, are summarised by Macklis and Beresford (1991) and are reproduced here in modified form as Table 2.

Feinendegen *et al.* (1987) and Loken and Feinendegen (1993) explain the mechanism as due to the effect of ionising radiation on cells at the molecular level. Ionising radiation, whether in the form of energetic charged particles or electromagnetic in character (X-rays or γ-rays), deposits its energy through excitation and/or ionisation of the atomic constituents of the cells of biological systems lying in its path. Water molecules make up a high percentage of the mass of biological systems, and interactions of ionising radiation with these molecules produce hydrogen peroxide and many oxygen-containing free radicals identical to those created in the course of normal metabolism. These are highly oxidative and readily interact with various cellular components including DNA, and are a major cause of radiation injury at high doses. There are enzymes in the living cells which are capable of neutralising these radicals, however. These enzymes are called free radical scavangers and they increase within the cells of any biological system after low-dose radiation exposure. Work with lymphocytes by Wolff (Loken and Feinendegen, 1993) and others provides convincing evidence that DNA repair is indeed enhanced by exposure to radiation. Following exposure to a low dose of ionising radiation, DNA is more readily repaired after a subsequent exposure to a large dose of radiation or to other mutagens. This explains why cells exposed to LLIR may, in the long run, be able to resist diseases and repair DNA damage better than other cells (Loken and Feinendegen, 1993).

Alternative mechanisms have recently been suggested by Kondo (1988), Feinendegen *et al.* (1989), Liu (1989) and Henshaw and Eatough (1992). According to Kondo the beneficial effects

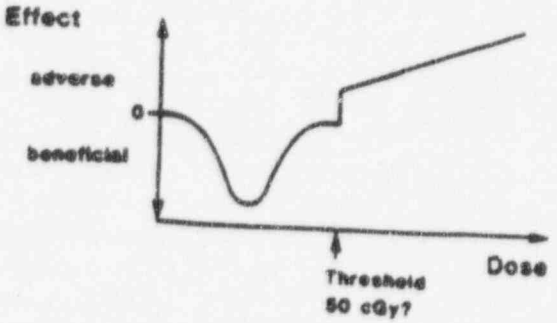

Figure 1 *Hypothetical dose-response curve showing schematically the degrees of adverse and beneficial effects of ionizing radiation on human health as a function of the dose. The threshold value separating the beneficial and adverse effects has been estimated to be approx. 50 cGy yr^{-1} (Macklis and Beresford, 1991, Figure 1). The curve for beneficial effects may be taken to reach its maximum at about 25 cGy, based on an assumed analogy between the spectrum of the effects of nutritional trace elements on human health and that of ionising radiation.*

of LLIR are a result of what is called the cell-replacement repair which means a mechanism in which 'suicide' of certain cells stimulates a proliferation of healthy cells, which in turn replace the former, the overall result being a complete elimination of the injury. Feinendegen *et al.* (1989) and Liu (1989) stress the enhancement of the production of immune cells after an exposure to LLIR (Sagan, 1989). Henshaw and Eatough (1992) emphasise the interaction of carcinogens and the antagonistic effect of various environmental factors towards each other. The antagonism is thought to result from a process in which mutations induced by one carcinogen are removed by cell-killing effect of a second carcinogen.

Is There a Threshold Separating Adverse and Beneficial Levels of Radiation?

According to the radiation paradigm, the basic philosophy behind radiation protection since 1956, all radiation at all dose levels is harmful and there are no effects at low doses that cannot be predicted from the effects observed at higher doses (Loken and Feinendegen, 1993, p. 447). Any question of a threshold value separating doses causing adverse and putative beneficial effects is, therefore, absurd against such a background. A number of students of the problem have recently questioned the validity of the philosophy lying behind the radiation paradigm however, especially since Loken and Feinendegen recently (1993, p. 447) pointed out that epidemiological investigations have failed to show any effects in human populations exposed to LLIR. Indeed, such studies have, on occasion, indicated possible benefits of such exposures. If, therefore, low levels of radiation are assumed to have beneficial effects, and as large doses are known to be adverse, there should indeed be a threshold value separating the two extremes.

According to Loken and Feinendegen (1993, p. 448), the stimulatory effect of LLIR on the proliferation of some Protozoa and Cyanobacteria at low doses, disappeared when the value of approximately 50 mGy per year was exceeded. At the other extreme, Macklis and Beresford (1991) considered doses of up to 50 cGy (total absorbed dose) to fall within the range at which radiation hormesis is possible. These two values give rough bounds for the area within which the threshold (if one exists) should lie.

Assuming for the moment that there is indeed a threshold value separating beneficial and adverse doses (perhaps at 50 cGy), one can speculate further that if LLIR is analogous in its effect to nutritional trace elements, it may exercise its maximum beneficial effect at roughly the midpoint between zero and the threshold value (Figure 1; see also, Macklis and Beresford, 1991, Figure 1).

Contemporary Attitudes

Scientists involved in studying the concept of radiation hormesis can roughly be divided into two groups: those who are against the hypothesis (sometimes called paradigmatists) and those who at least cautiously accept the idea and use it as a working hypothesis (sometimes called hormeticists). The number of hormeticists seems to be increasing, as is evident from the conclusion of Sagan (1989): 'There does appear to be a movement away from an attitude of general skepticism to one of a new willingness to consider the evidence'.

The work of the earliest advocates of radiation hormesis, Atkinson (1898); Davey (1919); the US National Cancer Institute; Lorenz, Seltzer, and Sartwell (1958); Henry (1961); Congdon (1987) and Tietjen (1987) has been summarised above. In addition, Cohen (1991) recently found a negative correlation between radon levels and incidences of lung cancer. His encouraging attitude is evident from his own words: 'The tentative conclusion of earlier papers that radon may cause these diseases (cancer), seems unlikely to be correct'.

In addition to Cohen, cautious acceptance of the idea of radiation hormesis has recently been expressed by Sagan (1989), Pilspanen (1991), Webster (1993) and Loken and Feinendegen (1993). Sagan's view is evident from his summary of the experimental and other work done on the topic up to 1989: 'The inquiry has raised the surprising possibility that very low doses of ionising radiation may not be harmful after all or may even have net benefits'. Having found in 1991 that there was a statistically significant negative correlation between the incidence of lung cancer and the uranium content of the groundwater in northern Finland, I concluded: 'The (close) negative correlation between groundwater uranium and various types of cancer is also a new and thought-provoking observation running contrary to previous thinking. Uranium and radon, the latter being assumed to be in positive correlation with the former, are commonly believed to be able to bring about cancer, especially lung cancer (Archer, 1987) and therefore a positive correlation between cancer of the lung in particular and the uranium in the groundwater could be expected. The negative correlation recorded here is an unexpected feature which warrants further statistical study based on larger data sets before any conclusion can be drawn about the possible ability of natural radioactive radiation of moderate intensity to destroy cancer cells in their early phase of development and simultaneously hinder the growth of tumours in human tissue. If the above mechanism, based here on very limited data and therefore presented highly tentatively and with much caution, proves to be the general case, then natural radioactive radiation must at least in some instances be deemed to act as a kind of natural supplementation for artificially produced radiotherapy, which is known, of course, to have a retarding effect on the growth of cancer cells and tumors' (Pilspanen, 1991, p. 68–69).

Approval has also been expressed by Webster (1993) and Loken and Feinendegen (1993): 'Radiation hormesis is now an established area for serious evaluation in scientific circles' (Webster, 1993). 'We can no longer ignore this concept' (Loken and Feinendegen, 1993).

On the other hand, several writers have expressed opinions against the hypothesis. This criticism and scepticism is primarily based on the fact that, as pointed out by Sagan (1989), carefully conducted epidemiological studies are rare or lacking and the existence of the phenomenon has not been verified by this means. Another weakness in the theory has been pointed out by Koppenol and Bounds (1989) who are also sceptical. They maintain that 'any discussion of the beneficial, neutral, or harmful effects of low-level ionising radiation is seriously flawed if the "background" flux of oxyradicals is not taken into account', and that this consideration is missing from the discussions on the topic. They note that the steady-state concentration of oxyradicals in normal cases is of the order of 0.1 to 1 nM L^{-1} and would rise in individuals exposed to LLIR to about 3 nM L^{-1} if the dose was 0.5 cGy. Thus they would find it 'most surprising if such a small *transient* concentration were to cause damage sufficient to activate repair mechanisms'.

Catlin (1989, p. 311) also takes a generally pessimistic view of the idea. He points out several examples of what he considers flaws in the thinking of those who are in favour of the idea of rad

hormesis. One is the poor definition of the concept: '"hormesis" being applied collectively to a diverse conglomeration of species, biological material (organism, tissue, cells) and types of response (stimulation or beneficial response)'. He therefore concludes that '...the thesis for such effects remains unproven...'. Similarly Macklis and Beresford (1991, p. 350) arrived at a negative conclusion: 'We find the data in support of most of the hormesis postulates intriguing but inconclusive'.

Conclusions

As is evident from the above, the problem of the putative hormetic effects of low-level ionising radiation is highly topical, intriguing and controversial. The number of scientists who cautiously accept the concept, at least as a working hypothesis, is increasing, but more work is needed before one can speak of it as a firmly established scientific fact. More attention should be paid in the future to the separate effects of various forms of ionising radiation and radioactivity as Okamoto (1987) and Henshaw and Eatough (1992) have emphasised, since cancerous diseases can simultaneously show a positive correlation with radon but a negative one with background gamma radiation.

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