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The Debate on the Health Effects Attributable to Low Radiation Exposure

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BACKGROUND

The LNT Controversy: A Passionate Dispute

Few scientific issues have aroused passions more than the dispute about the health effects attributable to low levels of exposure to ionizing radiation (or radiation in short) and the currently authoritative dose-response hypothesis, termed "linear non-threshold," or LNT. Finding out whether health effects are induced by low-level radiation exposures, and if so, what they are, has become a kind of contest rather than a serious scientific inquiry. Sometimes it seems that rationality, or a methodical examination of the unknown, has disappeared from this debate. While the confrontation of different hypotheses is typical in academic discussions – at least until analysis and experimental work probes more deeply into what is more correct or plausible – it is strange that the premises under discussion differ to such an extent that they oppose each other. This is the case in the dispute known as "the LNT controversy." One extreme is the "radiation-is-good-for-you" group, advocating not only that low-level-radiation exposure is not detrimental, but that it is in fact beneficial for health. The other extreme is the "radiation-phobic" group advocating that exposure to (artificial) radiation is the fifth rider of the Apocalypse leading to the destruction of the human race. On the one side, the radiation promotion extremists presuppose that, because radiation exposure is an inescapable natural phenomenon that has existed since the beginning of time, after billions of years of life on Earth there must have been a natural – and *full* – biological adaptation to it (they cannot explain, however, why life has not fully adapted to other primordial harmful natural phenomena). On the other side, the radical contesters seem to believe (perhaps honestly, but wrongly) that, because (artificial) radiation exposure is a pollutant of the modern technological world, it should necessarily be highly detrimental to humans, their descendants, and their environment.

Prevalent Opinion

In the middle of this battlefield stands a large majority of scientists whose prevalent opinion is that exposure to radiation, however small its level might be, is not necessarily good for health but that its associated risks are extremely small. Members of this group are not necessarily homogeneous in their positions, some inclining more towards the view that radiation exposure can be quite harmful while others have the "gut-feeling" that, at low levels, radiation is possibly not so detrimental.

An International Mechanism for Global Consensus: UNSCEAR

It is surprising that such disparity of opinion can exist in this field of knowledge, as in no field of scientific investigation does an international mechanism to achieve global consensus exist that is similar to that specifically set up for estimating radiation health effects. Nearly half a century ago, the United Nations (UN) created the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) specifically for that purpose. UNSCEAR has since annually assembled leading radiation specialists to provide the most plausible estimates of the health risks attributable to radiation exposure. UNSCEAR periodically presents its findings to the highest UN body – the UN General Assembly (UNGA) – where representatives of all countries of the world have acknowledged the UNSCEAR reports as the best available understanding of the topic.[1]

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1. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) was established by the General Assembly at its tenth session, in 1955. Its terms of reference are set out in Resolution 913 (X) of 3 December 1955. The Committee was originally composed of the following Member States: Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, Egypt, France, India, Japan, Mexico, Sweden, Union of Soviet Socialist Republics, United Kingdom of Great Britain and Northern Ireland and United States of America. The membership of the Committee was subsequently enlarged by the Assembly in its resolution 3154 C (XXVIII) of 14 December 1973 to include the Federal Republic of Germany, Indonesia, Peru, Poland and the Sudan. By its resolution 41/62 B of 3 December 1986, the General Assembly increased the membership of the Committee to a maximum of 21 members and invited China to become a member. For the reports of UNSCEAR, see Official Records of the General Assembly, Thirteenth Session, Supplement No. 17 (A/3838); Seventeenth Session, Supplement No.16 (A/5216); Nineteenth Session, Supplement No. 14 (A/5814); Twenty-first Session, Supplement No. 14 (A/6314 and Corr.1); Twenty-fourth Session, Supplement No. 13 (A/7613 and Corr.1); Twenty-seventh Session, Supplement No. 25 (A/8725 and Corr.1); Thirty-second Session, Supplement No. 40 (A/32/40); Thirty-seventh Session, Supplement No. 45 (A/37/45); Forty-first Session, Supplement No. 16 (A/41/16); Forty-third Session, Supplement No.45 (A/43/45), Forty-eighth Session, Supplement No. 46 (A/48/46); Forty-ninth Session, Supplement No. 46 (A/49/46); Fifty-first Session, Supplement No. 46 (A/51/46). These documents are referred to as the 1958, 1962, 1964, 1966, 1969, 1972, 1977, 1982, 1986, 1988, 1993, 1994 and 1996 reports, respectively. The 1972 report, with scientific annexes, was published as *Ionizing Radiation: Levels and Effects, Volume I: Levels and Volume II: Effects* (United Nations publication, Sales Nos. E.72.IX.17 and 18). The 1977

Why then all this fuss about the health effects of low-level radiation? The mission-impossible aim of this article is to clarify this conundrum.

THE UNSCEAR POSITION

The extremely detailed reports regularly submitted by UNSCEAR to UNGA are a synthesis of thousands of peer-reviewed references. While it is certainly unfeasible to summarize accurately such a vast amount of information, nearly a decade ago I made a brief account of UNSCEAR estimates aimed at a broad audience.[2] UNSCEAR's position has not changed substantially over the past years and the following paragraphs aim to highlight it again.

Radiation Exposure Mutates Genes

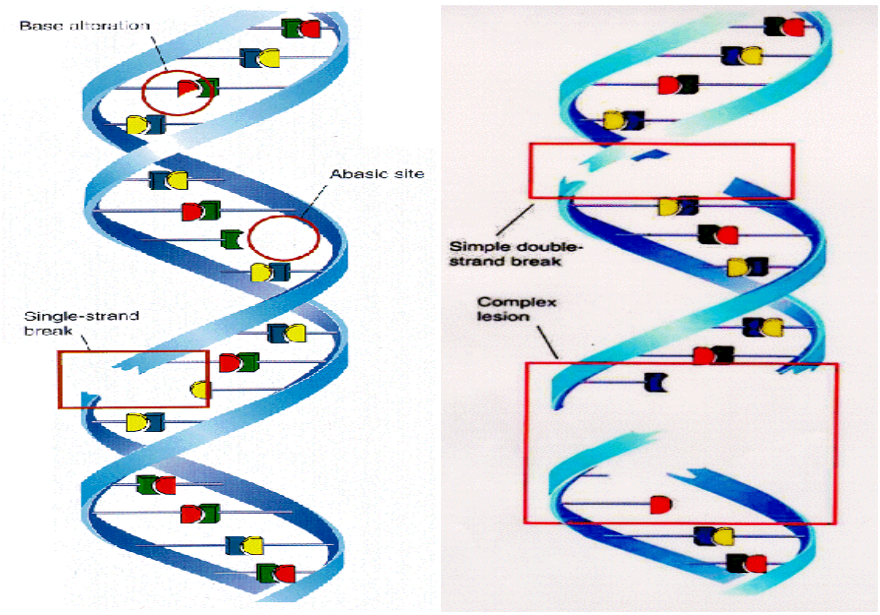
Human exposure to ionizing radiation necessarily ionizes and may alter atoms and molecules constituting the body. The biological effects of radiation derive from modifications in the chemical structure of the human cells, particularly in the DNA in the cell's nucleus. The damage may be expressed as changes in the *genes*, the specific DNA sequences that carry the information needed to control cellular functions such as growth/division and differentiation, which are termed *genetic mutations.* DNA damage can be simple, such as single sites of base damage, or single strand breaks – see following Figure 1 right – or clastogenic, such as complex lesions involving several bases or double-strand breaks – see following Figure 1 left.[3]

report, with scientific annexes, was published as *Sources and Effects of Ionizing Radiation* (United Nations publication, Sales No. E.77.IX.1). The 1982 report, with scientific annexes, was published as *Ionizing Radiation: Sources and Biological Effects* (United Nations publication, Sales No. E.82.IX.8). The 1986 report, with scientific annexes, was published as *Genetic and Somatic Effects of Ionizing Radiation* (United Nations publication, Sales No. E.86.IX.9). The 1988 report, with scientific annexes, was published as *Sources, Effects and Risks of Ionizing Radiation* (United Nations publication, Sales No. E.88.IX.7). The 1993, 1994 and 1996 reports, with scientific annexes, were published as *Sources and Effects of Ionizing Radiation* (United Nations publication, Sales Nos. E.94.IX.2, E.94.IX.11 and E.96.IX.3, respectively). Recently, UNSCEAR has issued its 2000 and 2001 reports which are available in the web at <http://www.UNSCEAR.org> (accessed December 2002).

2. Abel J. González, *Biological Effects of Low Doses of Ionizing Radiation: A Fuller Picture*, 36 IAEA Bull. 4 (1994).

3. *See* Richard J. Reynolds & Jay A. Schecker, *Radiation Protection and the Human Experiments*, 23 Los Alamos Sci. 51 (1995).

Figure 1
Single and Double Stranded DNA Breaks



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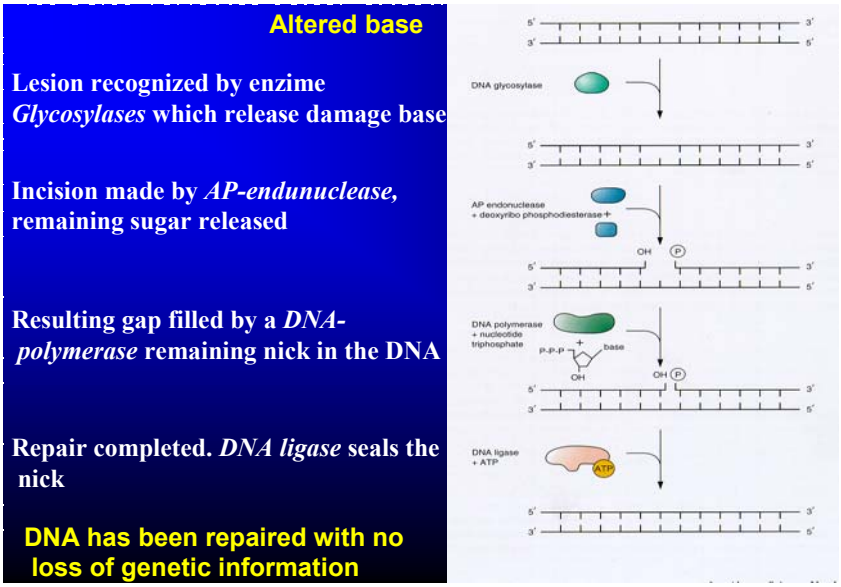
If the process occurs in genes of stem cells (i.e., those cells that are able to reproduce a progeny of cells), the mutation can be transmitted from a cell to its progeny and proliferate. These radiation-induced mutations are the origin of the health effects attributable to radiation. In summary, damage to DNA may: (i) induce mutations that alter the information encoded in the code of life and the genome; and (ii) be the main initiating event by which radiation causes long-term harm to the body's organs and tissues.

Repairing the Induced Harm

The cell has developed a sophisticated mechanism for repairing DNA damage, and a large number of repairing genes have evolved in all organisms. The simpler forms of DNA damage are likely to be repaired, rapidly and efficiently, by a base-excision repair process that uses a number of repairing enzymes and the undamaged DNA strand as a template for repair. See Figure 2.

Figure 2
DNA Repair Mechanisms



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However, while genetic mutation is subject to this efficient repair mechanism, the repair is not error-free. Most damage is repaired but some damage remains or it is wrongly repaired. For instance, clastogenic damage is more difficult to repair correctly. Thus, while highly sophisticated and efficient biochemical mechanisms usually repair genetic damage, the system is not perfect and a low but finite likelihood exists that radiation-induced damage and genetic mutation remains or is misrepaired.[4]

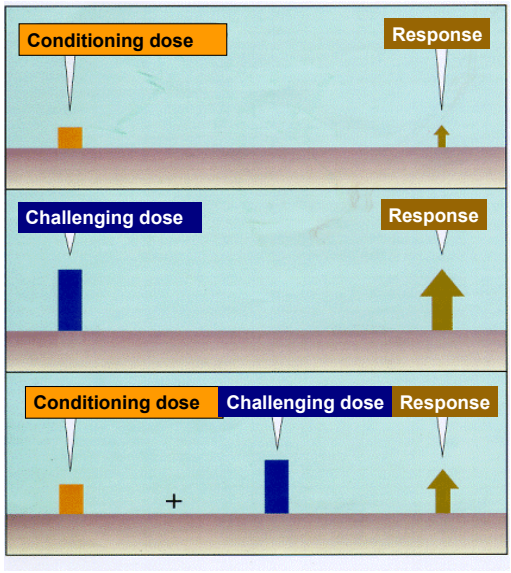
Dynamic Repair Mechanisms

The repair mechanisms reaction seems to be dynamic and responsive to radiation dose changes. There is experimental evidence that DNA mutation caused by a *challenging* radiation dose can be reduced by prior exposure to a *conditioning* dose. This phenomenon, termed *adaptive response*,

4. Mutation of genes involved in the repair process, which include genes controlling damage repair and cell-cycle regulation, is reflected in several disorders of humans that confer radiation sensitivity and cancer proneness on the individuals. For example, mutation of one of many so-called checkpoint genes may allow insufficient time to repair damage, because the cell loses its ability to delay progression in the cell cycle following radiation exposure.

is probably the result of stimulation, by the conditioning dose, of the repair mechanism acting on the damage induced by the challenging dose. As a result, the effect of the conditioning dose plus the challenging dose is lower than the effects of each dose delivered independently. See Figure 3.

Figure 3
Adaptive Response



The adaptive response is transient and inhomogeneous; the conditioning doses seem to be responsive only through a limited range; the time between the conditioning and the challenging dose seems to be critical for the stimulation of repair; and the response varies greatly between individuals. The mechanistic basis of the process has yet to be well characterized although association with the induction of biochemical stress responses seems likely.

PROPORTIONALITY BETWEEN RADIATION DOSE AND MUTATED CELLS

If the number of mutations relates to the number of radiation interactions with the DNA, presuming that there is no exchange of genetic information between cells, it can be mathematically shown that the probability of mutation should follow a relationship with the dose, of the type:

$$p = (a\,D + b\,D^2 + \ldots\, n\,D^n)\, e^{-cD}$$

where a, b, n, and c are constants.

The power terms are related to multi-track interactions. At high doses and dose rates, 'n' ionizing events may be able to combine effects before the repair mechanisms could cancel the effect of the first event – producing enhancement in the probability reflected by the terms nD^n. The factor e^{-cD} is the survival fraction of exposed cells at dose D (i.e., the fraction of cells that were not killed at that dose and that could therefore undergo mutation).

For the range of doses where the surviving fraction of cells is still significant, the terms of power higher than the quadratic are nil and the foregoing formula can be approximated as:

$$p \cong (a\,D + b\,D^2)\, e^{-cD}$$

which is known as the "linear-*quadratic relationship*" and is the one used by UNSCEAR for the full dose range.

For very low radiation doses the expected frequency of radiation interaction per cell is extremely small (for background radiation there should be around one interaction per year per cell!). If bystander effects of genetic communication among neighboring cells are discarded, mainly single interactions rather than multi-track effects will be dominant. Therefore, the probability of interaction and consequently of mutation must simply be proportional to dose:

$$p \cong a\,D$$

In conclusion: if a fraction of mutations induced by a radiation exposure remains unrepaired, the expected number of mutated cells attributable to the exposure should be proportional to the radiation dose.

Outcome at Cellular Level

If genetic damage does occur and is not adequately repaired, it may prevent the cell from surviving, reproducing, or performing its normal functions. Alternatively, it may result in a still viable cell, but with modifications in its original genetic information. The potential outcomes at the cellular level may therefore be summarized as follows: most probably, radiation exposure does not produce any change at the cellular level either because it does not interact with the cell constituents or because the damage is repaired; however, a small but finite probability remains that damage might occur and not be repaired, and, as a result, either the cell is killed or

it survives, but its genetic information is modified. The health effects of radiation exposure are the final expression of these potential outcomes: cell death or cell modification.

Cell Death: Deterministic Effects

Cell death usually occurs by means of *apoptosis*, a process of programmed cell killing in which cells neatly commit suicide by chopping themselves into membrane-packaged pieces. Most organs and tissues of the body are not affected by the killing and loss of even a considerable number of cells. However, if the cell deficiency becomes large, there will be observable harm to the organ or tissue, and therefore to the individual, which may lead to death. Serious harm to health will only occur if the radiation dose is large enough to kill such a great number of cells that cell reproduction cannot compensate the loss. Thus, this type of harm occurs in all individuals who receive a dose in excess of a relatively high dose-threshold that is characteristic for the effect. The effect is called *deterministic* because harm is determined to occur for exposures above the threshold.

Cell Modification: Stochastic Effects

If the cell is not killed but only modified and remains viable for reproduction, the genetic change will be transmitted to daughter cells. If the modified cell is a somatic cell, the mutation can be the origin of *carcinogenesis*, i.e., of an eventual malignancy in the exposed individual. The modified cells can also be germ cells (i.e., any in the series of cells eventually producing ova and spermatozoa such as those from oogonia to ovum cells through oocyte cells and those from the testis seminiferous tubule cells to spermatozoa cells through spermatogonia, spermatocytes, and spermatids cells), which transmit genetic information to the descendants of the exposed individual. Mutation of germ cells may conceivably generate *hereditary effects*, i.e., disorders in the exposed individual's progeny. All these long-term effects, i.e., carcinogenesis in the individuals or hereditary effects in their descendants, are called *stochastic* because they are expressed in an aleatory, random manner. Stochastic effects may manifest themselves decades after the exposure and do not differ from the same effects arising spontaneously or which can be attributed to other factors. It should be noted that apoptosis is instrumental in preventing some damaged cells from progressing into a stochastic effect.

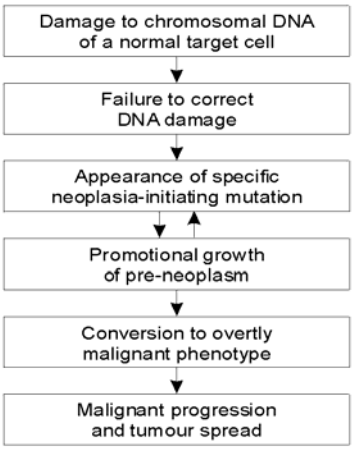
Carcinogenesis:

A most important effect of genetic mutation is carcinogenesis, or the initiation of a process that eventually leads to cancer. It is a multi-stage process usually divided, albeit imprecisely, into three phases: cancer initiation, tumour promotion and malignant progression. Radiation-induced mutation is certainly an initiator and could also be a promoter and a progressor. As for low radiation doses, the likelihood of initiation by mutation is proportional to dose, it follows that the likelihood of cancer should also be proportional to dose and may eventually lead to long-term maladies in the tissue or organ of the exposed individual. Radiation exposure has been associated with most forms of leukaemia and with cancers of many organs, such as lung, breast and thyroid.

The process leading from DNA damage to cancer is extremely complicated and is described briefly in Figure 4.

Figure 4

Simple Generalized Multistage Oncogenesis Scheme



A simple generalized scheme for multistage oncogenesis.

Even with protective processes induced and acting, misrepaired radiation damage can develop into cancer. Mutation of proto-oncogenes (genes that may be activated inappropriately and then participate in tumorigenesis) and tumor-suppressor genes can compromise the natural controls of cell reproduction and contribute to the multistage development of cancer. Genomic instability through further mutations in clones of cells may be a critical event in the transformation from a benign to a malignant state of a

tumour. Loss of apoptotic control is also believed to be important throughout the complicated process of the genesis of cancer.

UNSCEAR recognizes that much knowledge still needs to be gained about the multi-stage nature of this process. Although the concept of sequential, interacting gene mutations is firmly established as the driving force for the genesis of cancer, there is a lack of understanding of the complex interplay between these events and the consequences for cellular behaviour and tissue homeostasis; uncertainty also exists about the contribution made to the malignant development of non-mutational (epigenetic) cellular events such as gene silencing and changes in cellular communication.

Hereditary effects:

Radiation-induced non-lethal mutations in germ cells can conceivably develop into hereditary effects. These effects have been seen in experiments with flora and fauna. Mutation in the *dominant* allele of a gene can be inherited from only one parent and leads to *dominant* disorders in the first generation that can be passed unexpressed through several generations. Mutation in the *recessive* allele can only be inherited from both parents and produces few *recessive* disorders in the first generations, but may accumulate in the population's gene pool. Mutations resulting from the interaction of various mutagenic factors may produce *multifactorial* disorders.

JUDGING THE SHAPE OF THE DOSE-RESPONSE RELATIONSHIP

Within the unavoidable uncertainties in our knowledge of this complicated phenomenon, it is necessary to judge whether there might be a threshold level of exposure below which biological response does not occur. This judgement can be guided by mechanistic considerations. Specifically, there is a need to know whether at very low doses the repair processes are more efficient and perhaps enhanced by the adaptive response, preventing any damage to the cellular components. Such a threshold could occur only if repair processes were totally effective in that dose range or if a single track were unable to produce an effect. The absence of consistent indications of significant departures from linearity of response at low doses in cellular endpoints (chromosome aberrations, gene mutation, cell transformation), the activity of well characterized error-prone DNA repair pathways, and the evidence on the nature of spontaneous DNA damage in mammalian cells, all argue against adaptive responses or other processes that might provide for a dose threshold for radiation effects. The

cellular processes such as apoptosis and cellular differentiation that can protect against later phases of tumorigenesis are judged to be efficient but can be bypassed. There is no reason to believe that these defenses act differently on spontaneous and radiation-induced effects, or have specific dose dependencies.

It may therefore be concluded that, as far as is known, even at low doses, radiation may act as a mutational initiator of cancer and hereditary effects and that defenses are unlikely to show low-dose dependency. In general, response does not therefore appear to be a complex function of increasing dose, with the simplest representation being a linear relationship that is consistent with mechanistic modelling and most of the available quantitative data. There may be differences in response for different types of effects, and statistical variations in each data set are inevitable.

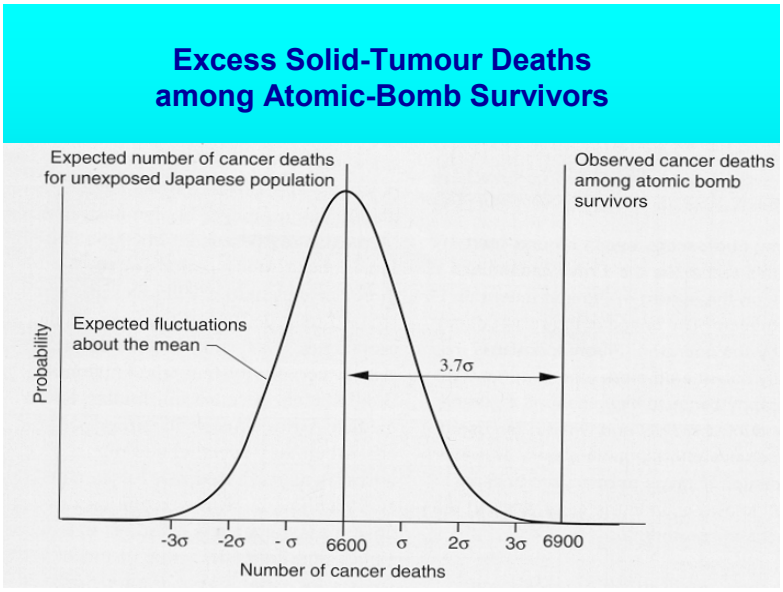
The Epidemiological Evidence

The previously described mechanistic and radiobiological considerations for the health effects attributable to radiation exposure should be substantiated by factual clinical evidence of expression of the effects. While it is not yet possible to determine clinically whether a specific malignancy was caused by radiation exposure, radiation-induced tumours and leukaemia have been detected and statistically quantified by epidemiological studies of populations exposed to relatively high radiation doses. These epidemiological studies have demonstrated that there is an unequivocal association between radiation exposure and cancer, but also that the latency period (i.e., the time elapsing from initiation until the clinical expression of the cancer) is very long, stretching from years in the case of leukemia to decades for solid tumors. The larger epidemiological study of exposed individuals is the "life span study" (LSS) of the survivors of the atomic bombing of the cities of Hiroshima and Nagasaki. The LSS has shown that radiation risk is extremely small. It is now estimated that the 86,572 individuals in the cohort of survivors of atomic bombings suffered (up to 1990) 7,578 solid mortal tumors (previous estimate: 6,600) and 249 leukemias. Of those, in spite of the high doses received by the cohort, only 334 tumors (previously 300) and 87 leukemias can be attributed to radiation exposure.[5] The numbers of attributable solid tumours are not far from the limit of statistical detectability, as they correspond to a standard deviation of around 3.7σ. See Figure 5.

5. United Nations Scientific Committee on the Effects of Atomic Radiation, *Sources and Effects of Ionizing Radiation; UNSCEAR 2000 Report to the General Assembly (with Scientific Annex)* vol. 1, 12 (United Nations 2000).

Figure 5

Excess Solid-Tumour Deaths Among Atomic-Bomb Survivors



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RELATIVELY SMALL EXCESS OF SOLID-TUMOUR DEATHS AMONG THE LSS COHORT

From the LSS data, the UNSCEAR 2000 report estimates the lifetime cancer mortality risk after a dose of 1 000 mSv[6] to be 0.9% for leukemia and 11.2% for solid tumors, as compared to 1.1% for leukemia and 10.9% for cancer estimated in 1994. From this, the radiation induced cancer risk is estimated to range from 0.004 to 0.006% per mSv, depending on the projection method used and applying a dose rate reduction factor of 2.[7] This factor, termed *Dose and Dose Rate Effectiveness Factor*, DDREF, is used in the extrapolation to the low dose region of the LSS epidemiological ob-

6. In this paper the *millisievert* or *mSv* (i.e., the unit of the quantity *effective dose* of radiation) will be used as unit of radiation dose in general, although in some quotations the use of the unit of absorbed dose would have been formalistically more appropriate. One mSv – or, in older units, 100 millirem (mRem) – represents the lower range of doses that people receive during one year as a result of exposure to natural radiation sources.

7. United Nations Scientific Committee on the Effects of Atomic Radiation, *supra* n. 5, at 361.

servations at high doses and dose rates, which is done by firstly assuming a straight line between the observation and the origin of the coordinates and then dividing the resulting slope by the DDREF. Using the linear-quadratic relationship, the probability of attributable cancer death at a high dose D extrapolated linearly to the origin would give a slope of a + bD. The DDREF is, therefore,

$$DDREF = (a+bD)/a = 1 + (b/a)D$$

Thus, DDREF increases linearly the values of D at which the effects are observed. At values of D where the linear component of the relationship contributes to the probability about the same as the quadratic (i.e., $(b/a) = 1\ mSv^{-1}$), and taking the range of doses at which the observations are maximized as one to two thousand mSv, the factor appears to be in the range of two to three, which corresponds to many reported human data.

UNSCEAR has also reviewed epidemiological studies of cancer mortality and incidence among patients exposed to radiation for diagnostic or therapeutic purposes, occupationally exposed workers and individuals subject to environmental radiation exposure. Results from these studies generally support the risk estimates derived from the LSS data, and provide information on issues that the LSS cannot address.

In its 2001 report, UNSCEAR reassessed its estimates of hereditary effects attributable to radiation exposure. The radiation risk to offspring following prenatal exposure is estimated to range between 0.0003 and 0.0005% per mSv to the first generation (i.e., between 3 and 4.7 cases per mSv per one million progeny).[8] This estimation, which includes multifactorial diseases, corresponds to approximately 1/10 the risk of fatal carcinogenesis and constitutes 0.4-0.6% of the baseline frequency. It is easy to demonstrate that an epidemiological study that can show a statistically significant increase in the radiation-induced hereditary effects would require the assessment of exposed and control groups of an extremely large number of people. Not surprisingly, epidemiological studies have not detected hereditary effects in humans.

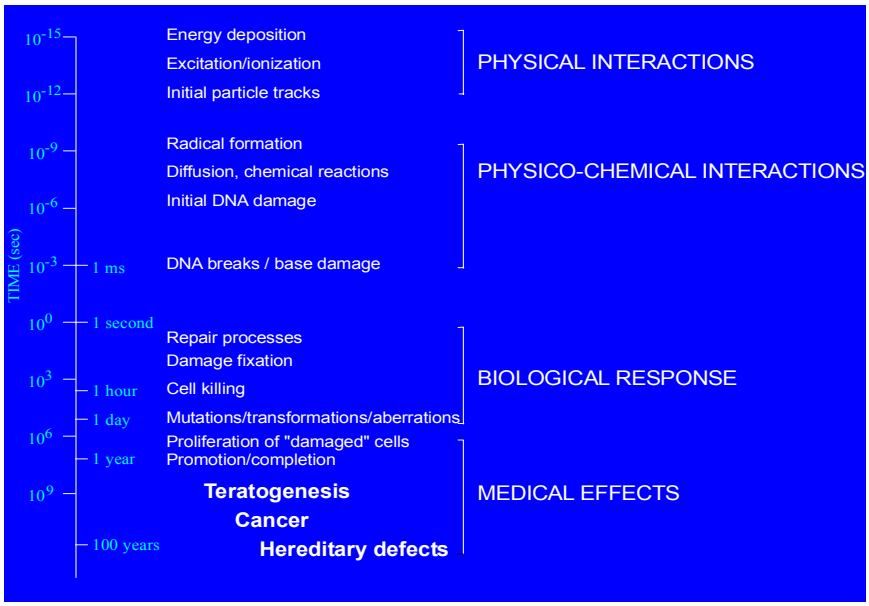
CONCLUDING UNSCEAR'S VIEW

The processes occurring from the ionization of living matter by radiation exposure up to the expression of the attributable detrimental health

8. United Nations Scientific Committee on the Effects of Atomic Radiation, *Hereditary Effects of Radiation; UNSCEAR 2001Report to the General Assembly (with Scientific Annex)*, 2 (United Nations 2001).

effects are extremely complicated. They extend over inconceivably different time periods: the physical interaction taking place in millionths of microseconds, the physiochemical interactions occurring in thousandths of microseconds up to milliseconds, the biological response arising in seconds up to days, and the stochastic medical effects expressed after years, decades and – in the case of hereditary effects – probably centuries (see Figure 6). Such a cumbersome progression can only be assessed with tremendous uncertainties.

Figure 6
Expression of Health Effects from Exposure to Ionizing Radiation



Until the uncertainties about low-dose response are better understood, UNSCEAR estimates that:

- an increase in the risk of induction of stochastic effects, proportionate to an increase of radiation dose, of around 0.004 to 0.006% per mSv for cancer and of 0.0003 to 0.0005% per mSv for hereditary effects is consistent with developing knowledge;[9] and

9. United Nations Scientific Committee on the Effects of Atomic Radiation, *Sources and Effects of Ionizing Radiation*; *UNSCEAR 1994 Report to the Genera Assembly (with Scientific Annex)*, 3 (United Nations 1994).

- accordingly, the existence of these risks – which are extremely small but finite – remains the most scientifically defensible approximation of low-dose response.

THE CONTESTERS' POSITIONS

Against the large amount of evidence provided by UNSCEAR, there still exists a large number of contesters of the UN position on the non-threshold, low but finite health risk attributable to radiation exposure. Some of them are radiation-"pro," presuming that radiation exposure is less detrimental than estimated and indeed curative; others are radiation-"con," presuming that radiation exposure is much more detrimental than estimated.

The Radiation-Pro Arguments

A so-called "anti-LNT" group maintains that risk at low doses has been overestimated claiming that no excess cancers have been detected at doses below circa 200 mSv and that reasons for this lack of experimental evidence at low doses include the following:

- DNA repair would be more efficient than UNSCEAR estimates, and the *adaptive response* process would create conditions of error-free repair.
- The dose-response relationship should be strongly curvilinear, with a *de facto* dose threshold, because the genetics of cancer development requires several mutations for initiation, promotion and progression into malignancies – at least for some types of cancer.
- *Apoptosis* would be more efficient than mutagenesis and would in fact create conditions for radiation *hormesis*.

Experimental Evidence: Limits of Epidemiology:

The lack-of-experimental-evidence argument is easy to refute. It has already been noted[10] that the presumption that predictions made by radiobiological modelling are unscientific because of the lack of epidemiological data in the region of doses of the predictions is in itself utterly unscientific. The discovery of a new planet and the observation of the prediction of relativity were examples shown to dispose of the criticism. As noted,

10. Dan J. Beninson, Sievert Lecture, *Risk of Radiation at Low Doses* (Vienna, Austria, 1996) (copy on file with the Austrian Association of Radiation Protection).

while some natural science is a description of what is observed, most of it is a blend of modelling from some observations, prediction sometimes leading to other observations, theoretical constructions and the search for new and crucial experiments.

Radio-epidemiology shows clearly positive results at doses towards a thousand mSv simply because this is the region of dose where the effects are most probable. The location of region of dose where the probability of seeing effects is maximized can be assessed by seeking the maximum of the linear quadratic relationship:[11]

$$p \cong (a\,D + b\,D^2)\,e^{-cD}$$

To find the dose D_m that would maximize p, the expression should be derived and the derivative equalized to zero. The expression obtained is as follows:

$$cD_m = [\,(a/b) + 2D_m\,] / [\,(a/b) + D_m\,]$$

The product cD_m would vary between around 2 and 1, resulting from the extremes in which the ratio a/b is very small or very large compared to D_m. The cell-killing coefficient c has been experimentally measured for many tissues, and for humans a value of around 1000 mSv can be taken as typical. It follows that the region of dose with good radio-epidemiological results is predicted to be between 1000 and 2000 mSv. It should therefore not be surprising that for doses much lower than around 100 mSv radio-epidemiology does not show the same positive results as in the 1000 mSv area.

Then there is the issue of the statistical limitations of radio-epidemiology. Epidemiological studies compare an *exposed* group of people against a similar but unexposed *control* group. In order to quantify the effect in the group exposed to the radiation doses additional to the background dose, it will be necessary to assess the difference between the number of cancers in the exposed group (E) and those in the control group (C), E-C. If this difference is to be seen with statistical confidence, it should be about twice as large as its standard deviation, √E-C. With 500 people in each group and an expected cancer incidence of 25% in the study group, N would be 125 and C 100. The expected difference would be 25 with a standard deviation of √225, or 15. This difference would then be observable with a confidence of about 90%. An incidence of fatal cancer of 25% (i.e., an increase of 5% over the normal probability of 20%), corresponds

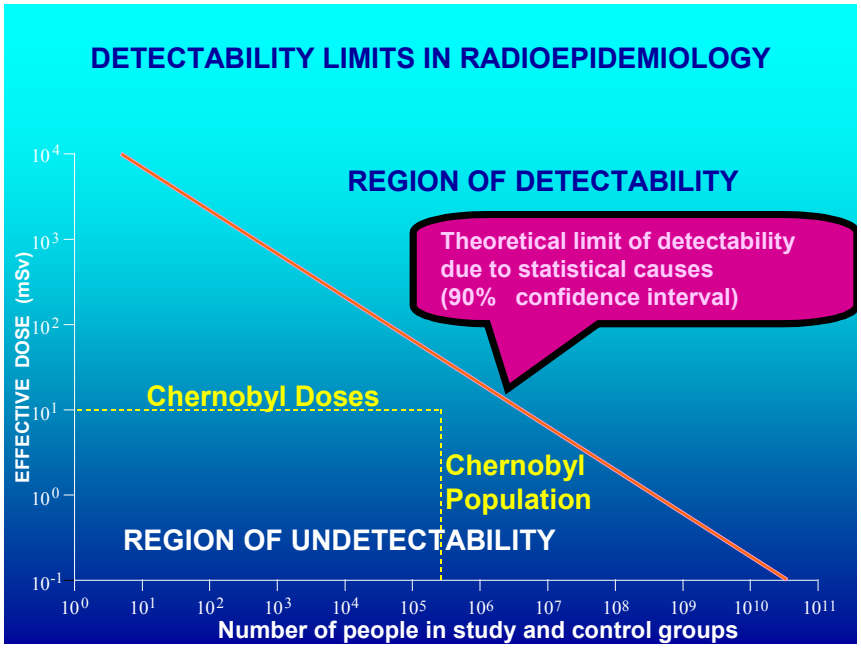
11. *Id.*

to an excess dose in the exposed group over that in the control group of about 1 Sv. To detect the effects of 0.1 Sv, the groups would each need to be increased to about 50,000 people, giving a difference (N-C) of 10,250 – 10,000 = 250 with the standard deviation of √20 250 or 142. To observe the effects of a dose of 10 mSv in excess of the background dose, with a confidence of about 90%, would require groups numbering 5,000,000 each and to observe effects at 1 mSv (the current dose limit for members of the public) would require to compare to homogeneous groups of half a billion people each, one homogeneously exposed to background radiation and another to 1 mSv of additional dose – an obviously unfeasible experiment.

The line demarking the epidemiological detectability of long-latency solid cancers (i.e., other than e.g. thyroid cancers) attributable to radiation is in the high dose range in a population vs. dose diagram (see Figure 7). It is not surprising that, for medium size populations, effects can only be observed down to doses of around 100 mSv, no less; the unfeasibility to detect solid cancers other than thyroid cancers in the population exposed to residues from the releases from the Chernobyl accident was not unexpected.

Figure 7

Detectability Limits in Radioepidemiology



Repairing mutation through adaptive response:

Another scientific argument against the LNT relates to the adaptive response phenomenon indicated earlier. While it has been shown that a pre-given dose can stimulate repair mechanism and increase repair rate, this does not prove that the repair mechanism will be error-free. The argument does not withstand the available mechanistic and experimental evidence. The issue is very complex: an increased rate of repair could also increase the rate of misrepairs, the misrepairs making up a small fraction of the repairs. While the balance between the stimulated repair and the residual damage remain dubious and uncertainties continue to surround the significance of the adaptive response process to the genesis of cancer, so far there appears to be no generally reproducible reduction in tumor induction following low-dose irradiation. In an extensive analysis of adaptive response data, UNSCEAR concluded that extensive animal experiments and limited human data provide at present no evidence to support the view that the adaptive response in cells either decreases or increases human risk at low doses.

Supra-Curvilinearity of the Dose-Response:

The argument that the dose-response relationship should be strongly curvilinear, with a *de facto* dose threshold, because the genetics of cancer development requires several mutations for initiation, promotion and progression into malignancies, has also been shown to be fallacious.[12] If the target for each mutation requires at least one ionizing event then the probability of mutation can be expressed as:

$$[1 - e^{-kD}]$$

and for similar n targets the overall probability p will be given by:

$$p = [1 - e^{-kD}]^n$$

With known experimental values of k and n, the argument seems quite correct because for some cancers the value of n is at least 7. However it should be remembered that there are also "spontaneous" mutation rates (i.e., rates of mutations not attributable to radiation for the same targets). These rates must be substantial to account for the relatively high cancer

12. *Id.*

frequency prevailing in humans. The cancer probability attributable only to radiation, Δp, is then given by the difference:

$$\Delta p = [1 - e^{-(S+kD)}]^n - [1 - e^{-S}]^n$$

where S is the rate of spontaneous mutation. Thus, as S is substantially larger than kD, Δp will be linear with dose whatever the value of n is. It follows that it is necessary to have important spontaneous mutation frequencies to experience radiation risks at low doses; this is unfortunately the case.

Apoptosis:

The argument of an over-efficient process of apoptosis is more plausible than the others, but has not been demonstrated either. Apoptosis is a complex process essential to normal development and functioning of multi-cellular organisms and, importantly, it seems to be altered by radiation exposure. It is triggered by mutation (including radiation-induced mutation) in a process involving a large array of genes and is one of the weapons the immune system employs to eliminate the transformed cells. Failure of damaged cells to kill themselves via apoptosis may result in these cells proliferating into tumours and malignancy formation. However, the transformed cells may also employ the weapon to counterattack the immune system and they can even gain the upper arm in the combat. Evidence is accumulating that apoptosis plays an important role in not only eliminating transformed cells but also in actively evading the immune surveillance.[13]

If it could be proved that at low radiation doses the process of apoptosis is really more efficient than that of cancerogenesis (i.e., if a given low radiation dose kills a larger number of initiated cells than the number of cells it initiates), then radiation would be *hormetic*. But this "gut feeling" premise is far from being proven. In fact, until now, there is no evidence that this is the case. However, radiation hormesis is being claimed and substantiated with allegedly solid epidemiological data.

Hormesis:

The term *hormesis* generally refers to the stimulation of any biological system by low doses of any agent. The defenders of hormesis recognize

13. Fan Xiao Qiang & Ya Jun Guno, *Apoptosis in Oncology,* 11(1) China; in Cell Research 1 (2001).

that large radiation doses produce negative effects and that they are nemetic rather than hormetic. However they claim that, as homeopathy is based on the belief that low doses of many agents evoke a biopositive effect; similarly low radiation doses would be positively hormetic. The argument is simple: small and large doses would induce opposite physiologic results; therefore, while it is recognized that small doses of radiation can stimulate cancer cell growth, the stimulation of different components of the complex immune system would more than compensate for simple cellular effects and the net effect would be a decrease in cancer mortality.[14] As a result of this hypothesis, there have been suggestions that we all need more radiation exposure for good health! Claimers of radiation-induced-hormesis allege that there is evidence that a moderate annual dose of radiation increases longevity and provide selected examples intending to prove the assertion. A case recently reported refers to British radiologists who would have entered the field between 1955 and 1979 and would have experienced a 29% lower cancer death rate compared to all other male English physicians of the same age. Radiologists, it is claimed, would also present a 36% lower death rate from non-cancer causes and a 32% lower death rate from all causes, while the chance of such a health improvement being accidental is, allegedly, less than one in a thousand. The lower death rate from all causes would result in more than a three-year increase in longevity – the same increase in longevity that would result if all cancers were curable. Another case refers to a U.S. government sponsored study, which would show that 28,000 nuclear shipyard workers with the greatest radiation doses, when compared to 32,500 shipyard workers who had no on-the-job radiation, had significantly less cancer and a 24% lower death rate from all causes. As a result, it is claimed that the nuclear workers had an almost three-year increase in longevity. The chance of that health improvement being accidental is, allegedly, less than one in 10 million billion.[15] Studies of this type are not new; many have appeared in the literature before. Each time, they fail to pass the test of sound peer-review by professional epidemiologists. It is early to judge whether or not these new cases will follow the pattern of previous frustrations.

14. T.D. Lucky, *All Studies Show Low-Moderate Dose Exposed Nuclear Workers Have Lower Cancer Rates Than Unexposed Workers*, Newsletter of the Radiation, Science, & Health, Inc. 2 (last updated Aug. 21, 2002).

15. *See e.g.* John Cameron, *Radiation Increased the Longevity of British* Radiologists, 75 British J. of Radiology 673 (2002); *Forum on Physics & Society* <http://www.aps.org/units/fps/oct01/a5oct01 .html > (last updated Oct. 5, 2001).

The Radiation-Con Arguments

The "third constituency" maintains that radiation risks – including those for low doses and low dose rates – have been underestimated, and claiming that epidemiological studies have shown clusters where the radiation risk is higher than current estimates (e.g., the "Gardner" study) and that reasons for this experimental evidence of high risk at low doses include the following:

- the phenomenon of *genomic instability*;
- the *bystander effect* among cells.

While again the epidemiological argument is easy to refute (e.g., the Gardner study proved to be wrong), the two other arguments are plausible although, again, not yet demonstrated.

Genomic instability:

The term *genomic instability* was originally applied to the experimentally observed process according to which radiation-induced dominant lethal mutation in one generation would propagate to subsequent generations against the established theory. The "third constituency" claims that any radiation-induced mutation would generate genomic instability and, therefore, the falsehood of the UNSCEAR tenet according to which the mutation becomes fixed and replicated in a stable manner. Along with this presumption, the affected cell would behave apparently normally through several generations of progeny cells and then exhibit exposure related effects, thus propagating mutation through generations at a higher rate than currently estimated. The problem with this theory is that it has not been convincingly demonstrated and the experimental evidence is scarce and questionable.

Bystander effects:

The term *bystander effect is* used to characterize radiation effects that would appear in cells not affected by radiation but which are in the vicinity of a cell where a radiation-induced mutation has occurred. Bystander effects are attributed to a not-well-understood signalling process from one cell to another, which will proliferate the radiation effect in an initially affected cell to neighbouring cells that were at first unaffected by the radiation exposure. Should this be correct, the presumption that at low doses the dose-response relationship could be reduced to a linear expression (see "*Proportionality between Radiation Dose and Mutated Cells*," above) would be incorrect. Again, while genetic intercommunication among cells may well occur, there is no evidence that this effect would affect the linear

dose response at low doses. Rather, the available evidence from experiments in vitro and in vivo seems to aim at the opposite conclusion.

SIGNIFICANCE OF THE DEBATE FOR RADIATION PROTECTION PURPOSES

Does It Matter?

Conceivably both contester groups, the radiation-pro and radiation-con advocates, could eventually produce evidence that they are an illustrious minority who believe to know better than the majority of scientists who provide the consensus on which UNSCEAR estimates are based. Should this happen, it would be proved that very small levels of radiation dose could theoretically induce either higher or lower harm than the current estimates. But, would this hypothetical scientific revolution really influence practical radiation protection decisions? Let's see.

Radiation Protection and the IAEA: The LNT Presumption for Radiation Protection Purposes

Within the United Nations family, the International Atomic Energy Agency (IAEA) is the body aimed at building global governmental consensus on radiation protection. In this respect, the IAEA has unique functions, which are clearly spelled out in its statute, namely: (i) to establish international standards of radiation protection and (ii) to provide for their application. The IAEA has no program of its own for estimating radiation health effects, as its related activities are limited to setting up an international framework for international consistency and homogeny in practical radiation protection and it therefore relies on the UNSCEAR health risk estimates.

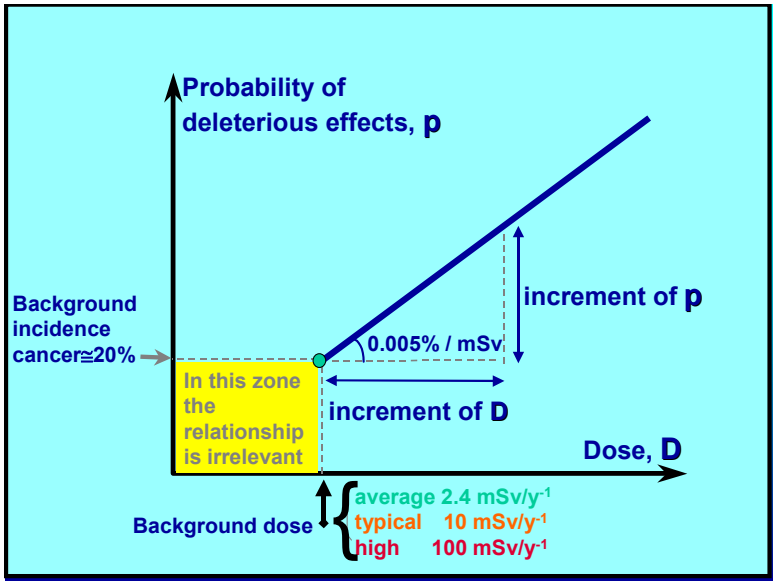
Within this framework, the IAEA has established, jointly with all other relevant organizations within the UN system, Basic Safety Standards for Radiation Protection – the so-called "BSS."[16] The BSS position on low-level radiation health effects for purposes of radiation protection is based on the UNSCEAR estimates and can be implicitly formulated as follows: above the prevalent background radiation dose, an increment in dose

16. *International Basic Safety Standards for Protection Against Ionizing Radiation and for the Safety of Radiation Sources*, Safety Series No. 115 (1996). <http://www.iaea.or.at/ns/CoordiNet/safetypubs/sftypubrs.htm > (accessed December 2002).

would result in a proportional increment in the likelihood of incurring a health detriment attributable to the increment of dose.

At low doses, increases in the likelihood of incurring detriments attributable to the dose increase is extremely small but not zero: the BSS presume it to be around 0.005% per mSv of dose and attribute it mainly to an excess of malignancies, with smaller contributions from excess benign tumours and hereditary effects. This hypothesis of proportionality between excess harm and excess radiation dose was termed according to the somewhat confusing LNT motto: "linear, non-threshold." Confusing because many have interpreted the non-threshold qualifier as expressing continuity in the absolute dose-response relationship, however small such an absolute dose might be. For purposes of radiation protection, however, the non-threshold concept at doses below background doses is not relevant. It is applicable only for doses above the prevalent background dose that is unavoidably incurred. The background annual dose is estimated by UNSCEAR to average 2.4 mSv worldwide, varying between minimums of around 1 mSv and maximums above 100 mSv, with typical elevated values of around 10 mSv. But the doses in the upper end of the scale are those pertinent for purposes of public protection, since it is not feasible to shield people in high background areas against doses attributable to releases of radioactive substances into the environment arising from activities carried out in low-background areas. See Figure 8.

Figure 8
Linear Representation of Deleterious Effects



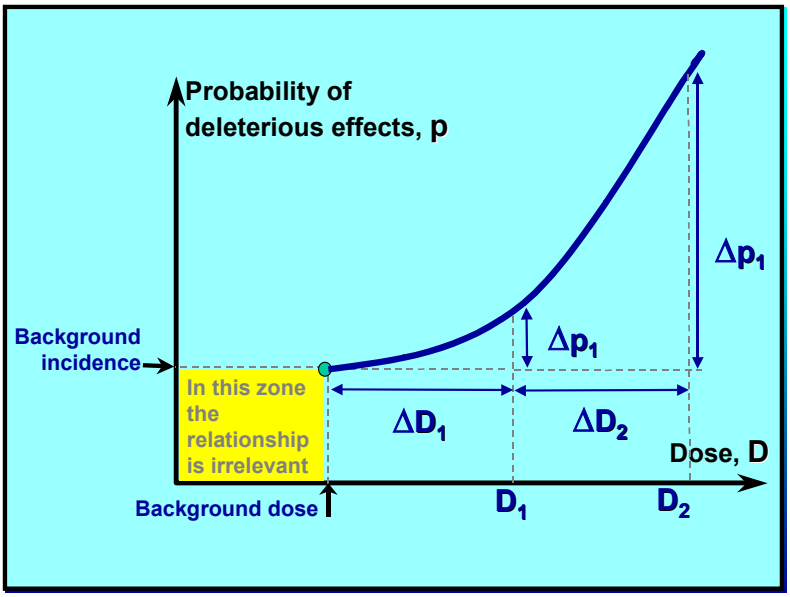
As few people doubt that doses in the order of many mSv per year will increase the chance of deleterious effects, it would appear extremely implausible that increments of dose above such values would change the slope of the dose-response and turn the correlation into one of positive health effects.

Academically Interesting but Practically Meaningless Controversy

Therefore, the discussion on whether a small *absolute* dose, say some μSv/y (micro Sievert/year), would be able to induce health effects, or whether the dose-response relationship is LNT at such small doses is an interesting academic question but meaningless for practical radiation protection purposes. The relevant radiation protection issue is whether or not a relatively small additional dose above the relatively high background doses incurred by people would cause an increment in the incidence of deleterious effects that could be attributed to such background doses. If it is plausible that this increment in detrimental effects may occur and it is feasible and reasonable to protect people against the incremental exposures causing the effects, then radiation protection measures should be implemented. LNT above high background doses should be the topic under discussion rather than LNT for small absolute doses that people cannot experience in real life.

Moreover, should the relationship prove to be curvilinear, radioprotectionists may still need to use a linear approximation; otherwise radiation protection could become unmanageable. In fact, should this be the case, as doses increase from background dose to D_1, and from D_1 to D_2, where $D_2>D_1$, with similar increments of dose, $\Delta D_1=\Delta D_2$, the probability of deleterious effects would increase from the background incidence with increments of Δp_1 and Δp_2, respectively, where $\Delta p_1<\Delta p_2$. See Figure 9. Thus, similar ΔD would correspond to different Δp, making the administration of protection unfeasible.

Figure 9
Curvilinear Representation of Deleterious Effects



Misconception of LNT: The Radiation Protection System

This misconception of the meaning of LNT is subjacent in the irrationality of the LNT debate. It has induced much confusion, mainly but not exclusively among the public and their political representatives, over the issue of regulating low doses. People become astonished when they discover that the regulated public dose *limit* is much lower than the doses caused by natural background. In fact, decision makers rarely understand that the international radiation system has a dual objective: on the one hand, it is conceived to control through dose limits and optimization of protection (or ALARA) *prospective additional doses* to background doses, which may result from the introduction of endeavours termed *practices*; and, on the other hand, it aims to reduce *extant doses* (including high background doses) through a process termed *intervention*. A typical example of the confusion between limiting additional doses through prospective *a priori* design of practices and reducing extant doses through intervention with protective actions was the contradictory advice that decision makers received in Europe at the time of the Chernobyl accident: they were suggested to apply dose limits intended for additional doses from practices when the situation called for reducing doses through intervention. I am

convinced that misunderstandings about the basic radiation protection philosophy are a major cause of the nonsensical debate on LNT.

LOOKING AHEAD

Forthcoming Developments

But even if the current LNT controversy came to an end, this would not be the end of the story. Scientific evolution (and, sometimes, Nobel Prize winning revolutionary innovations!) will continue to be the basic ingredient for scientific development . . . and radiation science is not an exception to this rule. The current impressive developments in molecular biology, and the quasi-completion of human genome mapping, will facilitate a more precise understanding of the actual effects of radiation on health. Fundamental differences in our present vision of the dose-effect relationship may come to mind – for instance, whether changes in the dose-rate could play a fundamental role in the detrimental outcome attributable to radiation exposure.

New Research Programs

A number of "low dose radiation research programs" have been launched worldwide over the last years,[17] which intend to use modern molecular tools with the aim of developing a better scientific basis for understanding exposures and risks to humans from low dose radiation. They usually focus on mechanistic models and biologically-based risk models. Mechanistic models are defined as mathematical descriptions of the molecular and cellular processes involved in biological responses to radiation. One goal for such models will be to develop predictive capabilities for the range and nature of biological responses expected in a given system following exposure to different doses of radiation. Biologically-based risk models are defined as mathematical constructs of the key events involved in the production of an adverse health effect, e.g., cancer, in response to radiation across a range of doses of interest. Such models are likely to describe both continuous and probabilistic variables that range from key molecular probabilities of inducing cell death, replication or specific gene expression to modifiers of responses at the tissue level or even at the level of the entire organism. Mathematical predictors or estimators of radiation

17. *See e.g.* U.S. Department of Energy, *The Low Dose Radiation Research Program* <http://www.er.doe.gov/production/ober/lowdose.html> (accessed December 2002).

risk can include both epidemiological and experimental information. One likely source of input for the development and use of biologically-based risk models is mechanistic models for radiation-induced biological responses. For example, if a mechanistic model for the induction of a bystander effect by low doses of radiation existed, information from that model could, in theory, serve as a direct source of information on an "effective radiation dose" in a biologically-based risk model. Unfortunately all these efforts have been limited to the search for responses to doses and dose rates.

Dependency on Time-Variation of the Dose Rate?

On a number of occasions I have expressed to my colleagues in the radiation-science community my perplexity about the fact that nearly a century of scientific research on radiation health effects has been confined to the relationship between dose, D, and probability of effects, p, and, sometimes, involving the dose-rate (i.e., the first derivative of dose, $\delta D/\delta t$), but that there seem to be no systematic studies on the influence on p of the dose-rate time-variation, namely the second derivative of dose, $\delta^2 D/\delta t^2$.[18] In summary, on whether or not $\delta^2 D/\delta t^2$ influences the current estimation of risk per unit dose, namely $(\Delta p/\Delta D) \cong 0.005\%/\text{mSv}$.

This lack of knowledge is surprising. Casual comparison with other detrimental phenomena, such as non-ionizing radiation exposure, would lead one to believe that changes in the dose rate should influence the risk per unit dose. The current estimated slope of 0.005% per mSv mainly derives from epidemiological studies of the atomic bomb survivor cohorts who experienced very high levels not only of dose but fundamentally of $\delta^2 D/\delta t^2$. The levels of $\delta^2 D/\delta t^2$ should be much smaller for occupational exposed workers, and even lower for members of the public subject to usually stable dose-rates of environmental radiation exposure.

The hypothesis that the risk per unit dose should be somehow related to $\delta^2 D/\delta t^2$ should be seen as a plausible inference arising from the experimental data on adaptive response. If the efficiency of the repair mechanisms of radiation-induced mutations depends on irradiation history, e.g., with the existence and timing of a prior conditioning dose, it is evident that the risk per unit dose should be a dynamic variable depending on the pre-

18. *See* Abel J. González, Address, *Challenges in Radiation Protection in the 21st Century* (10th International Congress of the International Radiation Protection Association (IRPA), Hiroshima, Japan, May 14, 2000); *see also* Abel J.González, Lecture, *Radiation Safety in the Dawn of the 21st Century: Challenges and Opportunities* (Health Physics Society's American Radiation Safety Conference and Exposition, Denver, Colorado, June 25, 2000).

evolution of dose over time. It follows that: (i) if there is an abrupt change in the dose rate, $\delta D/\delta t$, over time (i.e., if the second derivative of dose, $\delta^2 D/\delta t^2$, is very high), there should be a correspondingly higher risk per unit dose because presumably the repair mechanisms had no conditioning dose nor time to be activated before the challenging dose was delivered; and (ii) conversely, if $\delta D/\delta t$ is virtually constant (i.e., if $\delta^2 D/\delta t^2$ is nil), the repair mechanisms are constantly activated and the risk per unit dose should be smaller albeit not necessarily zero. This hypothesis would be valid under the assumption that the incidence of apoptosis is stable. Should this be correct (i.e., if the risk per unit dose would somehow increase as $\delta^2 D/\delta t^2$ increase), it would be logical that the recent risk estimations from epidemiological studies of occupationally exposed workers would be consistent with but seemingly lower than the nominal risk used in radiation protection standards. Obviously, should the incidence of apoptosis also depend on $\delta^2 D/\delta t^2$ – which is also a plausible possibility – the outcome would be even more complicated.

It should not be difficult in the near future to test this proposition and its potential significance. Firstly, mechanistic theoretical models can be experimented with the already available data from research on adaptive response. Second, plant and animal studies with variable $\delta^2 D/\delta t^2$ may be troublesome but are certainly feasible. Third, there is a potential cohort of humans particularly tailored to the test, namely aircrew members and frequent flyers, which are regularly exposed to high levels of positive $\delta^2 D/\delta t^2$ during take-off (and to similar but negative high levels during landing). I am sure that plenty of modelists, radiobiologists and radio-epidemiologists would be tempted by the challenge.

OUTLOOK

A Confusing and Puzzling Debate

The professional debate on the health effects of low-level radiation has been, to say the least, confusing. Not surprisingly, the regulation of relatively low radiation doses has been ambiguous. This equivocal treatment of a serious problem has predictably caused bewilderment among the public at large and favored sensationalism in the media. As a result, in a number of cases, the regulatory process has imposed severe penalties on society and, unwittingly, hindered the utilization of beneficial practices involving radiation exposure.

Perhaps the problems first arose as a result of misinformation: communication among radiobiologists, radiation protectionists and regulators, and between them and the public and its political representatives, has been

far from good. Vested interests may have played a role also. At the one extreme the wide spectrum of advocate groups, there is a very active anti-technological community of self-proclaimed environmentalists – the so-called "greens." At the other extreme, there is a pioneering community of self-proclaimed defenders of the nuclear industry – the so-called "pro-nuclears." Both these intemperate groups, whatever their intentions, have taken equally dogmatic positions on the issue of regulating low radiation doses. They have focused on the sophisticated radiobiological sciences they do not understand rather than on sensible regulation. Thus, either unfounded dose thresholds have been proposed for facilitating the regulatory process or, conversely, exaggerated risks have been attributed to extremely low radiation doses.

Challenging the Health Physics Community

New knowledge on the interaction between radiation and life is already in the pipeline. Much more information will be available on the dose-response relationship and this might well result in being far more complicated than the current static assumption of constant risk per unit dose. These developments will not necessarily make life easier for radio-protectionists who, for practical reasons, may well have to adhere to the current practical hypothesis – the so defamed LNT.

The extreme positions on the effects of low-level radiation will have proved to be unsound: in the light of current knowledge, they can already be shown to be simply unscientific. Ironically, they are not even necessary. Twisting the arm of the radiobiologists with the intention of forcing science to proclaim either radiation *hormesis* or radiation *nemesis* is a fantasy with no real prospects of success. Conversely, requesting that the competent authorities responsibly exercise their function of regulating activities delivering low radiation doses with sensible and practical approaches seems to be the most judicious path to follow.

Inducing level-headed attitudes to radiation safety regulators is the real challenge of a conscientious health physics community!