Biological effects of low doses of ionizing radiation: A fuller picture

The two latest reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) provide a comprehensive overview of current knowledge

by Abel J. González

When the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) submitted its 1994 report to the United Nations General Assembly this year, the international community received a fuller picture of the biological effects of low doses of ionizing radiation. The 272-page 1994 report specifically addresses epidemiological studies of radiation carcinogenesis and adaptive responses to radiation in cells and organisms.

The report is designed to supplement the more extensive 928-page report that UNSCEAR presented to the UN in 1993.* That report addressed global levels of radiation as well as major issues of radiation effects, including the mechanisms of radiation oncogenesis; the influence of level of dose and dose rate on stochastic effects of radiation; hereditary effects of radiation; radiation effects on the developing human brain; and late deterministic effects in children.

Taken together, these two reports provide an impressive account of current knowledge on the biological effects of ionizing radiation. This article — though by no means an account of all essential information — summarizes the highlights of UNSCEAR's assessment of the effects of low doses of ionizing radiation, hereinafter called "low radiation doses" *(see box, page 39)* in the context of available radiobiological evidence.

Radiobiological effects: The current understanding

Since the beginning of the 20th century, it has been known that high doses of ionizing radiation produce clinically detectable harm in an exposed individual that can be serious enough to be fatal. Some decades ago, it became clear that low radiation doses also could induce serious health effects, although of low incidence and only detectable through sophisticated epidemiological studies of large populations. Because of the work of UNSCEAR, these effects are now better and more widely understood and better quantified.

Effects at the cellular level: DNA damage and repair mechanisms. The biological effects of radiation derive from the damage it causes to the chemical structure of the cell. For low radiation doses, damage to the *deoxyribonucleic acid (DNA)* in the cell's nucleus is of concern. The damage is expressed as *DNA mutation* occurring in genes in chromosomes of *stem cells*, which can alter the information that passes from a cell to its progeny.

While DNA mutation is subject to efficient repair mechanisms, the repair is not error free. Most damage is repaired, but some damage remains or is badly repaired, and this has consequences for the cell and its progeny. *(See box, page 38.)*

Evidence of cell adaptation. There is experimental evidence that DNA mutations can be reduced by a small prior conditioning dose of radiation, probably because of stimulation of the repair mechanisms in cells. *(See box, page 42.)* Such a process of *adaptive response* has been demonstrated in human lymphocytes and in certain mouse cells. The cellular response is transient and there appear to be individual variations. As it is recognized that the effectiveness of DNA repair is not absolute, adaptation is likely to occur together with the processes of DNA mutation and its subsequent effects. The balance between

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* See the 1994 UNSCEAR Report, *Sources and Effects of Ionizing Radiation*; UN Pub. Sales No. E.94.IX.11; United Nations, New York, (1994), and the 1993 UNSCEAR Report: *Sources and Effects of Ionizing Radiations*; UN Pub. Sales No.E.94.IX.2.; United Nations, New York (1993). Also see the *IAEA Bulletin*, Vol. 35, No. 4, page 49 (1993), for highlights of the 1993 report.

Radiation Exposure and Living Matter

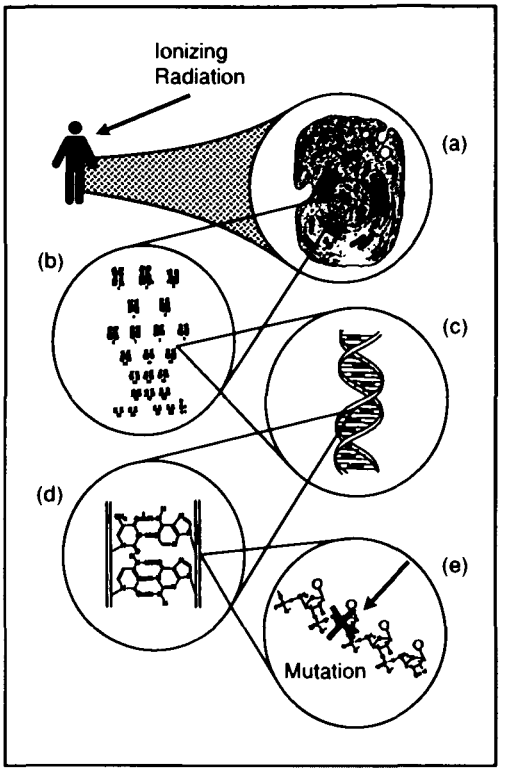
Interaction of radiation with biological material affects the smallest unit of living matter capable of independent existence: the ***cell,*** **(a)**. A typical cell is a sack of fluid, or ***cytoplasm***, enclosed by a membrane, which embeds a ***nucleus*** containing the ***chromosomes*** — threads of complex biological substances, including the more essential compound of life, ***deoxyribonucleic acid or DNA*** — that carry life-sustaining information. The chromosomes hold the ***genes***, a segment of DNA that codes the information, and allows its transmission from a cell to its descendants. The cytoplasm also embeds ***organelles*** governing important metabolic functions of the cells and the generation of vital energy.

The human body contains a total of around one hundred trillion (or 10^{14}) cells. They are variable in shape and size, the average diameter being lower than 10 micrometres. The large majority of cells are ***somatic cells***, i.e. those which make up the bulk of the organism. A relatively minor number of cells pass on hereditary information from the organism to its descendants during reproduction: they are called ***germ cells***[1]. From the large number of human cells, only a fraction has stem-like properties, i.e. are able to reproduce a progeny of cells. The human body contains a total of around 10^{10} to 10^{11} of these ***stem cells***; their fraction varies among tissues and organs, and also with age.

Radiation can ionize any atom in the cell components. An important outcome is the production of active ***chemical radicals***, extremely reactive compounds, able to promote chemical changes in the cell. These changes may either damage essential cellular functions, and potentially kill the cell or prevent it from reproducing, or alter the genetic information. The ***target cells*** for the radiation effects that are expressed as a modification of the cell's genetic information are the stem cells. Interactions of radiation with cell material may occur at random at any moment during the dynamic process of reproduction of stem cells. At low radiation doses, there may be a great deal of incident radiation per cell but the frequency of interactions is extremely low. UNSCEAR estimates that a low radiation dose (e.g. 1 mSv per annum) will produce, on average, circa one interaction per cell in a year.

The human cell contains 46 chromosomes **(b)** and a large number of genes that determine the characteristics of an individual. Genes exist in alternative forms called ***alleles*** — one from each parent — which occupy the same relative position in chromosomes having the same structural feature. One allele may be ***dominant*** over the other, determining which aspect of a particular characteristic the organism will display; the only "dominated" allele is known as ***recessive***.

The gene component, DNA **(c)**, is a pair of linear long chain-like molecules called ***polynucleotides*** wrapped around one another, as a spiral ladder-shaped double-helix complex molecule composed of



two chains — or strands — wound around each other. This complex molecule comprises numerous individual units or ***nucleotides*** **(d)**. Nucleotides are made of four types of complementary bases called ***adenine*** and ***guanine*** and ***thymine*** and ***cytosine***. The sequences of the bases express the genetic code.

Directly, or indirectly by the action of chemical radicals, radiation can induce changes in the sequence of bases and therefore alter the genetic code. This process is referred to as ***mutation***, or a sudden random change in the nucleotide sequence of a DNA molecule **(e)**, resulting in alterations in the genetic code that, as a consequence, may cause the cells and all cells derived from it to differ in appearance or behaviour — referred to as a change in ***phenotype.*** Possible alterations are ***point mutation,*** or replacement of one nucleotide by another, and ***clastogenic mutation*** including ***insertion*** or ***deletion***, which is the addition or removal of any piece of DNA, from one base pair to quite extensive parts, and ***inversion***, which is the excision of a portion of the double helix followed by its reinsertion in the same position but in reverse orientation. Mutation is passed on from an individual to his or her progeny during reproduction via the ***germ cells.***

A cell or organism whose phenotype has been altered by mutation is referred to as a ***mutant.*** The more common generator of mutants is random errors in DNA replication during cell reproduction. The mutation rate is increased if the cell is exposed to physical or chemical ***mutagens*** or agents able to cause mutation. Heat is probably the most important

environmental mutagen. Radiation is a rather mild mutagen.

Mutation is effectively repaired by the cell through mechanisms which are not yet well understood. It is likely that, if a point mutation occurs in just one base of one DNA strand, repair would be easy as the complementary base in the other strand apparently can act as a template for the repair; but for mutations occurring in the same location of both strands, or if clastogenic damage occurs, error-free repair would be less likely.Radiation seems to be a stimulant of the repair process. *(See box on Adaptive Response, page 42.)* It seems, however, that there is always a chance of misrepair, even in single strand point mutations.

Unrepaired mutation is responsible for the detrimental fate of a mutated cell. If a mutation is not properly repaired, the outcome for the cell can be twofold: either the cell dies — for instance through *apoptosis*[2] — or it survives as a viable but transformed cell that may give rise to a new family of mutant cells. The two outcomes will have very different consequences for the organism. At low radiation doses, the killing of cells is sparse and does not usually have serious health consequences. But a mutant cell can evolve to cause serious health effects: if it is a somatic cell, it can be the initiator of a malignancy, and if it is a germ cell, of hereditary diseases.

[1] ***Germ cells*** are: the ***testis seminiferous tubule cells*** which divide by mitosis into ***spermato gonia*** and then into ***spermatocytes***, followed by a meiosis into ***spermatids*** which eventually develop into ***spermatozoa***; as well as the special ***oogonia*** cells within the ovary which divide by mitosis into ***oocytes*** which after two meiotic divisions become an ***ovum***. The fusion of a spermatozoon and an ovum forms a ***zygote***, the origin of a new being.

[2] ***Apoptosis*** is an orderly, systematic and programmed process of self-destructive death of the cell. Probably as a result of genetic altrations, the cell enters into a period of cytoplasmic basophilia and nuclear condensation, followed by eosinophilia and cytoplasmic condensation, cell fragmentation, and dissolution and, typically, phagocytosis by neighbouring cells. Contrary to ***cell terminal differentiation***, which is a cessation of cell replication, to cellular ***senescence***, which becomes manifest only at the end of the life span of the cell, and to the disorganized cellular death by ***necrosis***, apoptosis is an orderly cellular process of self-destruction which can be initiated at any moment in the cell life. It is speculated that radiation can be an important initiator of apoptosis which might have a potentially beneficial influence in tumour promotion and malignant progression.

Radiation Doses

The term ***radiation*** means energy propagating in the form of electromagnetic waves or photons, or in the form of subatomic particles. Ionizing radiation is radiation of sufficiently high energy to cause — in the medium through which it passes — the production of pairs of ions, i.e. of atoms or groups of atoms that have either lost or gained one or more electrons to become positively or negatively charged, and the corresponding complementary electrons. For biological effects, the medium in which ion pairs are produced is biological material, more specifically cellular material.

The term ***radiation (absorbed) dose*** generally means the amount of energy which is absorbed from ionizing radiation by a unit mass of material. This quantity is expressed in unit energy per unit mass, that is in joules per kilogram, which takes the special name gray (Gy); [1 Gy = 1000 milligray (mGy)]. For radiation protection purposes, the absorbed dose is weighted to take account of the effectiveness of different radiation types and the radiosensitivity of various organs and tissues. The resulting quantity is termed effective dose, and its unit sievert (Sv) [1Sv = 1000 millisievert (mSv)]; for photons in the intermediate energy range, 1 mGy is approximately equal to 1 mSv.

The term ***low radiation dose*** is used to mean a radiation dose lower than designated levels; sometimes it is also informally used to mean a low dose rate, i.e. low dose per unit time. In specialized radiobiological forums, low radiation dose (and dose rate) refers to exposures for which it is very unlikely that more than one event of energy absorption from radiation will occur in the critical parts of a cell (and damage it) within the time during which repair mechanisms in the cell can operate. Thus, UNSCEAR concluded that low radiation dose refers to a total dose of less than 200 mSv and dose rates below 0.1 mSv per minute (which in fact is a very high dose rate of around 5000 mSv per annum).

For the non-specialized public, low radiation doses are deemed to correspond to levels similar to those from, for instance, natural background exposure or some very common radiation exposures such as those arising during air travel. Natural background exposure varies widely around the world. Some "normal" [and "elevated"] values of annual dose rates are as follows: for cosmic rays, 0.38 mSv [2.0 mSv]; for terrestrial radiation 0.43 mSv [4.3 mSv]; and for exposure to radon, 1.2 mSv [10 mSv]; leading to an average total of around 2.4 mSv per annum. The average annual dose for very frequent flyers (such as aircrew) is around 2.5 mSv. These dose rate levels of a few mSv per annum are expected to deliver, during a lifetime, doses of above around 100 mSv, which are of the order of magnitude of the low radiation doses designated by UNSCEAR.

stimulated cellular repair and residual damage is not yet clear.

Dose-response relationship. If DNA mutation depends on radiation's interaction with a single cell, then the frequency of DNA mutation — in cases of no interaction between cells — should follow a linear-quadratic relationship with dose. *(See box, page 42.)* Furthermore, if it is assumed that, for low radiation doses, mainly single interactions of radiation rather than multitrack effects are dominant, the frequency of cells with one or more interactions, and consequently the frequency of DNA mutations, will simply be proportional to dose. Thus, if a fraction of mutations remain unrepaired, the expected number of mutated cells will be proportional to the dose.

Cell killing: deterministic effects. A number of radiation interactions in the cell and some of the unrepaired DNA mutations may lead to the death of the mutated cell, or prevent it from producing progeny. This may occur as a result of the cell's *necrosis* (i.e. its pathological death as a result of irreversible radiation damage) or *apoptosis* (i.e. a programmed self-destruction of the cell) or because the normal cellular reproduction is hindered. For low radiation doses, cell killing is sparse and therefore of no negative consequence to health owing to redundancy of cellular functions and cellular replacement. For high radiation doses which could kill large numbers of cells in an organ or tissue, the cell-killing effect could be lethal for the tissue and, if vital tissues are involved, for the individual concerned. Although killing of individual cells occurs at random, the health effects resulting from the extensive cell killing at high doses are called *"deterministic effects"* because they are predetermined to occur above a threshold level of dose. Deterministic effects, therefore, are not clinically expressed at low radiation doses. Exceptionally, the killing of a few essential cells during organ development *in utero* may result in severe harmful effects clinically expressed in the newly born; these effects are generally referred to as *"effects in embryo"*.

Cell transformation: stochastic effects. Other unrepaired DNA mutations may produce modified but viable stem cells. If the modified cell is a *somatic cell*, it can be the initiator of a long and complex process that may result in severe "somatic health effects", such as cancer. Alternatively, if the cell is a *germ cell*, the mutation could be expressed as *hereditary health effects* in the progeny of the exposed person. These health effects, both somatic and hereditary, deriving from a cell modification are called *"stochastic effects"* because their expression is of an aleatory, random nature.

Carcinogenesis

A most important stochastic effect of irradiation is *carcinogenesis*. It is believed to be a multistage process and is usually divided, albeit imprecisely, into three phases: cancer *initiation*, tumour *promotion*, and malignant *progression*. *(See box, page 41.)* It is presumed that radiation is important as an *initiator* rather than as a *promoter* or *progressor*. For low radiation doses, therefore, as the likelihood of initiating mutations is proportional to dose, the likelihood of carcinogenesis should also be proportional to dose.

Immune response and cell surveillance mechanisms. It is argued that immune response may not play a major role in moderating human radiation carcinogenesis. However, specialized immune functions in certain organs and the existence of non-immunogenic cell surveillance mechanisms suggest that a proportion of early pre-neoplastic cells may be eliminated before they become established. Other mechanisms defending against tumour induction and development include the already mentioned DNA repair, apoptosis, terminal differentiation and phenotypic suppression. Altogether, these mechanisms will reduce the probability that a specifically damaged target cell will progress to frank malignancy; to estimate this probability, however, is extremely difficult.

Adaptive response in organisms. Evidence of organic adaptive response to radiation exposure in laboratory mammals has been reported in the literature. However, because of the lack of conclusive evidence, UNSCEAR remains doubtful whether adaptation also occurs at the cellular system level and whether the immune system plays any role in the process.

Epidemiological evidence of carcinogenesis. Although it is not yet possible to determine clinically whether a specific malignancy was caused by radiation, radiation-induced tumours and leukaemia have been detected and statistically quantified by epidemiological studies of populations exposed to relatively high radiation doses. From initiation until the clinical expression of the cancer, a period of time — termed the latency period — elapses. The duration of the latency period varies with the type of cancer from a few years in the case of leukaemia to decades in the case of solid tumours. The action of radiation is only one of many processes influencing the development of malignancies and, therefore, the age at which a radiation-induced malignancy is expressed has been found to be no different from the age for malignancies arising spontaneously.

Epidemiological studies of a number of populations exposed to generally high-dose and high-dose-rate radiation — including the survivors of the atomic bombing of Hiroshima and Nagasaki in Japan and patients exposed in therapeutic medical procedures — have provided unequivocal association between radiation dose and carcinogenesis.

The most comprehensive source of primary epidemiological information is the Japanese survivors' "life span study". This has demonstrated a positive correlation between the radiation dose incurred and a subsequent increase in the incidence of, and mortality due to, tumours of the lung, stomach, colon, liver, breast, ovary, and bladder, and also of several forms of leukaemia but not for lymphoma or multiple myeloma. Of the 86 300 or so individuals in the "life span study" cohort, there were 6900 deaths due to

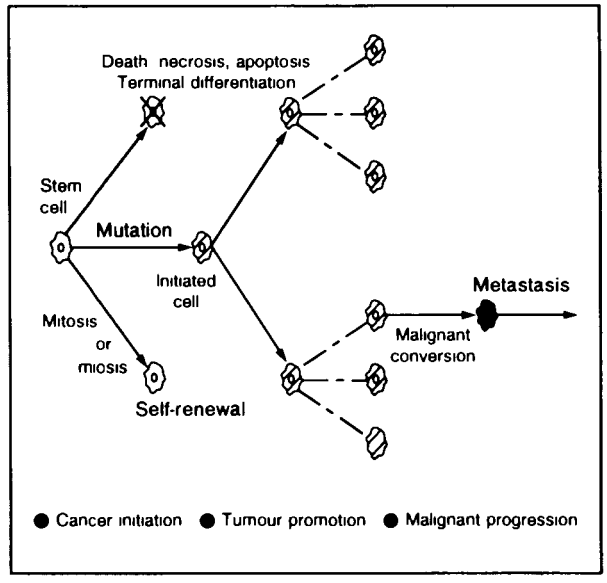
Carcinogenesis: A Multistage Process

Carcinogenesis is believed to be a multistage process usually divided into three phases: cancer initiation, tumour promotion, and malignant progression.

Cancer initiation. Most, if not all, cancers seem to "initiate" from DNA mutation in a single stem cell which thus becomes a modified, carcinogenic cell. This process involves loss of control over the cellular reproduction cycle and differentiation. It is presumed to start as a result of deactivation of ***tumour suppressor genes*** that seem to play a crucial role in regulating cellular proliferation. The loss in activity of these genes, through for instance a deletion or a mutation, can lead to uncontrolled cell growth. The process of initiation of carcinogenesis might also be the result of conversion of ***proto-oncogenes***, which seem to be involved in regulating the proliferation and differentiation of cells and can potentially become oncogenes and transform the cell into a malignant cell. Relative target sizes for the induction of these events would tend to indicate tumour suppressor genes as the most radiosensitive targets. It is presumed that the initiating event centres on single gene deactivation in a number of possible genes and that initiation is an irreversible process.

Tumour promotion. The promotion stage involves the clonal expansion of an initiated stem cell into a focus of non-terminally differentiated cells. The initiated cell can be stimulated or "promoted" to reproduce by agents that, alone, may have low carcinogenic potential but that are able to enhance greatly the yield of neoplasms induced by prior exposure to an initiator. Radiation, like many other agents, can act independently as initiator and promoter. After initiation, the transformed cell may have some proliferative or selective advantage over normal cells, such as a shorter reproduction time. However, the transformed cells and their immediate progeny are surrounded by normal cells, which constrains their pre-neoplastic properties as they are prone to be eliminated in the competitive reproductive process. Elimination becomes more unlikely as the number of transformed cells increases. Thus, the promotion stage seems to be potentially interruptible and reversible.

Malignant progression. After initiation and promotion, a futher stage of "progression" is needed to complete the multistage carcinogenesis. It is characterized by a progressive tendency towards increasing malignancy. Progression might be facilitated by additional alterations in initiated and promoted cells to become promoter - independent and invasive. The principal phenotypic characteristic of the malignant progression is the ability to spread, or metastasize, from the primary tumour mass and to establish secondary growth foci, or metastases, at other sites. This is a complex, multifaceted process that appears to involve a series of subsequent genetic changes within the evolving pre-neoplastic clone of cells, including changes in growth rate, growth factor response, invasiveness, and metastatic potential. The progression stage includes angiogenesis, detachment, invasion, release, survival (host interaction), arrest, extravasation and invasion, new growth, angiogenesis. Thus the process is repeated until clinically important metastases are produced. Whether and how radiation exposure influences the changes leading to progression and the different stages of the progression process is not yet known. The progression stage also appears to be irreversible.



solid tumours during 1950-1987, but only approximately 300 of these cancer deaths can be attributed to radiation exposure. The epidemiological data for leukaemia incidence in this same period indicate statistically that 75 cases out of a total of 230 leukaemia deaths can be attributed to radiation exposure. The incidence data also provide evidence of excess for thyroid and non-melanoma skin cancers. The study provides little or no evidence of radiation induction for cancers of the rectum, cervix, gall bladder, larynx, prostate, uterine cervix, uterine corpus, pancreas, kidney, renal pelvis, or testes, or for chronic lymphocytic leukaemia and Hodgkin's disease.

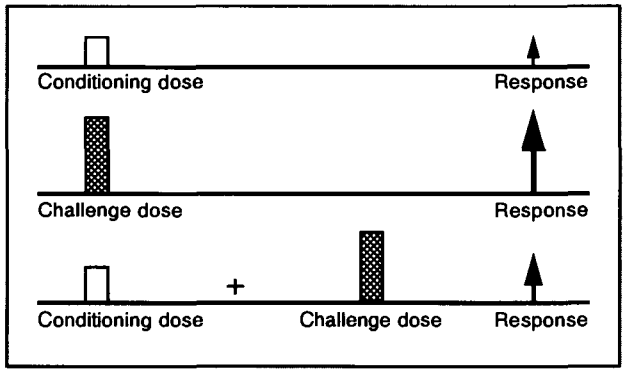
Epidemiological studies on the effects of low-dose-rate exposure undertaken for occupational exposures have shown conflicting evidence. While a number of occupational studies have reported a significant excess risk of leukaemia in workers exposed to radiation — which is broadly in agreement with the estimates derived from high-dose-rate studies — other studies have failed to demonstrate any positive correlation. *(See author's note, page 45.)* Studies of lung cancer in miners occupationally exposed to radon, however, have been able to provide a consistently positive correlation between excess cancer incidence and radiation dose.

Many environmental exposure studies have been carried out, notably on the incidence of

Adaptive Response

The possibility has been known for many years that low doses of radiation may cause changes in cells and organisms, reflecting an ability to compensate for the effects of radiation. It has been suggested that estimates of the risk of stochastic effects from low-level radiation may have been overstated because no allowance has been made for this process, which is referred to as adaptation or ***adaptive response***. The term adaptive response is used to refer to the possibility that a small dose of radiation — which is variously referred to as the *adapting, inducing, priming, or* ***conditioning dose*** — may condition cells by inducing processes that reduce either the natural incidence of malignancies or the likelihood of excess malignancies being caused by a further radiation dose — usually referred to as the ***challenge dose***. *In vitro* adaptive response of lymphocytes takes place between about four and six hours after exposure to a conditioning dose within a range of dose of about 5 mGy to 200 mGy, and remains effective for around three cell cycles. Following a challenge dose, repair is manifested as a reduction — below the expected levels — in chromosomal aberrations, sister chromosomatic exchanges, induced micronuclei, and specific locus mutations, sometimes by a factor of about two. Moreover, bone marrow cells and spermatocytes from mice exposed to a challenge dose that followed a conditioning dose also showed reduction in the number of chromosomatic breaks compared with cells exposed to the challenge dose alone.

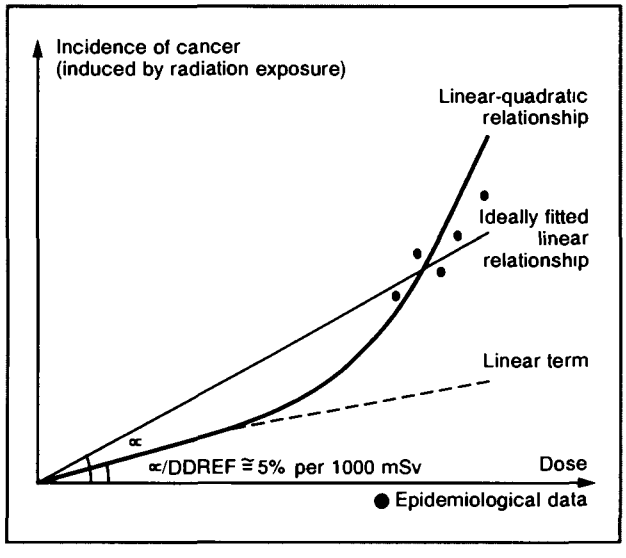
It seems that many agents can be activated sometime after exposure to the conditioning dose and can reduce DNA mutations due to the subsequent exposures to the challenging dose. These include gene coding for transcription factors — i.e. factors affecting the process of transfer of genetic information of DNA — and synthesis of enzymes involved in the control of the cell cycle and therefore in the proliferation of cells as well as in the repair of damage. Observations support the hypothesis that conditioning doses activate certain genes and that this is quickly followed by the synthesis of enzymes responsible for DNA repair. If these enzymes become available in adequate concentration at the time the cells receive the challenge dose, the extent of DNA repair seems to be improved. The adaptive response mechanisms are thought to be similar to those operating after exposure to other toxic agents, including trace amounts of oxidizing radicals. The adaptive response to radiation, therefore, may be the result of a general mechanism of cellular response to damage.



Dose-Response Relationship

It is presumed that radiation acts through single track interactions occurring randomly according to a Poisson distribution in a homogeneous population of cells. It can be mathematically shown that a linear-quadratic expression describes the theoretical ***dose-response relationship*** — i.e. the mathematical relation between the dose incurred and the probability of expression of an attributable radiation effect. This relationship fits most of the available epidemiological data. For low radiation doses, there are so few radiation tracks that a single cell (or nucleus) is very unlikely to be traversed by more than one track. Thus, under these assumptions the dose-response relationship is almost bound to be linear, independent of dose rate and without dose threshold.

Since most available radioepidemiological data are for high doses only, the approach commonly used for assessing the risk at low doses is to fit an ideal linear dose-response relationship to the data in order to project it for low doses for which data are lacking. As the real dose-response curve is assumed to follow a linear-quadratic relationship, with the linear term prevailing at low doses, a reduction factor — which is called "dose and dose rate effectiveness factor" or DDREF — has to be applied . Based on experimental data, it seems that the DDREF should be small. For cell tranformation and mutagenesis in somatic and germ cells, DDREFs of around two or three have been observed, although at low dose rates no reduction in effects was observed (i.e. the DDREF was unity), over a large range of doses. Taken together, the available epidemiological data suggest that for tumour induction the DDREF adopted should have a low value, probably of around two and no more than three. In the case of hereditary disease, a DDREF of three is supported by most experimental data for animals.



leukaemia in populations living near nuclear installations. Although a few such studies were initially reported to have provided positive correlations between clusters of leukaemia cases and the proximity of nuclear installations, further evidence indicates that it is unlikely that such clusters can be attributed to radiation exposure. A particular exception is a study on people exposed to high level discharges of radioactive materials into the Techa River in the former USSR, among whom leukaemia was found to be in excess. Comparisons of cancer incidence in areas of high and low levels of exposure to natural background radiation have not produced any statistically significant associations.

Inconclusive epidemiological evidence of adaptive response. The human epidemiological studies on adaptation have been of lower statistical power. Therefore, they do not provide evidence of an adaptive response expressed as a decrease in the prevalence of spontaneously occurring human cancers. Moreover, the extensive animal experiments and limited human data provide no conclusive evidence to support the view that the adaptive response in cells either decreases or increases risks of cancer in humans owing to the effects of radiation at low doses.

Models for carcinogenesis. Risk assessments of carcinogenesis are carried out by extrapolation from the limited epidemiological data available, taking account of theoretical assumptions from plausible radiobiological models. For instance, in order to obtain the full lifetime risk in an exposed population, it is necessary to project the frequency of induction of excess cancers noted during the period of observation over the entire lifetime of the population. This is now done through a *"multiplicative" model* (rather than through a simple *"additive" model),* which assumes that the rate of induced cancers will increase with age, in proportion to the spontaneous cancer rate (which also increases with age).

Three multiplicative projections are used by UNSCEAR: one assumes that the excess relative rate remains constant throughout life, the others that it will decrease some time after the exposure (the risk of exposure induced death is higher with the constant model while the years lost per induced case can be higher with the other models).

On the other hand, the lack of epidemiological data on the induction of cancer and leukaemia at low doses means that incidence data at high doses must be used for risk estimates. A reduction factor should be applied to the risk deduced from a theoretical linear (non-threshold) fit to the high-dose and high-dose-rate epidemiological data. A reduction factor of about two, which is estimated with considerable uncertainty on the basis of theoretical assumptions and some epidemiological data, is used by UNSCEAR in its risk assessments. *(See box, page 42.)*

Hereditary effects

Any unrepaired DNA mutations in germinal cells that are non-lethal for the cell could in principle be transmitted to subsequent generations and become manifest as *hereditary disorders* in the descendants of the exposed individual. Epidemiological studies have not, with a statistically significant degree of confidence, detected hereditary effects of radiation in humans. However, on the basis of genetic experimentation with a wide range of organisms and cellular studies, and taking account of the statistical limitations of the negative human findings, it is conservatively assumed that there can indeed be induction of hereditary effects in humans following radiation exposure. The potential hereditary effects may be the result of:

- dominant mutation (i.e. a mutation in the *dominant allele* of a *gene*, which can be inherited from only one parent and which leads to disorders in the first generation and can be passed unexpressed through several generations);
- recessive mutation (i.e. a mutation in the *recessive allele*, which can only be inherited from both parents — otherwise, the dominant allele would prevail — and which produces little effect in the first few generations but may accumulate in the population's gene pool, i.e. in the whole of the genes that are present in a population; and
- potentially, *multifactorial disorders* due to mutations resulting from the interaction of several genetic and environmental factors.

The process of generation of hereditary disorders from radiation is less well understood than that of carcinogenesis but the assumptions made are similar: stochastic single cell origin of the disorder with any radiation interaction is fully capable of being an initiator. Therefore, the response at low radiation doses is also presumed to be linear with dose, with no dose threshold.

Models for hereditary disorders. In view of the lack of direct epidemiological evidence, incidences of radiation induced hereditary effects in humans are estimated through two indirect methods which use data from animal experiments. The *doubling dose (or relative mutation) method* provides the estimate in terms of the additional number of cases of hereditary disease attributed to radiation, using the natural prevalence (of such a disease) as a reference frame. It aims at expressing the likelihood of a hereditary disease being induced by radiation in relation to its natural general occurrence in the population. (Thus, the *doubling dose* is

the dose expected to produce as many mutations as those that occur spontaneously in a generation and it is obtained by dividing the spontaneous mutation rate in a locus — or position — of a relevant gene in a chromosome by the expected rate of induction of mutations per unit dose.) The *direct (or absolute mutation) method* directly assesses the expected incidence of hereditary diseases by combining the number of genes at which mutations can occur with the expected number of mutations per unit dose and the dose itself. It is therefore aimed at expressing the likelihood of hereditary diseases absolutely, in terms of the expected increase in the prevalence of the disease. The estimates of risk do not usually include the many hereditary diseases and disorders of complex, multifactorial aetiology, in view of the fact that any effect of radiation upon the incidence of multifactorial disorders should be only slight and is highly speculative.

Effects on the embryo

Effects of radiation *in utero* are generally referred to as effects on the embryo. They can occur at all stages of embryonic development, from zygote to foetus and may include lethal effects, malformations, mental retardation and cancer induction. The first three may be the possible outcome of deterministic effects during embryonic development, particularly at the period of formation of organs.

Evidence of effects on brain growth and development has emerged after observations of severe mental retardation in some children exposed *in utero* at Hiroshima and Nagasaki. The effects from high-dose, high-dose-rate exposure *in utero*, particularly linked to the period between 8 and 15 weeks after conception, seem to indicate a downward shift in the intelligence quotient (IQ) distribution. For low radiation doses, this potential effect on the embryo is undetectable in the newborn.

Studies of *in utero* exposures have given conflicting evidence of carcinogenesis in the child, from relatively high risk to essentially small undetectable risk, including (possibly) none at all. There is no biological reason to assume that the embryo is resistant to carcinogenesis but on the basis of current data such effects cannot be quantified with any certainty.

Highlights of UNSCEAR's conclusions

Taking account of the available radiobiological and radioepidemiological information, UNSCEAR has made a number of quantitative estimates in relation to health effects of low radiation doses. As a result, the scientific body continues to consider that radiation is a weak carcinogen and an even weaker potential cause of hereditary diseases. A summary of UNSCEAR's quantitative estimates follows:

- **Epidemiological Estimates:**

Lifetime mortality:

- 1.1% after exposure of 1000 mSv for leukaemia and 10.9% for solid tumours (12% in total). For reference, in UNSCEAR's 1988 report, the corresponding data was 1.0% for leukaemia and 9.7% for solid tumours.
- linear between 4000 mSv and 200 mSv (little evidence at lower dose).

- **Radiobiological Estimates:**

For low (chronic) radiation doses of around 1 mSv per year:

- *probability of an excess malignancy:* 10^{-4} per year
- *lifetime probability*: 0.5%
- *proportion of fatal cancerns in the population that may be attributed to radiation*: approximately 1 in 40.

The above estimates are based on the following assumptions and inferences:

Assumptions:

- *cells in the human body:* 10^{14} cells per individual
- *target stem cells:* 10^{10} to 10^{11} cells per individual
- *initiating event*: single gene mutations in one of around ten possible genes
- *induced mutation rate (per cell):* 10^{-5} per 1000 mSv
- *excess probability of malignancy:* approximately 10%; and
- *interactions per cell*: 1000 per 1000 mSv.

Inferences:

- *excess malignancy*: 1 per 10^{11} to 10^{12} target cells receiving 1000 mSv;
- *rate of target gene deactivation*: 10^{-4} per cell per mSv; and
- *probability that a single track will give rise to an excess malignancy:* 10^{-14} to 10^{-15}.

- **Risk Estimates**:

Risk of malignancies:

- *lifetime probability of radiation induced fatal cancers*:
  5% per 1000 mSv in a nominal population of all ages; and
  4% per 1000 mSv in a working population.

Risk of hereditary effects:
(via doubling dose method)

- *probability of hereditary radiation effects for all generations:*

1.2% per 1000 mSv (or 1.2% per generation for a continued exposure of 1000 mSv per generation)

- *probability of hereditary effects in the first two generations:*
  0.3% per 1000 mSv

(via the direct method)

- *probability of hereditary effects (clinically important disorders) in the first generation:*
  0.2% and 4% per 1000 mSv.

Risk of effects on embryo:

(for those exposed *in utero* in the period between 8 and 15 weeks after conception)

- *downward shift of IQ distribution:*
  30 IQ points for 1000 mSv
- *dose required to shift from normal IQ to severely mentally retarded:*
  1000 mSv or more
- *dose required to shift from low IQ to severely mentally retarded:*
  a few hundred mSv.

Taking UNSCEAR's estimates together and adding to them an estimated detriment from non-fatal cancers, the International Commission on Radiological Protection (ICRP) has recommended the use — for radiation protection purposes — of total nominal risks from stochastic effects of radiation of:

- 0.0073% per mSv for the whole population; and
- 0.0056% per mSv for all adult workers.

These have been the nominal risk factors used in developing the new International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources.*

Outlook

Thanks to the work of a unique body in the UN system, UNSCEAR, the biological effects of ionizing radiation are better known than those of many other chemical and physical agents affecting human beings and the environment. However, there are still many unanswered questions in radiobiology, in particular in relation to the effects of low radiation doses. One problem is the lack of empirical evidence. It should be emphasized that at low dose levels, epidemiological studies presently have only a restricted capability to detect and quantify statistically significant stochastic radiation effects — both somatic and hereditary. As a result, unequivocal direct observational evidence of the effects of low level radiation does not exist and will probably not be obtainable for a long time. Obtaining unequivocal evidence would require sound epidemiological studies, able to associate an increased incidence of specific health effects with radiation exposure. Such studies would have to overcome inherent statistical and demographical limitations and moreover should include correct case ascertainment, appropriate comparison groups, sufficient follow-up, control of confounding factors and well-characterized dosimetry. It is not now feasible to obtain such evidence for the effects of low radiation doses and therefore a continuing lack of direct evidence on such health effects is to be expected.**

Because of these limitations, radiation risk estimates have to rely on an idealized radiobiological model, intended to provide the basis for interpreting the available epidemiological results for high radiation doses. Although the model reflects sound understanding so far, it is rather simple, perhaps even simplistic, and it is still evolving. Scientific developments are taking place that will extend knowledge of the biological effects of radiation and may necessitate changing the model. Research in molecular biology, for instance, may provide new information on the mechanisms of cancer induction. The mechanisms of adaptive response and the role of radiation exposure in the initiation, promotion, and progression of cancer will be better understood. The coming years might change our view of the health effects of low radiation doses.

Notwithstanding the rapid progress in relevant scientific branches, UNSCEAR has not yet found it necessary to make any major revision to its perception of the biological effects of radiation and the consequent risk estimates. Nearly a quarter of the human population incurs fatal malignancies but, as UNSCEAR indicates, only "about 4% of deaths due to cancer can be attributed to ionizing radiation, most of which comes from natural sources that are not susceptible to control by man". ❐

* The standards were developed under the auspices of the IAEA and five other organizations: the Food and Agriculture Organization, International Labour Organization, Nuclear Energy Agency of the Organization for Economic Co-operation and Development, Pan-American Health Organization, and World Health Organization. For a report on the new standards, see the author's article in the *IAEA Bulletin*, Vol. 36, No. 2 (1994).

** Author's note: At the time this article is being issued, the International Agency for Research on Cancer is releasing the results of an epidemiological study on cancer risk among 95 673 nuclear industry workers. The study gives the most precise direct estimates of mortality due to protracted low radiation doses. As reported in *Lancet* (344: 1039-43), the estimates "provide little evidence that the [UNSCEAR] estimates...are appreciably in error".