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The radiobiology/radiation protection interface in healthcare

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Abstract

The current knowledge of radiation effects is reviewed and implications for its application in healthcare considered. The 21st L H Gray conference gathered leading experts in radiobiology, radiation epidemiology, radiation effect modelling, and the application of radiation in medicine to provide an overview of the subject. The latest radiobiology research in non-targeted effects such as genomic instability and the bystander effect challenge the old models, but the implications for health effects on humans are uncertain. Adaptive responses to external stresses, of which radiation is one, have been demonstrated in cells and animal models, but it is not known how these might modify human dose–effect relationships. Epidemiological evidence from the Japanese A-bomb survivors provides strong evidence that there is a linear relationship between the excess risk of cancer and organ dose that extends from about 50 mSv up to 2.5 Sv, and results from pooled data for multiple epidemiological studies indicate that risks extend down to doses of 20 mSv. Thus linear extrapolation of the A-bomb dose–effect data provides an appropriate basis for radiological protection standards at the present time. Risks from higher dose diagnostic procedures fall within the range in which health effects can be demonstrated. There is therefore reason for concern about the rise in the number of computed tomography (CT) scans performed in many countries, and in particular the use of CT for screening of asymptomatic individuals. New radiotherapy techniques allow high dose radiation fields to be conformed more effectively to target volumes, and reduce doses to critical organs, but they tend to give a higher and more uniform dose to the whole body which may increase the risk of second cancer. It is important that radiation protection practitioners keep abreast of developments in understanding of radiation effects and advise the medical community about the implications of fundamental research when planning medical applications for the future.

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1. Introduction

Radiation has provided the cornerstone for medical imaging and much of the diagnosis and treatment undertaken in modern hospitals would not be possible without it. Medical exposure is the largest contributor to the radiation dose received by an average member of the public from artificial sources and makes up between 10% and 20% of the total radiation dose that an average person receives. Currently the use of radiation in medical diagnosis in high technology societies is expanding (Brenner and Hall 2007, Hall and Brenner 2008), and in the United States medical exposure now makes up over 50% of the dose for an average person (Mettler *et al* 2008). Control of radiation exposure, like many other aspects of modern life, can involve a substantial amount of administration as well as potential restrictions on the provision of services. The question of how far regulation should go in restricting medical exposures is difficult to assess and will always be a matter of debate. Too much control will place unnecessary administrative restrictions on already overloaded healthcare systems. Too little could lead to thousands or even millions of additional cancers in the future with the expansion in medical applications. The approach adopted must be derived from an understanding of evidence available from fundamental research, taking account of the attendant uncertainty. Significant developments in this research have taken place over the last twenty years and it is important that experts in radiation protection, both legislators and practitioners, maintain an understanding of the current state of knowledge in the radiobiology and epidemiology that underpins their subject in order to ensure that the decisions made about regulation are appropriate. The aim of this paper is to provide an overview of the subject matter in order to assist radiation protection practitioners in keeping abreast of work going on in laboratories and research institutes from around the world.

The making of balanced political judgements on radiological protection has always been affected by the public perception of radiation. This has been a problem ever since images of the destruction caused by the atomic bombs in Hiroshima and Nagasaki first appeared. Radiation is uniquely terrifying, because it cannot be seen or felt, so damage can occur without an individual being aware that anything has happened. Incidents, such as the Chernobyl accident and the poisoning of Alexander Litvinenko with polonium-210 (Harrison 2007, Gent 2009), occur from time-to-time and re-awaken these fears. Awareness of the potential risk of terrorism incorporating radioactive materials (Coleman and Parker 2009) has further highlighted the public fear of radiation in recent years. These factors lurk in the background whenever issues relating to radiological protection controls are debated. Experts need to ensure that the controls in place are appropriate and need to have a firm basis for justification of practices, if any changes are made.

The most important effect in humans resulting from low doses of radiation is the induction of cancer. The traditional understanding of radiation effects has been based on the assumption that DNA is the primary target and effects are induced by the deposition of energy in the DNA. Knowledge of the cellular responses is used to assist in understanding effects on tissues and whole organisms. Epidemiological studies of the Japanese survivors of the atomic bombs dropped on Hiroshima and Nagasaki have demonstrated a clear linear relationship between cancer incidence and organ dose over a range extending between two and three orders of magnitude (Preston *et al* 2003, 2004, 2007, UNSCEAR 2000, 2008) and this is supported by other epidemiological data. This has become the gold standard for prediction of malignancy based on a linear no-threshold 'LNT' extrapolation, which links risk directly to radiation dose (Hall 2009). However, questions about whether the extrapolation down to the low doses received from medical and occupational exposures has a justifiable scientific basis and whether this represents a reasonable solution for practical implementation must be addressed. There is

also a question whether deviations from linearity at high doses may affect the risk of second cancer in patients treated with radiotherapy.

The radiation standards designed to protect the public from exposures to low dose ionising radiation are based on the LNT model. One outcome from this is the concept that no radiation dose however small is regarded as safe and this further enhances the terrifying reputation that radiation holds with the general public. The ALARA principle of ensuring that doses are as low as reasonable achievable has been a fundamental concept in radiation protection practice for over 30 years. The whole principle of dose limitation is based on the assumption that all doses received have an associated risk and that these risks are additive. This applies both to an individual and a group. As a result, collective doses are derived for populations by summing small doses for individual members and are used to predict the likely number of cancer deaths from actual or potential radiation exposures. Dose constraints of 0.3 mSv yr^{-1} are used in radiological protection design in the UK and smaller doses to critical groups are often used when evaluating practical methodologies for treatment of radioactive discharges. If the linear relationship between cancer incidence and radiation dose were not approximately true, for instance if there were a dose threshold of 50, 10, or even 1 mSv, these methodologies would not be appropriate.

The evidence for effects at lower doses can only be based on an understanding of the interaction mechanisms derived from experiments on cell systems and animals. At the low doses to which radiation workers are exposed, the effects can be divided into three types: somatic, primarily carcinogenesis; germline, the production of heritable genetic effects; and developmental effects from foetal exposures. The original hypotheses on which the current system has been developed assume the following.

(1) Radiation effects result from damage to DNA molecules caused by direct or indirect (free radical interaction) effects, which may be base damage, single strand breaks (SSBs), double strand breaks (DSBs) or DNA cross-links.
(2) There is high fidelity in the repair of DNA damage and errors in this process are dealt with through senescence (ageing process) or cell death through apoptosis (programmed cell death) or linked to the meitotic process.
(3) The sensitivity to radiation damage is influenced by a range of cellular molecular factors.

The effectiveness of different types of ionising radiation in producing biological damage such as DSBs is related to the linear energy transfer (LET), which is a measure of energy deposition per unit length of track through the tissue. X-rays and γ-rays are low LET radiations and are less damaging than high LET radiation such as neutrons or α-particles.

Recent research has shown that the situation is not as simple as suggested by the hypothesis, because there are other non-targeted mechanisms which may affect cells that are not directly exposed through the passage of radiation (UNSCEAR 2000, BEIR 2006, UNSCEAR 2008). These effects, which have been demonstrated both in cell cultures and in animals, must be produced by a mechanism involving some form of communication from irradiated cells. Such effects could be beneficial through the elimination of damaged or initiated cells, or detrimental through the induction of damage in non-irradiated cells.

The 21st L H Gray conference brought together leading experts from around the world to review current research and discuss the implications for radiological protection now and in the future. This paper attempts to summarise the main points discussed at the conference for radiation protection practitioners in healthcare. It considers whether current practice is justified by the evidence and possible developments in the future. Subsequent papers in this issue describe research results in more depth. The evidence for effects from radiobiology and epidemiology will be considered first. The uncertainties in the derivation of doses, particularly

for radionuclides, which rely on the use of biokinetic and dosimetric models, will be discussed. Finally the implications for the application of radiation in medicine will be considered.

2. Results from radiobiology studies

Cells have evolved sophisticated mechanisms to detect and signal the presence of any damage to DNA, and these bring about delays in cell-cycle progression and coordinate DNA repair (Hall 2000). Together all these events comprise the so-called 'DNA damage response' and they are brought to bear on the wide range of DNA lesions induced by ionising radiation. The processes involved in repairing radiation-induced DNA lesions such as SSBs, DSBs of varying complexity and DNA cross-links are reasonably well understood and the last decade has seen significant advances in our knowledge of how signal transduction pathways triggered by DNA damage alter cell behaviour. More recently, insights have been gained into the mechanisms involved in sensing DNA damage. Radiation is only one factor in the environment which may produce damage to cells and tissues (Mothersill 2009). Every radionuclide is by definition a chemical as well as a source of radiation, and as such may affect a cell into which it comes into contact. Other factors such as heat or electromagnetic fields will stress cells and tissues and may produce a range of effects. Whether the effects that have been observed are important, even if not demonstrably harmful, is open to question, but there is undoubtedly interaction between radiation and the various stressors, and this further complicates the situation.

The mechanisms underlying the response to DNA damage can be regarded as three inter-linked processes comprising recognition of injury, damage assessment and response implementation. The recognition and response processes are not activated in a simple linear fashion because there are multiple responses to DNA damage that trigger both repair and apoptotic processes. Malfunctioning of these pathways may result in genetic instability and malignancy. These responses include cell-cycle checkpoint arrest that allows for a period of damage assessment and recruitment of DNA repair proteins or, if the damage exceeds the repair capacity of the cell, the initiation of apoptotic processes. Damage response checkpoints have been identified at the G1/S and G2/mitosis phase boundaries in the cell cycle as well as during S phase and potentially in mitosis. The DNA DSB is generally considered to be the principle cytotoxic lesion for ionising radiation and radio-mimetic chemicals but can also be caused by mechanical stress on chromosomes or when a replicative DNA polymerase encounters a DNA SSB or other type of DNA lesion. The repair of DSBs in normal human cells involves one of two possible pathways; non-homologous end-joining or homologous recombination.

2.1. Non-targeted effects

Chromosome aberrations, gene mutations and cell death induced by ionising radiation are conventionally attributed to the DNA being irreversibly changed immediately after exposure, either during the processing and enzymatic repair of the damage or during DNA replication. Consequently, all the progeny of a single irradiated cell should show any transmissible genetic change that has been induced by radiation, i.e. the effect would be clonal. This can be observed readily in experimental studies and it has been widely accepted that most of the lethal or mutational changes take place at the time of radiation exposure. As malignant transformation is generally regarded as being initiated by a gene mutation or a chromosomal aberration, the initiating lesion for malignant transformation has been attributed in the same way to DNA damage in a directly irradiated cell that leads to the emergence of a pre-neoplastic clone of 'initiated' cells that, with time, accumulate further mutations to produce a fully malignant clone (Luebeck and Hazelton 2002).

Recently, the view that radiation-induced deposition of energy in the nucleus of an irradiated cell leads to all the adverse consequences of radiation exposure has been challenged by observations showing the effects of ionising radiation are demonstrated in non-irradiated cells that are either the descendants of irradiated cells (radiation-induced genomic instability) or have communicated with irradiated cells (radiation-induced bystander effects) (Kadhim *et al* 1992, Mothersill and Seymour 2001, Morgan 2003a, Hall 2003). Radiation-induced genomic instability (RIGI) is characterised by the appearance of a number of delayed non-clonal effects in the clonal progeny of irradiated cells, including delayed chromosomal aberrations and gene mutations, reduced plating efficiency and delayed cell death. Radiation-induced bystander effects (RIBEs) are generally demonstrated very rapidly after irradiation but are characterised by appearing in non-irradiated cells that are in close proximity to irradiated cells or have received damaging signals from more distant irradiated cells. Reported bystander effects include increases or decreases in damage-inducible and stress-related proteins, increases or decreases in reactive oxygen species, cell death or cell proliferation, cell differentiation, radio-adaptation, induction of mutations and chromosome aberrations, and chromosomal instability.

RIGI is a genome-wide process induced at very high (epigenetic) frequencies, and persisting over many cell generations, perhaps indefinitely (Kadhim *et al* 1992, Morgan 2003a). The response appears to saturate at low doses, and observed lesions tend to have characteristics of 'spontaneous' abnormalities. Most studies have been carried out on cell lines *in vitro*, and expression of aberrations is not universal, but influenced by cell type and genetic factors. Genetic studies indicate that the expression of RIGI is genetically recessive and that chromosomal instability is likely to be associated with the arrest/repair/mis-repair versus apoptosis response. Compared to *in vitro* data, *in vivo* measurements show significantly less damage per cell and fewer cells demonstrating chromosomal instability, but confirm significant inter-individual variability. At present the mechanism of induction of instability by ionising radiation is not understood, and it is unclear whether all endpoints reflect a common mechanism. Inter-cellular mechanisms have been implicated, as have mechanisms involving oxidative stress and free radical-mediation processes.

Many RIBE responses have been reported including damage-inducible stress responses, chromosomal abnormalities, gene mutation, chromosomal instability, transformation of rodent cells and apoptosis (Mothersill and Seymour 2001, Hall 2003). Whilst many of the studies have concentrated on genome damage endpoints, there have also been reports of other effects being induced in bystander cells including increased cell proliferation and release of growth inhibitory factors. A protective adaptive response has also been reported, where bystander cells that are subsequently irradiated are more radio-resistant than cells not exposed to bystander signals. Bystander induction of terminal differentiation with loss of proliferative potential may also be regarded as a protective response. Thus, it appears that there are both damaging and protective cell signals that are encompassed within the general field of bystander effects and that the potential consequences of these effects reflect a balance between the type of bystander signals produced and the responses of cell populations to such signals, both of which may be significantly influenced by cell type and genotype (Seymour and Mothershill 2004). Like RIGI, RIBEs are not universally expressed and the response appears to saturate at high doses.

The evidence for a bystander effect *in vivo* is limited. There have been numerous reports of clastogenic factors in the plasma of radiotherapy patients, which were capable of causing chromosome breaks in unirradiated lymphocytes, although there is considerable variation between individuals (Mothersill and Seymour 2001, Morgan 2003b). Clastogenic factors have also been demonstrated in plasma taken from atomic-bomb survivors and Chernobyl liquidators, and from patients with a variety of chromosome instability syndromes. In addition, there is evidence from clinical and experimental radiotherapy data concerning, so-called,

'abscopal effects' of radiation, where responses are noted in unrelated organs or tissues that are not irradiated. A potential mechanism for the various indirect *in vivo* effects of ionising radiation is the generation of inflammatory-like processes and it is of interest that a persistent sub-clinical inflammation has been reported among Japanese A-bomb survivors.

2.2. The adaptive response

Many studies have demonstrated that exposure of cells or animals to ionising radiation, at a low dose and dose rate, induce mechanisms that protect against the detrimental effects of other events or agents, including radiation (Azzam *et al* 1994, Wolfe 1998, Feinendegen 1999). The first of the regularly reproducible experiments to show that very low doses of ionising radiation could induce an adaptive response were carried out on the induction of chromosome aberrations in cultures of human lymphocytes. If cells that had been exposed to a very low dose (10 mGy) of x-rays prior to irradiation with a relatively high dose (1 Gy), approximately half as many chromosome breaks were induced, as when no prior low dose was given. The adaptation induced by low doses of radiation was attributed to the induction of a novel efficient chromosome break repair mechanism that if active at the time of challenge with a high dose would lead to less residual damage (Wolfe 1998). This hypothesis was strengthened by experiments showing that an inhibitor (3-aminobenzamide) of poly(ADP-ribose) polymerase, an enzyme implicated in DNA strand break rejoining, prevented the adaptive response, even when it was administered after the challenge dose, provided it occurred within the time before induced chromosome breaks rejoined. Thus, the decreased damage resulting from the challenge dose was caused not by a change in the initial sensitivity of the cells but by mechanisms acting post-exposure. Subsequent experiments showed that this adaptive response to low doses required a certain minimal dose before it became active, occurred only within a relatively small window of dose; was dose-rate dependent; and depended on the genetic constitution of the people or animals exposed, with some being unresponsive. It was further shown that the response to the low dose pre-exposure was not instantaneous but required ∼4–6 h to become fully active and the response could be prevented during this period if protein synthesis was inhibited. In addition to the protective mechanism of DNA repair, an increase in the frequency of apoptosis has been found when a lower dose of radiation is given 24 h prior to a dose of several gray (Cregan *et al* 1999). The mammalian adaptive response to ionising radiation has been extensively documented for DNA damage, chromosome damage, mutation, cell transformation and cell killing and adaptation to radiation exposure has been demonstrated in single cell organisms, insects, plants, lower vertebrates, mammalian (including human) cells and mammals. It is evident that the adaptive response is an evolutionarily-conserved response.

Recent investigations have demonstrated that a small adapting dose can influence subsequent health outcomes in irradiated mice. An interesting example is the adaptive response on acute myeloid leukaemia induced in CBA/H mice by a chronic radiation exposure (Mitchel *et al* 1999). Results indicate that an earlier exposure to a small adapting dose of radiation or to a mild heat stress can influence secondary steps in radiation-induced carcinogenesis. Other studies have examined the effect of adaptation using mice heterozygous for the Trp53 tumour suppressor gene (Mitchel *et al* 2003). These mice are radiation-sensitive and cancer-prone, spontaneously developing a variety of cancer types. A single low dose induced a small protective response in Trp53 mice, reducing the carcinogenic effects of a subsequent large, high dose-rate exposure by increasing tumour latency. The upper dose threshold at which low dose protective effects gave way to detrimental effects was tumour type-specific and appeared to be lower (below 100 mGy) for radiation-induced tumours than for the same tumours appearing spontaneously. The studies are consistent with a very low dose fractionated exposure above a

threshold level inducing a protective adaptive response in both Trp53 normal and heterozygous mice.

The range of investigations demonstrating adaptation responses at low radiation doses are not consistent with high dose responses being simply extrapolated to low doses. Upper and lower dose thresholds for reduced risk exist in both normal and cancer-prone mouse models where p53 function modifies the magnitude and dose thresholds of the protective mechanisms. Thus, on the basis of these investigations, at low doses the assumptions of the LNT hypothesis and radiation protection practices are often not compatible with experimental observations *in vitro* or *in vivo*.

2.3. Radiobiology conclusions

The demonstration that adaptive responses occur and modify dose–effect relationships in specific experiments does not provide universal or sufficient evidence to prove that the LNT model is not the most appropriate. When all the radiobiological evidence currently available is reviewed, it is far from clear what implications non-targeted effects might have for risk assessment. Non-targeted effects that produce detrimental effects at low doses might elevate the risk, whereas protective bystander effects could decrease it. Although these effects have the potential to alter the shape of the dose–effect relationship for low radiation doses, it would be premature to suggest that they either raise or lower the risk above that indicated by the LNT extrapolation until a better understanding of the mechanisms and the biological significance *in vivo* has been gained.

3. Evidence from epidemiology

3.1. The A-bomb survivors

The majority of our understanding of mechanisms through which radiation affects cells and tissues has been derived from radiobiology experiments. However, the assessment of the magnitude of any risk from radiation exposure must be based on studies of humans. Over the last 60 years, the concern about effects from exposure to ionising radiation has changed from an emphasis on possible heritable effects to one on carcinogenesis. The most significant risk to humans from radiation exposure is now recognised to be from cellular transformations which may lead to the development of cancer. This has become evident from a massive epidemiological study of the survivors of the atomic bombs detonated over Hiroshima and Nagasaki (Preston *et al* 2003, 2004, 2007, UNSCEAR 2000, Little 2009). This study has also shown that the risk of genetic effects is much lower than had been thought, based on data from animal experiments (Hall 2009). In addition to the A-bomb survivor data, there is evidence of a link between radiation and cancer from other exposed population groups including: people exposed to large doses of radiation at work, patients undergoing medical exposures, and individuals exposed following the Chernobyl accident. Epidemiology studies of cancer incidence among these groups are essential for establishing a quantitative link between radiation dose and risk.

The Japanese A-bomb survivor group provides data for a population with a wide range of ages who received relatively high doses primarily from external radiation. They were exposed mostly to γ-radiation with 1–2% of neutrons from the Nagasaki bomb (Preston *et al* 2003, Pierce and Preston 2000, UNSCEAR 2006, Little 2009). In 1950, five years after the bombings, a cohort of 195 000 residents present in the two cities at the time of the bombings was identified for a life-span health study and a further 32 000 people not in Hiroshima and Nagasaki at the

time established as a control group. Dose assessments have been made for each person based on their position and orientation with respect to the points of the bomb detonations taking account of shielding by buildings. The data have allowed site-specific risk estimates to be made for persons exposed at different ages. The results have proved that there is a linear relationship between cancer risk and organ dose between about 100 mSv and 2.5 Sv (Hall 2009). If data from A-bomb survivors who received doses between 5 and 125 mSv are grouped together and the excess risk plotted against a mean dose, the data give a definite excess relative risk for cancer mortality and a value which agrees with the LNT extrapolation of the A-bomb survivor data for a mean dose of about 40 mSv (Brenner *et al* 2003).

Until the mid-1980s the risk models used to fit the data were either a time-constant absolute organ dose model or a relative risk model (ICRP 1991). In the absolute model the same risk to organ dose proportionality was applied to all individuals for a particular type of cancer, while in the relative risk model the risk for each type of cancer was taken as a multiple of the natural incidence in the population including an age-dependence. However, differences between individuals such as gender, age at exposure and time since exposure are important and should be taken into account, and more generalised risk models are now fitted to the data. A dose and dose-rate effectiveness factor (DDREF) is used to reduce the risk when extrapolating from a population receiving a single high dose and high dose-rate exposure to other exposed groups who have received lower doses over a longer period of time. A value of 2.0 is used in current International Commission on Radiological Protection (ICRP) radiological protection recommendations (ICRP 2007).

3.2. Medical exposures

When comparisons are made between risks calculated for the A-bomb study and those on radiotherapy patients there are certain sites which have significantly higher or lower risks than might be suggested from the A-bomb data. However, the dose distributions are different and the doses to specific organs adjacent to the target in radiotherapy studies are generally much higher and fall within the range where cells that already have a malignant transformation may have further damage inflicted which results in the cell either entering apoptosis or failing to divide successfully. More recent analyses, which have accounted for different radiation doses to bone marrow compartments, suggest reasonable agreement for radiation-induced cancer risks between A-bomb and medically irradiated individuals. Another area of study which is relevant when considering carcinogenic effects at low doses is the induction of childhood leukaemia in children radiographed *in utero* with doses of 10–20 mSv (Stewart *et al* 1956, Knox *et al* 1987). These studies provide further evidence that effects do occur at doses down to 10 or 20 mSv. An increase in childhood leukaemia is not seen among children of the A-bomb survivors irradiated *in utero*, but this would be within the statistical variation in the data.

3.3. The Chernobyl accident

The Chernobyl accident in 1985 resulted in exposure of several different groups; 240 000 liquidators received a mean effective dose of 100 mSv, 116 000 evacuees received a dose of 33 mSv and over 5 million people living in areas contaminated with caesium-137 in Russia, Belarus, Ukraine and elsewhere received smaller doses (Cardis *et al* 2006). The exposure for the later groups was primarily through intake of radioactive material and in particular substantial doses to the thyroid were received from uptake of ^{131}I. The median thyroid dose for those exposed in Belarus was 356 mSv with a maximum of 9.4 Gy, while the median for the Russian group was 39.4 mSv and the maximum 5.3 Gy. A deficiency in iodine resulting

from low levels in the local soil may have contributed to the high doses. Nearly 5000 cases of thyroid cancer have been reported in those under 18 at the time of the accident during the period 1992–2002 (Cardis *et al* 2005a). The incidence of thyroid cancer in children under 15 years increased rapidly at an early stage, reaching a peak about 10 years after the accident and has since declined, but the incidence of thyroid cancer in other groups continues to rise steadily. Results suggest that the risk of thyroid cancer following exposure to ^{131}I is similar to the risk from external photon exposure. The consumption of potassium iodide tablets decreased the risk by a factor of three. The prognosis for individuals with thyroid cancer is good and only 15 deaths have been reported up to 2006 among those exposed in childhood. A two-fold increase in leukaemia has been reported in the most highly exposed of the liquidators, but dose estimates are uncertain and other data from the exposure of children are inconsistent. No significant increase in incidence has yet been reported for other cancers, but doses to organs other than the thyroid tended to be low. There is a suggestion that there may be a rise in breast cancer for those receiving doses above 40 mSv. Since the minimum latent period for other cancers is longer than that for leukaemia or thyroid cancer, it is too early to evaluate the full radiological impact of the Chernobyl accident.

3.4. Radiation worker data

The study of those exposed to radiation during the course of their work presents an opportunity to assess directly the effects of protracted exposure to low levels of external radiation. The doses are in the range of primary interest, but the incidence of effects is low because in most cases the doses themselves are small (Wakeford 2009). Evidence for an increased risk of leukaemia has been found among US and British radiologists due to early exposures with minimal protection when doses are presumed to have been relatively high (March 1944, Berrington *et al* 2001). Radium dial painters demonstrated a clear excess risk of mortality from bone and other cancers from intake of ^{226}Ra and ^{228}Ra (Fry 1998). Underground hard-rock miners (e.g. uranium, iron, gold and tin) inhale radon and its radioactive daughter products. Exposures of many groups have been high and a clear linear relationship between risk of lung cancer and cumulative dose has been demonstrated (BEIR 1999).

Studies of the nuclear industry workforce, which have good personnel dosimetry records, have been carried out in the UK, USA and Canada and more recently in Russia. The average doses are low, so pooling of data from several studies has been used to improve the statistical power. Data from the UK, USA and Canada have been combined to give results for 95 000 radiation workers who received a mean individual cumulative dose of 40 mSv (Cardis *et al* 1995) and data from 15 countries pooled to give 400 000 workers with a mean cumulative dose of 19.4 mSv (Cardis *et al* 2005b). Results from both studies indicate an excess relative risk of leukaemia that is statistically significant. A study has recently been carried out of workers at the Mayak Nuclear Weapons Plant in Russia which began plutonium production in 1948 (Sokolnikov *et al* 2008). The risk of lung cancer increased with cumulative lung dose and there was a higher risk of mortality from bone and liver cancer among the most highly exposed groups.

3.5. Data from high background areas

Natural background radiation makes up the largest source of exposure to the world population, and there is the potential to obtain information about risks from epidemiological studies of health effects among populations living in regions where the level of background radiation is high (Hendry *et al* 2009). Such regions occur in parts of Brazil, China and India due to

the presence of ^{232}Th and ^{238}U in the rocks, and in parts of Iran where the levels of ^{226}Ra and daughter products in hot springs are high (UNSCEAR 2000). Average levels of exposure in these areas are between 3 and 7 mSv. Most people in these populations do not receive doses more than a factor of two greater than the average exposure of the world population, but doses for some individuals may be up to 50 mSv or even 100 mSv yr^{-1}. Comparative studies on groups exposed to different levels of natural background radiation do not have the statistical power to detect effects on cancer incidence, because of the small numbers receiving higher doses (BEIR 2006, Hendry *et al* 2009). Based on current risk estimates a population of 10 million would be required in order to prove whether there was a high incidence of solid cancer in an area where the population was exposed to 10 mSv yr^{-1}, whereas the populations that have been studied comprise less than 100 000 individuals. Populations that have higher doses from radon exposure provide the best indicator of a link between cancer and dose at lower dose levels. Results of a European project, which combined data from a number of individual case control studies in member states, show a clear increase in the risk of lung cancer among residents of homes with an enhanced concentration of radon (above 150 Bq m^{-3}), although the link with smoking is about 25 times stronger (Darby *et al* 2005, Hendry *et al* 2009).

Another approach to the study of populations living in high background areas is to observe bio-markers such as chromosome aberrations in the exposed populations. Data sets from Yang Jiang in China (Jiang *et al* 2000) and Ramsar (Ghassi-Nejad *et al* 2004) in Iran show higher frequencies of aberrations in peripheral blood lymphocytes. An experiment was carried out in which lymphocytes from 15 residents of Ramsar who received doses up to 260 mGy yr^{-1} and 30 controls were given a challenge dose of 1.5 or 2.0 Gy (Mortazavi *et al* 2000, Ghassi-Nejad *et al* 2002). A significant radio-adaptive response was observed for the more highly exposed residents of Ramsar, which increased linearly with the dose they received. However, it is difficult to draw conclusions about the health implications of these results.

3.6. Non-cancer effects

As far as radiation effects other than cancer are concerned, a link has been established between circulatory disease and radiation exposure at higher dose levels (Little 2009). There is an increase in circulatory disease among patients following radiotherapy exposures over 5 Gy as a consequence of acute tissue damage. A clear increase in incidence is seen in individuals who received a dose above 1 Sv in both the A-bomb survivors and in Chernobyl recovery workers. However, in contrast with cancer, there is less consistency in risk estimates between studies and no reliable conclusions can be drawn.

3.7. Epidemiology conclusions

Summarising the findings from epidemiological studies, the data on excess solid cancer incidence among the A-bomb survivors support a model for low LET radiation in which there is a linear extrapolation to low doses, but there is insufficient data to verify the extrapolation at doses below 50–100 mSv. The increase in thyroid cancer in those exposed following the Chernobyl accident is broadly in line with risks predicted from external radiation exposure results. For those exposed to lower doses over protracted periods, increases in certain cancers, particularly leukaemia and lung cancer have been observed among workers occupationally exposed to doses as low as 20 mSv accumulated over their working lives. No evidence for increased rates of cancer incidence has been found among populations living in regions with higher levels of natural background radiation, but the populations studied have not been large enough for a statistically significant excess cancer rate to be expected. Thus the evidence from

epidemiology supports a model in which the risk of cancer induction is proportional to organ dose. This risk appears to extend down to 20 mSv, but it is not possible to prove definitively whether there could be a threshold below 20 mSv for which there is no increase in risk of cancer and epidemiology studies are unlikely to have sufficient statistical power to answer this question.

4. Risk models and uncertainties

4.1. Biokinetic and dosimetric models

Results from epidemiological studies form the foundation on which the ICRP has built the framework for estimating risks from radiation exposure (ICRP 2007). As described in section 3, these results are dominated by epidemiological data from populations exposed to external radiation. Information on exposures from the intake of radionuclides is both hard to gather and difficult to assess. There is enough epidemiological data for inhalation of ^{222}Rn to draw conclusions about intake-dose–effect relationships (Darby *et al* 2005), but for all other radionuclides taken into the body models are needed to enable uptake to be predicted and radiation doses to be evaluated. The biokinetic and dosimetric models developed by the ICRP enable calculation of the macroscopic distributions of radioactive deposition within organs and tissues following inhalation or ingestion for a wide range of radionuclides. The available models consider inhalation or ingestion by workers and members of the public and allow estimation of committed, equivalent and effective doses using calculated dose coefficients expressed as Sv Bq^{-1}. Dose coefficients are also given for a range of radiopharmaceuticals used in diagnostic medicine. As well as ICRP models there are other dosimetric phantoms, which can be applied in the respiratory tract, such as the MIRD or voxel based approaches, that generate geometric models of the airways to allow dosimetric assessments.

Different biokinetic models have been developed for various population groups (e.g. adult, child, foetus) and different radionuclides. Each model (e.g. respiratory tract, systemic) simulates the transfer of radiation to multiple organs and tissue compartments following inhalation or ingestion (Harrison 2009). For example, the human respiratory tract model includes extrathoracic (nasal, oropharynx, larynx) and thoracic (bronchi, bronchioles, alveolar interstitial) compartments. The models take into consideration not only the transfer, retention and excretion of radioactive material in relation to the anatomy of the target tissue, but also the radiation type and route of exposure. Dosimetric models are then used to convert exposure to tissue dose. Dedicated models are required for bone dosimetry that take account of both trabecular and cortical bone, as once a radionuclide is deposited in bone, the source cells can be in the bone volume, in the bone marrow or on the bone surfaces. The relevant biological targets are bone marrow for leukaemia induction and the endosteal layer for induction of bone cancer. Biokinetic and dosimetric models are validated and improved by fitting data from exposed individuals (Harrison 2007). They are also used to calculate best estimates of doses and risks to individuals in epidemiological studies and to determine probability of cancer causation. Once absorbed doses have been determined, the protection approach is to calculate equivalent dose to various radiosensitive tissues to derive effective doses using appropriate radiation and tissue weighting factors. Effective dose is a protection device which allows summation of external and internal exposures for very different distributions of organ/tissue doses, independent of the time course for dose delivery (ICRP 2007). It relies on the assumption of the LNT dose–response and utilises organ equivalent doses that represent the average values for males and females, so there is a need for gender-specific voxel based phantoms. Effective dose can be used for regulatory purposes for comparisons with dose limits and constraints.

4.2. Uncertainty in risk estimates for internal emitters

The quantification of radiation risks is far more advanced than for other environmental toxins. Dose limits are set in terms of effective or equivalent dose as surrogates for whole body/tissue risks. A complicated but crude system is used to achieve additivity of risk from all exposures that is convenient for rough planning purposes in radiological protection but only provides ball-park estimates. The large variety in the types of exposure and the limited data available mean that uncertainties in risk estimates are large. New data continue to emerge relating to differences in the type and quantity of risk, so that the process is continually evolving. Examples of uncertainty in cancer risk estimates for external low LET radiation are a factor of ∼8 for fatal cancers estimated from the NCRP126 report (NCRP 1997) and a factor of ∼5 from the ICRP estimates of risk of cancer incidence (ICRP 2004).

It is instructive to consider the radiation interactions on the microscopic scale in relation to the uncertainties. The insult to DNA, cells and tissues from ionising radiation that is analysed is always in the form of structured tracks of charged particles. Low LET radiations such as x-rays and γ-rays are sparsely ionising on average but about one quarter of the energy that is deposited results from denser clusters of ionisations from low energy secondary electrons. All radiation tracks are highly structured on the scale of DNA. DNA damage can be simple clustered damage or complex clustered damage consisting of three or more components. All radiations produce a substantial proportion of complex DSBs. Solid cancer risks fit well to a linear quadratic equation, in which 1 mSv represents about one track (per cell nucleus), 20 mSv about 20 tracks, and CT scans between one and fifty tracks instantaneously.

The uncertainties in the ICRP models for internal exposure are greater than for external emitters because of the number of elements in the calculation and the number of associated assumptions (CERRIE 2004). Uncertainty factors for internal dose coefficients range from about 5 for dose estimates for ^{137}Cs to thousands for plutonium deposition in bone marrow. These uncertainties are in addition to those inherent in both the risk coefficients themselves and the assessment of the actual intakes by inhalation and ingestion. ICRP has produced many volumes of tables giving dose coefficients in which the numbers of significant figures imply a high level of accuracy. There is no indication of the uncertainties, although these may be factors of 10, 100 or even more. One example of the uncertainty in the dose assessment process can be obtained by looking at the calculated contribution to the equivalent dose to red bone marrow of a child born in Seascale in 1950 up to their 50th birthday from all radiation sources. Calculations made in 1984, 1986 and 1999, using the coefficients available at that time, vary by a factor of 14. Another example is given by a comparison of the ICRP unified dosimetric approach with direct estimates of risk for incorporated α-emitters, which suggests that the dosimetric approach overestimates the risk of lung cancer from ^{222}Rn inhalation by a factor of between 3 and 10.

When one considers uncertainties from internal emitters, it is important to consider γ, α, β and Auger processes separately. Gamma-rays are mostly high penetration, low attenuation radiations which normally travel many centimetres before they randomly interact to produce an electron track. They are de-localised from the radionuclide site and consequently use of average organ dose is probably acceptable. Alpha-particles travel a few cell diameters and deposit energy very locally. Use of radiation weighting factors, indicating a 20 times greater risk of cancer induction for α-particles, neglects huge differences in heterogeneity and radiation quality (Goodhead 2006). Specific features for β-particles such as increased average ionisation density, short electron tracks and non-uniformity of dose are not incorporated into conventional radiation protection dosimetry. Some Auger electron emitters can show super high LET features, for example ^{125}I used in radiopharmaceuticals can emit twenty electrons in

a single decay. Most have low energy and there is a strong overlap of tracks on a nanometre scale around the decay sites, so the clustered damage in a DNA molecule may be even greater than from an α-particle.

4.3. Modelling conclusions

It is important to be aware that assessments of risk and relative doses from different types of radiation to different tissues have large uncertainties. ICRP models are for calculation of dose coefficients but are also used as best estimates of dose and risk (Harrison and Day 2008, Martin 2007). However, ICRP dose coefficients are not subject to uncertainty, as they are reference values. Awareness of the uncertainties involved in their derivation may help to inform judgements on the optimisation of protection, but for general protection purposes no routine assessment of uncertainties need be carried out.

The uncertainty in estimating risk is greater for internal emitters than for external radiation. Information on microscopic heterogeneity is essential for many higher dose assessments. Vigilance is required when dealing with unusual radionuclides and compounds, for which assessment methods may be misleading. Estimates of uncertainties should be included for all high dose estimates for radionuclide intakes. Detailed micro-dosimetric evaluations should be made of potential deviations from standard risk estimations, and epidemiological studies of specifically exposed groups should be considered even if only to place upper limits on possible risks.

5. Implications for medical exposures

5.1. Implications for diagnostic medical exposures

The early sections of this paper have reviewed the evidence from radiobiology and epidemiology for health risks from radiation and the methods used to apply the results to different exposure situations. So what can be concluded about the lowest radiation dose at which there are solid data showing an elevated cancer incidence? Evidence from studies of the A-bomb survivors indicates that the risk of developing cancer increases linearly with organ dose from about 50 mSv up to 2.5 Sv, but for doses outside this range the relationship to organ dose is uncertain (Hall 2009). It is more difficult to prove whether there is a small increase in cancer rate associated with low doses to adults, because the natural incidence of cancer in any population is high. Moreover the prevalence of different types of cancer varies between population groups. As a result cohorts containing hundreds of thousands of individuals for whom there is reasonably reliable organ dose data are required.

Leukaemia is a comparatively rare type of cancer that is induced by radiation exposure. It has therefore provided some of the more definitive epidemiological evidence. When data from studies of workers involved in the nuclear industry are pooled, these show an increase in leukaemia and an indication of an increase in solid cancer at organ doses of the order of 20 mSv. Brenner *et al* (2003) have taken these results and included them in a meta analysis with other sources, including the Japanese Long Term Survival Study data. Their results indicate a statistically significant linear relationship between excess risk and organ dose extending down to 20 mSv. Therefore, organ doses from a CT examination involving two to three scans fall into the dose range where there is direct evidence of excess cancer risk in epidemiological studies. Organ risk estimates should be made using the BEIR VII approach rather than the systemic ICRP formalism based on effective doses for assessing risks to individuals from these higher dose examinations (BEIR 2006).

The number of radiological and nuclear medicine examinations performed has been increasing rapidly in recent years, and the dose from medical exposures in the US has increased by a factor of six in the last 25 years (Mettler *et al* 2008). In particular, the number of CT investigations, which typically give a dose about ten times that of a radiograph, has expanded to encompass a wider range of procedures (Brenner and Hall 2007), so that over their lifetime the average person in the US now has a CT scan every four years and in the UK one every 16 years (Hall and Brenner 2008). The individual risks are comparatively small so the benefit/risk ratio for any individual will be large if there are justified health benefits. However, the population exposed each year may be very large (67 million CT scans in the US including 6 million children per year) and a very small individual risk when multiplied by such a large number of patients may result in significant long term public health concern. Emphasis should be placed on education of clinicians about the potential risks from CT and the need for careful consideration of any referral. Medical exposures should only be carried out if they are justified, i.e. the result is going to answer a clinical question that affects management of the patient. Equipment used should be optimised to enable images of a quality sufficient for the application to be obtained with a comparatively low radiation dose.

5.2. Screening programmes

Epidemiology cannot provide an answer to the question of whether there is a risk of cancer induction for organ doses less than 10 mSv. Whether the adaptive responses could provide any protection against induction of cancer is unknown. Therefore, the *status quo* that the relationship between cancer risk and organ dose is linear and that there is no threshold below which an exposure is safe, the so-called LNT model, is the most reasonable position to take based on the present state of knowledge. An unavoidable outcome from adoption of the LNT model is that screening programmes involving any dose of radiation, however low, require an estimate of the potential risk from the procedures.

Mammography screening programmes are justified if they result in a material decrease in breast cancer mortality for women starting the programme. Data on risk have been carefully analysed over many years and are continually revisited to reassess the justification. The relationship between risk of cancer and breast dose is complex and varies with age, as the composition of the breast changes during life. Thus the age at which individuals are asked to first attend a mammography screening programme must be evaluated carefully. Another factor that should be considered is the suitability of the radiation weighting factor used to describe the radiobiological effectiveness (RBE) of the mammography x-rays in damaging tissue. The high energy γ-rays to which the A-bomb survivors were exposed have LET values of 0.2–0.3 keV μm^{-1}, whereas the low energy x-rays used for mammography have values for LET between 10 and 20 keV μm^{-1} (Heyes *et al* 2009). For radiation protection applications all x-rays, γ-rays and electrons are allocated a radiation weighting factor of one in calculations of equivalent dose to a tissue. A larger radiation weighting factor of about four would reflect the potential biological damage of the higher LET values for mammography x-rays more accurately (Heyes *et al* 2009). Another issue for mammography screening is the range of doses from the examinations, as women who have larger breasts will be exposed to higher radiation doses in order for satisfactory images to be obtained. Taking these factors into account, then for women starting on a mammography screening programme at age 40 there would be a net benefit to the screened population if the programme reduced breast cancer mortality by 20% or more, but the benefit for screening women under 40 years would be questionable. For mammography screening programmes with appropriate follow-up arrangements such as in the UK NHS breast screening programme, the benefit safely exceeds the risk of possible cancer induction, so the

exposures are considered to be justified. Caution should be exercised when screening women in their 30s and early 40s, particularly if they have a family history of breast cancer or fall into the high dose sub-group outside the normal screening population.

The justification for more general screening programmes is less obvious. New CT scanners with 64–320 slices per rotation are able to scan large volumes of a patient rapidly, and this coupled with new methods of image presentation has opened up a wide range of new applications. CT can readily be used to image any part of the body with little trauma, and so some consider it an ideal tool for carrying out regular health checks (Elliott 2009). For screening the colon, CT is less traumatic for the patient, and easier and quicker to perform than the traditional method of colonoscopy. CT may be used for assessing coronary calcification, for detecting lung disease, and even for whole body screening of asymptomatic individuals. The risks for doses received from CT scans are non-trivial and those from multiple CT scans fall within the realm where the cancer risk from radiation is well established. Other issues must be considered when assessing the justification of screening programmes of asymptomatic populations. There will be a significant incidence of false positive findings, which may require further investigation and the associated anxiety for the patient. If appropriate arrangements are not in place as part of a planned health management programme as with mammography, special arrangements will be required for follow-up. Thus, for populations with a low disease prevalence, more individuals may suffer detriment from health screening using CT than gain any clear benefit. CT scanning of an asymptomatic population may provide benefit to a few individuals, but it is likely to have an impact on public health through less appropriate use of limited resources. A report for the UK government on the practice of personally initiated CT scanning of the asymptomatic individual concluded that there is no justification for whole body CT scanning of asymptomatic individuals or for lung screening by CT scan (COMARE 2007), but that CT scanning may be justified for evaluating coronary calcification and for screening against colorectal cancer for some individuals. The committee further recommended that services should provide comprehensive information about eligibility criteria, and dose and risk from the scan, and that the range of further investigations that might be required following any positive finding should be discussed with the patient beforehand.

5.3. Influence on radiotherapy

The important factors in radiotherapy are the radiation effects on malignant and non-malignant cells within and outside the high dose volume. Radiobiology plays a crucial role in understanding these effects. Treatments are planned based on the assumption that the effects of radiation on cells are targeted and occur only in cells in which damage is produced directly by radiation interactions. Understanding the processes that occur at the cellular level during a radiotherapy treatment presents major challenges (Munro 2009). At the present time it is not known which cellular processes might be triggered by non-targeted bystander effects. A range of bystander effects might occur, some of which could have potential advantages and others disadvantages in clinical radiotherapy. Potential advantages might encompass more effective killing of cells within the tumour volume, the elimination of adjacent pre-malignant cells, stimulation of increased proliferation of normal cells and adaptation to improve the radio-resistance of normal cells. Disadvantages could include increases in acute toxicity, stimulation of proliferation in tumour cells, and enhancement of late organ damage. These effects will depend on the cell type and the heterogeneity of the tissue, and may be affected by subtle differences between cells. They may be influenced by factors specific to each individual such as genetic make-up, physiology, drugs being taken, and therapies the individual is undergoing.

The other area where radiobiology and epidemiology have implications for radiotherapy is in the risk of induction of second malignancies in radiotherapy patients (Hall 2009). The shape of the curve describing the relationship between cancer risk and organ dose at higher doses determines the risk of second cancers. Results from epidemiology studies show that the risk of cancer induction increases linearly with organ dose up to about 2.5 Sv, but what happens at the higher doses encountered in radiotherapy is less well documented. With doses of many gray that might be delivered in radiotherapy, cell survival may be compromised and the risk of cancer induction may even fall as organ doses increase. The potential for induced malignancy depends on how the RBE for malignant transformations varies with dose. Experiments on induction of leukaemia, lymphomas and other malignancies in small animal models indicate that the risk may decline for doses above a few gray. Mathematical modelling of cancer induction based on radiation interactions suggests that the probability of malignant induction could reach a maximum between 1 Gy and tens of Gy depending on the radiosensitivity of the cell, the type of radiation and the fractionation regimen used (Jones 2009). Some information has been gained from studies of the incidence of second cancers in radiotherapy patients (Hall 2009). Suitable control populations are available for some cancers, such as the prostate and the cervix where surgery is an option, and Hodgkin's disease where there is a risk of breast cancer in young women (Sachs and Brenner 2005). For cancer of the prostate, there is a 30% increase in the risk of a second cancer for those given radiotherapy. Studies of breast, bladder and stomach cancer incidence all suggest that the excess relative risk increases approximately linearly up to about 5 Gy, but above this the risk either levels off or continues to increase, but at a slower rate (Hall 2009). If the rate of malignant transformation does not increase as rapidly with organ dose above 5 Gy, then the mode of treatment delivery could influence the risk of a second malignancy following radiotherapy. The implications will be even greater if the rate of cancer incidence began to decrease with increasing dose (Jones 2009).

The traditional external beam radiotherapy, which has been in use for many years, employed coplanar and rectangular fields which exposed tissues within the main beams between the entry points and the target volumes to high doses. There have been considerable advances over the last decade. New developments have included:

- Conformal radiotherapy in which the fields are shaped to the target volume using multi-leaf collimators and the beams delivering the treatment may be non-coplanar.
- Intensity modulated radiotherapy (IMRT) in which the fluence across the beam is varied using changes in beam attenuators within the LINAC collimator during an exposure.

These techniques have allowed higher doses to be given to target volumes while reducing the doses to critical organs to minimise the risk of severe complications and those to the tissues lying within the beam. Similar or higher integral doses are given to the target volumes, but more treatment fields are used, so that there is a low dose 'bath' effect which exposes greater volumes of surrounding tissues to lower dose levels (Hall 2009).

Another factor that may affect the induction of second malignancies is that IMRT may increase the treatment monitor units by a factor of two or three, so that the exposure to radiation leaking from the LINAC head is larger. The net result is that regions of high exposure of normal tissue are reduced, but the overall dose to the whole body may be increased by a factor of 2–3 (Hall and Wuu 2003). Therefore a larger volume of normal tissue is exposed to lower radiation doses at which the probability of inducing cancer per unit dose may be higher. The risk of radiation-induced malignancy following radiotherapy of the prostate may be between 2% and 5% Sv^{-1}. A doubling of the second cancer incidence from 1.5% to 3% may be acceptable for older patients if balanced by a significant improvement in local tumour control, but may not be acceptable in children where the radiation-induced second cancer incidence is

much higher. Therefore methods through which these problems may be mitigated need to be investigated.

Another radiotherapy technique that is being investigated, which could improve treatment dose distribution and reduce the incidence of second malignancies is the use of charged particle beams (Lomax *et al* 2004). Protons have a limited range and deposit most of their energy in the Bragg peak, so enabling the dose to be concentrated at the depth of the intended target. However, most current facilities use a scattering foil to enlarge the pencil beam, which emerges from the cyclotron or synchrotron, to enable it to cover the tumour volume. Proton interactions in the foil produce neutrons, which may deliver substantial whole body doses of neutrons (Hall 2009). It is important that risks from this are taken into account and alternative methods of treatment delivery are developed which minimise these doses.

6. Conclusions

Studies of radiation exposure show that the main health effect from low doses of radiation is cancer and the influence on other types of disease is minimal. Epidemiological evidence from the A-bomb survivors shows that there is a linear relationship between risk of cancer and organ dose between about 50 mSv and 2.5 Sv, and the levels of risk are supported by data from other groups. Pooled data from epidemiological studies of the nuclear industry show a higher incidence of leukaemia among workers who have received cumulative doses over their working life of about 20 mSv and this lies within the predicted range from a linear extrapolation of the dose–effect relationship from the A-bomb survivors. Since these doses were received over many years, it would appear that smaller doses summed over time also increase the risk of cancer. Radiobiology experiments have shown that there are non-targeted effects such as genomic instability and the radiation bystander effect, which may occur without the passage of radiation through a cell. Adaptive responses which may protect cells have been demonstrated both in cell cultures and animal models, but these are dependent on the cell type and exposure conditions, and there is insufficient evidence to determine how these might modify the overall dose–effect relationship. Since the bystander effect could potentially increase or decrease any damage from radiation exposure, it is not possible to derive a predictable overall relationship between dose and effect based on current data for cell responses. Thus the LNT dose–effect model is the most appropriate one to adopt to describe the risks of cancer and provides a workable practical framework for the operation of protection. However, a note of caution should be given about the approximate nature of many of the dose and risk calculations. The dose models, particularly those for radionuclides taken into the body, involve many assumptions and approximations. Doses and risks in some situations may be an order of magnitude different from the values given by calculation. This does not mean that the system is inappropriate. Results provide guidance on which a workable protection framework can be based, but it is important that practitioners are aware of the limitations. Epidemiology studies of radiotherapy patients also indicate that the linear dose–effect relationship for cancer induction does not continue to increase indefinitely. At doses above 2.5 Sv the cancer incidence may not rise as rapidly or may level off, and could start to decline at higher doses. This has implications for the new techniques being developed in radiotherapy.

So what are the implications of fundamental radiation effects research for medical uses of radiation? If there are risks from doses of around 10–20 mSv, the expansion in the use of CT and other high dose diagnostic techniques is a cause for concern. If this continues unchecked, it is highly likely that there will be significant numbers of excess cancers induced by medical radiation in the future. The introduction of conformal radiotherapy and IMRT allow the treatment dose to be shaped more effectively to the target tissue, thus sparing normal tissue,

and especially critical organs from higher doses. The new techniques spread the dose more uniformly over the surrounding tissues and may result in the whole body dose being higher with more tissues being exposed to doses below 2.5 Sv from which the risk of cancer per unit dose is greater. Second cancer induction should be included in the risk equation when planning tissue protection for radiotherapy treatments in the future. It is important that appropriate regulations are in place to require justification and optimisation of all medical exposures.

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